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High functioning autism and common coexisting conditions: An EEG investigation

Ashleigh Kate Saunders

The University of Auckland

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Psychology, the University of Auckland, 2015.
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Chapter 5: Study three

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ABSTRACT

Autism spectrum disorder is a lifelong neurodevelopmental condition for which there is no known cure. The rate of psychiatric comorbidity (and comorbidity with other neurodevelopmental disorders) in autism is extremely high, which raises questions about the nature of the co-occurring symptoms. It is unclear whether these additional conditions are true comorbid conditions, or simply behaviour that is better conceptualised through the ASD diagnosis. The overall aim of the current thesis is to investigate the shared behavioural and neural basis of coexisting ADHD and anxiety in ASD.

The studies in the current thesis consisted of an investigation of behavioural characteristics using profiling techniques (Total $n = 83$ (ADHD = 23; anxiety = 12; ASD = 25; controls = 23)), in addition to four experimental studies conducted during concurrent EEG recording. These tasks were: emotion processing (Total $n = 74$ (ADHD = 22; anxiety = 12; ASD = 20; control = 20)); lexical decision (Total $n = 83$ (ADHD = 21; anxiety = 12; ASD = 20; control = 20)); inhibitory control (Total $n = 57$ (ADHD = 16; anxiety = 9; ASD = 15; control = 17)) and a resting state recording (Total $n = 46$ (ADHD = 11; anxiety = 10; ASD = 13; control = 12)). The diagnostic categories listed above include those with a comorbid condition, the groups are split further with respect to comorbid condition (e.g., ASD pure, ASD and comorbid ADHD) in each study. Together, these experiments covered a spectrum of core difficulties evident in ASD: difficulties with social interactions; language; repetitive behaviour (inhibitory control) and aberrant brain growth. By examining difficulties with they occur alone in ASD versus together with ADHD or anxiety, we are able to build a profile of singular and co-occurring ASD.

In the behavioural profiling study, using the wider diagnostic categories (e.g., ASD, ADHD and anxiety), results demonstrate that each group was able to be distinguished from one another, and from neurotypical controls, using the profiling measures. In individuals who
present with both ASD and anxiety together, the symptoms of ASD are not significantly higher, but symptoms of anxiety do increase compared to those with ASD alone. This suggests that anxiety is a separate condition when it occurs together with ASD. When ASD and ADHD occur together, there were significantly higher ASD symptoms than in the ASD only group and significantly lower ADHD symptoms than the ADHD alone group (but not the ASD only group). This suggests that there might be some degree of symptom overlap when ASD and ADHD present as a comorbid condition.

In the emotion processing task, there were no group differences in the latency or amplitude of the N170. There were, however, differences in the amplitude of the P250. Those with ASD and ADHD showed a differential profile in response to sad and neutral stimuli on the P250 from one another. Those with ASD had larger amplitudes toward mouth stimuli than eye stimuli, and those with ADHD had larger amplitudes toward eye stimuli than toward mouth stimuli. In addition, there was larger N170 amplitudes in the ASD pure group versus those with ASD and anxiety or ADHD. This suggests an additive effect.

In the lexical decision task, overall, the results indicated larger P100 amplitudes in the right versus the left hemisphere (most strongly shown in control participants). When the ASD and ADHD present as a comorbid condition, the mean P100 latency for the comorbid group lay between the two means for the ASD and ADHD pure groups. This suggests an additive effect.

In the inhibitory control study, the group level analysis did not show any differences between the experimental groups on the latency or amplitude of the N2 or P3 components. Upon closer inspection using regression analyses, smaller N2 and P3 amplitudes were associated with more severe symptoms of ADHD. Therefore, it is possible that inhibitory control deficits are associated with ADHD but not ASD or anxiety.
In the resting state study, the results demonstrate patterns of decreased coherence in those with ASD, and patterns of increased coherence in ADHD and anxiety compared to neurotypical controls. The patterns of coherence established in the ASD pure group are no longer evident when comorbid conditions are included in the analyses. Thus, this suggests that the conditions are additive.

Taken together, the studies in this thesis demonstrate that when ASD presents as a comorbid condition, ERPs adopt unique characteristics of each condition in its pure form. We argue that this is evidence for an additive effect which suggests that the conditions are indeed separate, rather than a misinterpretation (or increased severity) of ASD symptoms. This information is important to researchers when screening for comorbid conditions in ASD research, as underlying brain activity appears to be altered in each condition. This may significantly influence research findings. In addition, the results of the current study will also help to inform medical practitioners when administering a diagnosis and deciding on a plan to treat specific difficulties associated with comorbid ASD.
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Though only my name appears on the cover of this thesis, many people contributed to its production. Firstly, I would like to thank my supervisor, Associate Professor Karen Waldie for her continuous support, patience, motivation and guidance over the course of my PhD. I would also like to thank Professor Ian Kirk for his guidance and wisdom.

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Table of Contents

Abstract ........................................................................................................................................... ii
Acknowledgements ...................................................................................................................... v
Table of Contents ........................................................................................................................ vi
List of Figures ................................................................................................................................... xiv
List of Tables .................................................................................................................................... xvii
List of Publications ........................................................................................................................ xix
Thesis Overview ............................................................................................................................ 1

CHAPTER 1: GENERAL INTRODUCTION ................................................................................. 4
1.1 Autism Spectrum Disorder ......................................................................................................... 4
1.2 History of Autism ....................................................................................................................... 4
    1.2.1 Leo Kanner ......................................................................................................................... 4
    1.2.2 Hans Asperger .................................................................................................................. 5
1.3 DSM History ............................................................................................................................. 5
1.4 Developmental Course ............................................................................................................. 9
    1.4.1 Epidemiology ................................................................................................................... 9
1.5 What Causes Autism? .............................................................................................................. 10
    1.5.1 Heritability ...................................................................................................................... 10
    1.5.2 Environmental factors .................................................................................................... 11
    1.5.3 Autism as a disorder of the brain .................................................................................... 11
1.6 Comorbidity ............................................................................................................................. 12
    1.6.1 The comorbidity debate .................................................................................................. 13
    1.6.2 Autism and comorbid ADHD ......................................................................................... 14
    1.6.3 Anxiety disorders and ASD as a comorbid condition ..................................................... 18
    1.6.4 Summary of comorbid conditions in ASD .................................................................... 20
1.7 Neuroimaging Research in ASD ............................................................................................ 23
    1.7.1 Language ......................................................................................................................... 23
    1.7.2 Language in ASD, ADHD and anxiety ......................................................................... 23
    1.7.3 Face processing .............................................................................................................. 25
    1.7.4 Face processing in ASD, ADHD and anxiety ................................................................. 25
    1.7.5 Executive functioning ..................................................................................................... 26
    1.7.6 Executive functioning in ASD, anxiety and ADHD ..................................................... 27
1.7.7 Connectivity ................................................................. 29
1.7.8 Connectivity in ASD, anxiety and ADHD .......................... 30
1.7.9 Summary ...................................................................... 30

1.8 Rationale for the Current Research ........................................ 30
1.9 Aims and Objectives ......................................................... 31

CHAPTER TWO – GENERAL METHODOLOGY ........................ 33
2.1 Participant Recruitment .................................................... 33
  2.1.1 Recruitment ................................................................ 33
  2.1.2 Participant screening .................................................. 33
2.2 Procedure ......................................................................... 34
  2.2.1 Behavioural profiling ................................................... 34
  2.2.2 Electroencephalography .............................................. 35
  2.2.3 Final EEG data .......................................................... 36
2.3 EEG as a Technique .......................................................... 36
2.4 Event-related Potentials ..................................................... 37
2.5 ERP Components .............................................................. 38
  2.5.1 The P100 component .................................................... 38
  2.5.2 The N100 and the N170 components ............................ 39
  2.5.3 N200 ........................................................................ 39
  2.5.4 The P250 and P300 ..................................................... 39
  2.5.5 Summary of ERP components .................................... 40
2.6 EEG Coherence ............................................................... 40
2.7 Measures .......................................................................... 41
2.8 Behavioural Measures ....................................................... 41
  2.8.1 The Integrated Visual and Auditory Continuous Performance task ................................................................. 41
  2.8.2 Behavioural Inhibition Activation Scale ................................................. 42
  2.8.3 The Generalised Anxiety Disorder Scale .......................... 43
  2.8.4 The Obsessive Compulsive Inventory – Revised .................. 43
  2.8.5 The Adult ADHD Self Report Symptom Checklist ............... 44
  2.8.6 The Autism Spectrum Quotient .................................... 44
  2.8.7 Wechsler Abbreviated Scale of Intelligence ...................... 44
2.9 Neurophysiological Measures .............................................. 49
  2.9.1 The lexical decision task .............................................. 49
2.9.2 The stop signal task

2.9.3 The reading the mind eyes task

2.9.4 Resting state

2.10 Data Preparation and Statistical Analyses

2.10.1 Artefact removal

2.10.2 Trigger insertion

2.11 Preliminary Analyses and Data Screening

2.11.1 Gender

2.11.2 Age and IQ

2.11.3 Missing values analysis

2.11.4 Data screening

CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

3.1 Study Overview

3.2 Introduction

3.3 Co-existing Conditions in ASD

3.3.1 ASD and ADHD

3.3.2 ASD and anxiety

3.3.3 Summary of common co-existing conditions in ASD

3.4 Aims and Hypotheses

3.5 Methods

3.5.1 Participants

3.5.2 Recruitment

3.5.3 Medication

3.6 Procedure

3.6.1 Equipment

3.7 Measures

3.7.1 The Integrated Visual and Auditory Continuous performance task

3.7.2 Behavioural Inhibition Activation Scale

3.7.3 The Generalised Anxiety Disorder Scale

3.7.4 The Obsessive Compulsive Inventory – Revised

3.7.5 The Adult ADHD Self Report Symptom Checklist

3.7.6 The Autism Spectrum Quotient

3.7.7 Wechsler Abbreviated Scale of Intelligence
3.8 Statistical Analyses........................................................................................................66
3.9 Results..........................................................................................................................67
  3.9.1 Discriminant function analysis.................................................................................67
    3.9.1.1 ADHD versus controls.......................................................................................67
    3.9.1.2 ASD versus controls.........................................................................................68
    3.9.1.3 Anxiety versus controls.....................................................................................69
  3.9.2 ANOVA analyses ....................................................................................................70
    3.9.2.1 BIS scores .........................................................................................................71
    3.9.2.2 Fun Seeking Scores ........................................................................................73
    3.9.2.3 Drive Scores .....................................................................................................73
    3.9.2.4 Response Reward ............................................................................................74
    3.9.2.5 GAD scores .......................................................................................................75
    3.9.2.6 CPT Scores .......................................................................................................76
    3.9.2.7 ASRS Scores .....................................................................................................77
    3.9.2.8 ASQ Scores .......................................................................................................78
    3.9.2.9 OCI scores .........................................................................................................78
  3.9.3 Non-parametric tests .............................................................................................79
    3.9.3.1 Comorbid ASD and ADHD...............................................................................81
    3.9.3.2 Comorbid ASD and anxiety..............................................................................82
3.10 Discussion..................................................................................................................83
  3.10.1 Limitations.............................................................................................................88
  3.10.2 Conclusions..........................................................................................................89

CHAPTER FOUR – STUDY TWO: EMOTION PROCESSING AND EEG....................90
4.1 Study Overview..........................................................................................................90
4.2 Introduction................................................................................................................90
  4.2.1 Common co-occurring conditions in ASD.........................................................91
  4.2.2 Brain basis of social processing difficulties......................................................91
  4.2.3 Social information processing and EEG..........................................................93
  4.2.4 Social information processing in ASD, ADHD and anxiety using EEG.........94
4.3 Aims and Hypotheses...............................................................................................96
4.4 Methods....................................................................................................................97
  4.4.1 Subjects................................................................................................................97
6.4.3 Diagnoses ................................................................. 160
6.5 Measures ........................................................................ 160
6.6 Procedure .......................................................................... 160
  6.6.1 EEG acquisition ......................................................... 161
  6.6.2 EEG processing ........................................................... 162
  6.6.3 ERP analysis ................................................................. 162
  6.6.4 Statistical analyses ....................................................... 163
6.7 Results ............................................................................... 163
  6.7.1 ANOVA analyses .......................................................... 163
  6.7.2 Regressions ................................................................. 166
6.8 Discussion .......................................................................... 168
  6.8.1 Main effects of the N200 and P300 ................................ 169
  6.8.2 The N200 and P300 in ASD, anxiety and neurotypical controls ......................................................... 170
  6.8.3 The N200 and P300 in ADHD ........................................ 171
  6.8.4 Limitations ................................................................. 172
  6.8.5 Summary and future directions .................................... 173

CHAPTER SEVEN – STUDY FIVE: RESTING STATE .......................................................... 174
7.1 Study Overview .................................................................. 174
7.2 Introduction ......................................................................... 174
  7.2.1 Connectivity in ASD .................................................... 175
  7.2.2 Neuroimaging research on connectivity in ASD .................. 176
  7.2.3 Connectivity in common co-existing conditions with ASD ................................................................. 176
  7.2.4 Connectivity and EEG ................................................... 177
  7.2.5 Coherence in ADHD, anxiety and ASD ................................ 178
7.3 Aims and Hypotheses .......................................................... 179
7.4 Methods ............................................................................. 180
  7.4.1 Subjects ........................................................................ 180
  7.4.2 Recruitment .................................................................... 181
  7.4.3 Diagnoses ...................................................................... 181
  7.4.4 Behavioural profiling measures ..................................... 182
7.5 Procedure ........................................................................... 183
  7.5.1 EEG acquisition .............................................................. 183
  7.5.2 EEG processing ............................................................... 183
List of Figures

Figure 1.1. Venn diagram visualising the overlap in the three conditions, where ASD occurs with ADHD 28% of the time and anxiety 41% of the time (Siminoff, et al. 2008)........13

Figure 2.1. An illustration of the distribution of electrodes in the Geodesic 128 sensor net used in the current thesis.................................................................37

Figure 2.2. The typical distribution of an ERP where time ‘0’ indicates stimulus onset. The typical peaks and troughs of the ERP are labelled accordingly (“N” indicates a negative and “P” a positive waveform).................................................................38

Figure 3.1. Histogram showing the scores of participants in the control and ADHD groups on the ASRS.............................................................68

Figure 3.2. Histogram showing scores on the ASQ for the ASD vs control groups........68

Figure 3.3 Histogram showing scores on the drive scale for the ASD vs control groups.....69

Figure 3.4 Scatter plot showing that the two best predictors of differentiating controls from the anxiety group are the “Drive” and the GAD measures.........................70

Figure 3.5. Main effect of experimental group on behavioural inhibition scores..........72

Figure 3.6. Main effect of gender on behavioural inhibition scores .......................72

Figure 3.7. Main effect of experimental group on fun seeking scores....................73

Figure 3.8. Interaction between experimental group and gender on drive scores ........74

Figure 3.9. Main effect of experimental group on response reward scores.............75

Figure 3.10. Main effect of experimental group on GAD scores..........................76

Figure 3.11. Main effect of gender of GAD scores...........................................76

Figure 3.12. Main effect of experimental groups on CPT scores.........................77

Figure 3.13. Main effect of experimental group on ASRS scores.........................77

Figure 3.14. Main effect of experimental group on ASQ scores..........................78

Figure 3.15. Main effect of experimental group on OCI scores.........................79
Figure 3.16. ASQ scores of groups when split by comorbid condition. 80
Figure 3.17. GAD scores of groups when split by comorbid condition. 80
Figure 3.18. ASRS scores of groups when split by comorbid condition. 80
Figure 3.19. OCI scores of groups when split by comorbid condition. 80
Figure 3.20. Fun seeking scores of groups when split by comorbid condition. 81
Figure 3.21. Response reward scores of groups when split by comorbid condition. 81
Figure 3.22. CPT scores of groups when split by comorbid condition. 81
Figure 3.23. BIS scores of groups when split by comorbid condition. 81

Figure 4.1. An example of stimuli presented for the social information processing experiment. The sad stimuli are above, with the neutral stimuli below. 100
Figure 4.2. Grand average ERP waveform for each experimental group toward the sad eye stimuli. The N170 and the P250 components are labelled. 106
Figure 4.3. Grand average ERP waveform for each experimental group toward the neutral eye stimuli. 106
Figure 4.4. Grand average ERP waveform for each experimental group toward the sad mouth stimuli. 106
Figure 4.5. Grand average ERP waveform for each experimental group toward the neutral mouth stimuli. 107
Figure 4.6. Significant interaction between area and expression of the N170. 108
Figure 4.7. Significant interaction between area and expression of the P250. 109
Figure 4.8. Significant interaction between experimental group and area of the P250. 109
Figure 4.9. Significant main effect of latencies toward mouth and eye areas of the N170. 110
Figure 4.10. Significant interaction between area and experimental group, where the ADHD and ASD groups had significantly different amplitudes of the P250, but not the anxiety or control groups. 111
Figure 4.11 Grand average waveform of the ASD pure and comorbid groups in the eyes sad condition. The difference in the N170 between groups is significant …………………….113

Figure 4.12 Grand average of the ASD pure and comorbid groups in the eyes neutral condition. The difference between groups on the N170 component is significant ………..113

Figure 5.1. Left hemisphere grand averaged ERP’s for each experimental group in the real word condition………………………………………………………………………………..138

Figure 5.2. Right hemisphere grand averaged ERP’s for each experimental group in the real word condition………………………………………………………………………………..138

Figure 5.3. Left hemisphere grand averaged ERP’s for each experimental group in the pseudo word condition………………………………………………………………………………..138

Figure 5.4. Right hemisphere grand averaged ERP’s for each experimental group in the pseudo word condition………………………………………………………………………………..138

Figure 5.5. Left hemisphere grand averaged ERP’s for each experimental group in the nonword condition………………………………………………………………………………..139

Figure 5.6. Right hemisphere grand averaged ERP’s for each experimental group in the nonword condition………………………………………………………………………………..139

Figure 5.7. Significant main effect of experimental group on the overall latency of the P100………………………………………………………………………………..139

Figure 5.8. Significant main effect of hemisphere for amplitudes of the P100………………139

Figure 5.9. Significant main effect of condition on the amplitude of the P100………………140

Figure 5.10. Interaction between experimental group and condition of the amplitude of the P100………………………………………………………………………………..141

Figure 5.11. Interaction between experimental group and hemisphere of the amplitude of the P100………………………………………………………………………………..142
Figure 5.12. Significant difference between the latency of the P100 in the ADHD and ASD group in the real word condition………………………………………………………………………………..143

Figure 5.13. Significant differences in the latency of the N100 in the pseudoword condition between the ASD and ADHD groups, and the ASD and ASD + ADHD groups…………143

Figure 5.14. Significant difference between the ADHD and ASD groups of the P100 in the illegitimate nonword condition………………………………………………………………………………..144

Figure 6.1. Example of the procedure of the Stop Signal task. A rapid presentation of letters where participants should ignore all letters other the R or S. However, if that R or S is followed by a stop signal participants should withhold their desire to respond………………161

Figure 6.2. Significant main effect of condition for the amplitudes of the N200…………164

Figure 6.3. Significant main effect of condition for the amplitude of the P300………………165

Figure 6.4. Grand averaged ERP waveform for each experimental group in the no-go condition………………………………………………………………………………………………………………………………………………………………………………165

Figure 6.5. Grand averaged ERP waveform for each experimental group in the go condition………………………………………………………………………………………………………………………………………………………………………………165

Figure 6.6. Grand averaged ERP waveform for each experimental group in the stop condition………………………………………………………………………………………………………………………………………………………………………………166

Figure 7.1. Interaction between gender and experimental group for the frontal-frontal inter-hemispheric coherence values in the alpha eyes closed condition………………………….186

Figure 7.2. Main effect of gender for frontal-frontal intra-hemispheric coherence values in the alpha eyes open condition………………………………………………………………………………….187

Figure 7.3. Interaction between gender and experimental group in the central-central inter-hemispheric coherence values for the alpha eyes closed condition………………………….188

Figure 7.4. Significant main effect of gender for central-central inter-hemispheric coherence values in the theta eyes closed condition……………………………………………………………………………………………………………………………………………………………………………….189
Figure 7.5. Significant main effect of gender for central-central inter-hemispheric coherence values in the theta eyes open condition……………………………………………………………………190

Figure 7.6. Significant main effect of occipital-occipital inter-hemispheric coherence in the theta eyes open condition……………………………………………………………………191

Figure 7.7. Significant interaction between experimental group and gender of central-central inter-hemispheric coherence values in the theta eyes open condition…………………………191

Figure 7.8. Significant main effect of experimental group in the alpha central-central inter-hemispheric eyes closed condition…………………………………………………………192

Figure 7.9. Significant main effect of experimental group in the theta frontal-frontal intra-hemispheric coherence eyes closed condition………………………………………………193
List of Tables

Table 1.1. DSM-V, the latest edition of the diagnostic manual, criteria for Autism Spectrum Disorder

Table 1.2 DSM-V criteria for Attention Deficit Hyperactivity disorder

Table 1.3 DSM-V criteria for Generalised Anxiety Disorder

Table 1.4 DSM-V criteria for Obsessive Compulsive Disorder

Table 2.1. A summary of research studies that have investigated the reliability and validity of each profiling measure

Table 2.2. Gender distribution and mean age of the participants in the study

Table 3.1. Gender and age of participants in each experimental group in the behavioural profiling study

Table 3.2. Discriminant function analysis reveals the percentage of predicted vs. actual group membership of study participants

Table 3.3. Means and standard deviations of each experimental group for each profiling scale

Table 3.4. Means and SD for each ADHD pure, ASD pure and comorbid ASD + ADHD on each profiling measure

Table 3.5. Means and SD for each anxiety pure, ASD pure and comorbid ASD + anxiety on each profiling measure

Table 4.1. Mean age, IQ and gender distribution, with standard deviations, for each experimental group in the social information processing study

Table 4.2. Means and standard deviations of accuracy and response time, for each experimental group, in each condition

Table 4.3. Means, with standard errors, of latencies toward the eye and mouth stimuli for each experimental group

Table 4.4. Means, with standard errors, of amplitudes toward the eye and mouth stimuli for each experimental group
Table 4.5. Correlations between the N170 amplitudes of each condition and the profiling measures........................................................................................................115
Table 4.6. Correlations between the N170 latencies in each condition and the profiling measures........................................................................................................116
Table 5.1. Mean age, IQ and gender distribution for each experimental group in the lexical decision study..................................................................................................................133
Table 5.2. Examples of the stimuli used for each condition in the lexical decision experiment.....................................................................................................................135
Table 6.1. Mean age, IQ and gender distribution for each experimental group in the inhibitory control study..................................................................................................................159
Table 6.2. Regression statistics for the amplitudes of the N200 and the variance on the CPT for each condition..................................................................................................................167
Table 6.3. Regression statistics for the amplitudes of the P300 and the variance on the CPT for each condition..................................................................................................................167
Table 6.4. Regression statistics for accuracy and the variance on the CPT for each condition.....................................................................................................................168
Table 7.1. Mean age and IQ with standard deviations in parentheses and gender distribution for each experimental group in the resting state task........................................................................181
Table 7.2. Table shows all electrode pairs selected for analysis in the experiment, the area of the brain they are located over, and whether they are inter-hemispheric or intra-hemispheric connections..................................................................................................................185
Table 7.3. Correlations between coherence measures for each area, with eyes open or closed for the Alpha band..............................................................................................................................195
Table 7.4. Correlations between coherence measures for each area, with eyes open or closed for the theta band..............................................................................................................................197
List of Publications

CHAPTER ONE


CHAPTER THREE


CHAPTER FIVE

Thesis Overview

This section will briefly describe each chapter in the current thesis. The five studies that comprise this doctoral thesis are included in Chapters 3, 4, 5, 6, and 7. These chapters are presented in manuscript style and include: study overview; introduction; methods; results; discussion and conclusion sections.

Chapter 1: General Introduction

The first chapter of this thesis provides a general introduction to autism spectrum disorders including the definition, history, developmental course, and possible causes. This chapter also provides an introduction to comorbidity in autism spectrum disorders and outlines how ADHD and anxiety manifest together with ASD. A review of the research relating to the domains of language, face processing, executive functioning and brain connectivity is presented for those with ASD, ADHD and anxiety. Finally, the rationale, aims and objectives of the current research are outlined.

Chapter 2: General Methods

This chapter describes the overall procedure and methods relevant to the five studies in this thesis. A detailed description of the participant demographics, recruitment and screening processes and study design is provided. In addition, detailed information about the behavioural profiling tools and electroencephalography (EEG) acquisition is outlined. This includes validity and reliability measures of each questionnaire and a general overview of EEG as a research technique. Finally, preliminary statistical analyses and data screening results are presented.

Chapter 3: Behavioural Profiling

This chapter describes an experimental study which investigates the behavioural profile of ASD, ADHD and anxiety compared to neurotypical controls. This is done by using
a number of profiling tools and a computer based tasks in order to measure the nature of symptoms in these groups.

Chapter 4: Emotion Processing

This chapter describes an experimental EEG study that investigates emotion processing in individuals with ASD, ADHD and anxiety when the conditions occur alone versus together. This is done using an emotion recognition paradigm (responding to sad versus neutral images of the eye or mouth area) during concurrent EEG recording. The main measure of interest in this study was the ERP waveform produced after the presentation of each stimulus. The specific ERP components of interest are the N170 and the P250.

Chapter 5: Lexical Decision

This chapter describes an experimental EEG study which investigates lexical information processing in individuals with ASD, ADHD and anxiety when the conditions occur alone versus together. This is done using a lexical decision paradigm (deciding between real English words, or nonwords) during concurrent EEG recording. Participants responses to real English words, pseudowords and nonwords were recorded. The main measures of interest in this study was the ERP waveform produced after the presentation of each stimulus. The specific ERP components of interest are the P100 and the N170.

Chapter 6: Inhibitory Control

This chapter contains a study that investigates the inhibitory control profile of individuals with ASD, ADHD and anxiety when the conditions occur alone versus together. This was done using a stop signal paradigm (a simple go/no-go paradigm with an additional element where participants must withhold a dominant response) during concurrent EEG recording. Participants responses to “go”, “no-go” and “stop” stimuli were recorded. The main measure of interest in this study were the ERP waveform produced after the
presentation of each stimulus. The specific ERP components of interest are the N200 and the P300.

**Chapter 7: Resting State**

This chapter contains a study that investigates resting state connectivity profile of individuals with ASD, ADHD and anxiety when the conditions occur alone versus together. This was done using a simple resting state task (where participants were asked to sit still with their eyes open for two minutes, then with their eyes closed for two minutes) during concurrent EEG recording. The coherence between electrodes in specific brain regions was then used as a measure of connectivity. This was done to investigate whether there are connectivity differences in those with ASD, ADHD or anxiety versus typically developing controls.

**Chapter 8: General Conclusion**

In this chapter of the thesis, the results from each study will be briefly summarised. The overall implications of the research with regards to each experimental group will then be discussed. Next, the implications of the results with regards to the experimental groups when they present as a comorbid condition will then be discussed. Potential causes for the high comorbidity rates given what the thesis found will also be discussed. Overall limitations and implications of the research will be outlined before a general conclusion of the thesis.
1.1 Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a lifelong neurodevelopmental condition that involves impairments in social, communication and behavioural domains (American Psychiatric Association, 2013). There is extreme phenotypic diversity in autism, with each individual displaying different levels of impairment in the three domains. Such impairments can result in stereotyped movements, an insistence of sameness, delayed speech including echolalia, and aberrant behaviour. There is also a failure to develop normal social interactions and relationships with others. The range of impairments in individuals with ASD is highly variable and can range from complete mutism coupled with low intellectual functioning, to those with unimpaired speech and good intellectual functioning. For those high functioning individuals, difficulties may be limited to impairments in social interaction. Thus, ASD is the umbrella term that encompasses the range of impairments of those affected. Autism is usually noticed in the first or second year of life by language delays, repetitive behaviour or preoccupation with objects such as ceiling fans (DiCicco-Bloom et al. 2006). Autism is a lifelong condition for which there is no cure (American Psychiatric Association, 2013).

1.2 History of Autism

There were two main investigators in the initial discovery of autism. Together, both were describing the key characteristics of what is now known as autism spectrum disorder.

1.2.1 Leo Kanner

Leo Kanner (1943) first described autism after observing a group of patients with similar impairments. Kanner’s landmark paper, Autistic disturbances of affective contact,
formed the basis of modern study of autism. The patients who he had seen in his clinic all exhibited: an inability to relate to people; failure to develop speech; abnormal responses to environmental objects and events; an obsessive desire for sameness; and excellent memory. Kanner labelled this condition ‘early infantile autism’.

Consistent with the thinking at the time, Kanner put the cause of autism down to psychogenic factors. He controversially associated the condition with ‘refrigerator mothers’ – that autistic children were a product of cold and detached mothers. He later retracted this viewpoint, but maintained the stance that autism was an emotional disorder (Feinstein, 2010).

1.2.2 Hans Asperger

Dr Hans Asperger was an Austrian paediatrician and medical professor who worked in the mid- to late 1900s. One year on from Kanner, Hans Asperger (1944) described a group of children using similar terminology. In addition to these characteristics, however, he also noted that the children had developed normal language but the content of their speech was slightly abnormal, with a tendency towards pedanticism. He also noted that the children had an intense interest in a particular subject. The most obvious impairment was of two-way social interaction. The symptoms characteristic of this higher functioning group became known as Asperger’s syndrome. Asperger thought of this syndrome as a personality disorder with organic causes.

1.3 DSM History

As early as 100 years ago, autism was a largely unknown disorder. As the occurrence of autism increased, researchers were perplexed as to what caused the disorder. Due to this uncertainty, the diagnostic criteria evolved as information about the disorder developed. Autism first appeared in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)
CHAPTER ONE – GENERAL INTRODUCTION

DSM-I in 1951, classified as a primary manifestation of childhood schizophrenia (Feinstein, 2010). This classification was met with scepticism by some who campaigned for it to be recognized as its own disorder. In 1980 this was achieved. The DSM-III introduced infantile autism as a subcategory of pervasive developmental disorder (American Psychiatric Association, 1980). Pervasive developmental disorder was a category of lifelong disorders that affected social interaction and communication (e.g., autism, childhood disintegrative disorder, Rett syndrome).

It soon became evident that autism has a vastly different developmental course from individual to individual, with some individuals more affected by the condition than others (Werner, Dawson, Munson, & Osterling, 2005). Accordingly, the DSM-IV listed autistic disorder and Asperger’s as separate conditions (American Psychiatric Association, 1994). The critical distinction between autistic disorder and Asperger’s is the absence of linguistic or cognitive delays in the latter condition. This diagnostic criteria closely followed the early work of Kanner and Asperger described above.

There have been recent changes to the new Diagnostic and Statistical Manual of Mental Disorders (DSM-V American Psychiatric Association, 2013). According to the new clinical manual, ‘Asperger’s syndrome’ no longer exists as a label to describe high-functioning autism. Instead, those affected by autism spectrum disorder are considered to lie on a continuum that includes high and low functioning individuals. For example, an individual with very low functioning autism may not develop language at all, make no eye contact and have persistent and uncontrollable body movements (i.e., hand-flapping). On the other end of the spectrum, someone with very high functioning autism may have intact speech and very few aberrant body movements, but do not show typical social interactions. Throughout this thesis, the term autism is used interchangeably with ASD to refer to all individuals on the spectrum. The current diagnostic criteria can be seen in Table 1.1.
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:</td>
</tr>
<tr>
<td></td>
<td>Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.</td>
</tr>
<tr>
<td></td>
<td>Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.</td>
</tr>
<tr>
<td></td>
<td>Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.</td>
</tr>
<tr>
<td>2.</td>
<td>Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history:</td>
</tr>
<tr>
<td></td>
<td>Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).</td>
</tr>
<tr>
<td></td>
<td>Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).</td>
</tr>
<tr>
<td></td>
<td>Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).</td>
</tr>
</tbody>
</table>
Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

3. Symptoms must be present in the early developmental period.

4. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

5. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.
CHAPTER ONE – GENERAL INTRODUCTION

1.4 Developmental Course

Autism is an incurable condition with an unknown cause (Bryson, 1996). This has led to widespread speculation and misinformation about its causes and characteristics. There have been claims that there is a link between vaccinations and autism (Wakefield, 1999), more specifically mercury and autism (Mutter, Naumann, Schneider, Walach, & Haley, 2005). Both theories have been quashed (Farrington, Miller, & Taylor, 2001). In the quest for a treatment, there have been claims that autism can be cured by a gluten-free casein-free diet, medicinal snake oil, vitamin therapy, drugs to purge the body of mercury or sensory integration therapy (pressure or sound applied to the body to reduce sensitivity). However, randomised case-controlled studies show that these ‘therapies’ have little impact on the lessening of autistic symptoms (Jacobson, Foxx, & Mulick, 2005; Millward, Ferriter, Calver, & Connell-Jones, 2008). It is now widely accepted that there is no permanent cure for autism, although early intense behavioural intervention (i.e., applied behavioural analysis therapy) can help improve symptoms (Peters-Scheffer, Didden, Korzilius, & Sturmey, 2011).

1.4.1 Epidemiology

Evidence on the prevalence of ASD is mixed, with estimates ranging anywhere from 5/10,000 to 72/10,000 (Newschaffer et al, 2007). Recent research estimates the prevalence of autism to be somewhere between 66/10,000 (Hill, Zuckerman, & Fombonne, 2014; Matson & Goldin, 2013a). This is an overall increase in prevalence from earlier estimates of 4.4/10,000 (Fombonne, 2003). The condition affects people in every nationality, race and socio-economic status (French, Bertone, Hyde, & Fombonne, 2013), and is more common is males than females, with a male to female ratio of 3-4/1 (Newschaffer et al, 2007).
1.5 What Causes Autism?

The cause of autism is largely unknown. In recent years there has been a shift in the focus on psychogenic factors to biological causes. The most recent consensus is that autism likely has a complex polygenic basis that causes abnormal pre- and post-natal brain development (DiCicco-Bloom et al. 2006). The prevalence of ASD appears to be steadily rising over a ten year period, as mentioned above. In part, the increase in prevalence is due to an increase in awareness, diagnosis at an earlier age and widening of diagnostic criteria (French et al., 2013). Nonetheless, a legitimate rise in prevalence is also likely (see Matson & Kozlowski, 2011 and Rubenstein & Merzenich, 2003 for reviews). Following about 50 years of intensive study, researchers now believe that autism is a complex disorder whose core aspects have distinct causes that often co-occur.

1.5.1 Heritability

There is convincing evidence that demonstrates the heritability of autism. The unequal male to female ratio suggests an x chromosome-linked disorder however, the data are inconclusive (Muhle, Trentacoste & Rapin, 2004). Familial studies reveal a 2 – 8 % recurrence rate in siblings of unaffected children, higher than the general population rate. Unaffected siblings are also more likely to display autistic-like behaviour (Constantino et al., 2014). Similarly, unaffected twins of those with ASD show increased anxiety (Hallett et al., 2013). Twin studies show a 60% concordance rate between monozygotic twins and 0% between dizygotic twins. Further, when the non-affected twin was reassessed for the sub threshold symptoms of autism (e.g., characteristics or phenotypes of autism that are not strong enough to merit a diagnosis) the rate jumped from 60% to 92% in monozygotic, and from 0% to 10% in dizygotic twins (Couteur et al. 1996). Such findings led the way for more intense genetic scrutiny. While there is no conclusive genetic evidence, data from whole
genome sequences of multiplex families suggest interactions in at least 10 genes in the causation of autism. The region most strongly linked is 7q31-q33, a gene thought to impact speech and language (Muhle, Trentacoste & Rapin, 2004; Talkowski, Minikel, Vallabh & Gusella, 2014).

Although there is strong support for genetic mechanisms of transmission in autism, each of the individual genetic alterations identified in genetic studies explains only a small proportion of the overall disorder variance; the most common genetic risk factors account for about 1% of all autism cases (Carter & Scherer, 2013).

1.5.2 Environmental factors

It is possible that environmental factors may contribute to the rising prevalence of autism. Exposure to air pollution during pregnancy and in the first year of life is associated with an increased risk of autism (Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013). Similarly, prenatal drug exposure (Christensen et al., 2013), perinatal respiratory distress (Froehlich-Santino et al., 2014), increased maternal age (Sandin et al., 2012), caesarean section, pre-term birth and being born low birth weight for gestational age (for a review see Guinchat et al., 2012) are all associated with increased rates of autism. It is thought that pre- and peri-natal exposure to toxins or stress may affect neurodevelopment (Roberts et al., 2013). Taken together, this evidence suggests it is possible that autism is a product of a gene x environment interaction where sub-optimal environmental conditions may alter the developmental course of individuals with a genetic risk.

1.5.3 Autism as a disorder of the brain

Abnormal brain development in those with ASD is widely acknowledged as a defining characteristic of the disorder. There is a vast body of evidence showing that the autistic brain is functionally and structurally different from typically developing individuals. For example, while normal brain volume is observed at birth, autistic individuals undergo a
Chapter One – General Introduction

Period of excessive brain growth at an early age that slows down later in development (Courchesne, Campbell & Solso, 2011). Magnetic resonance imaging (MRI) data reveals that by age 2-4, 90% of autistic children have a larger average brain volume than controls (Alschoomoff, Pierce & Courchesne, 2002). This overgrowth in brain volume leads to abnormal anatomical and functional organisation of the brain in those with autism (Akshoomoof, Pierce & Courchesne, 2002).

The nature of the growth also differs significantly from typically developing children. Evidence using tensor-based morphometry revealed that autistic individuals show abnormally slow white matter growth in parietal, temporal and occipital lobes, and excessive grey matter growth in structures including the putamen and anterior cingulate cortex (Courchesne, 2004). Interestingly, these structures are all implemented in communication deficits, social impairment and repetitive behaviours (Hua et al, 2013). Neural defects that cause early brain overgrowth may give us important clues about the neural basis of autism (Courchesne, 2011). Despite these findings, the underlying neural defects that cause ASD are still largely unknown. The current consensus is that ASD has a complex polygenic basis that is associated with abnormal pre- and post-natal brain development.

1.6 Comorbidity

Comorbidity is defined as the co-occurrence of two or more conditions in the same individual (American Psychiatric Association, 1994) and will be used interchangeably with the term co-occurring throughout this thesis. ASD is associated with higher rates of physical conditions such as: epilepsy; sleep disorder; gastrointestinal disorders and autoimmune conditions (Matson & Goldin, 2013b). Additional neuropsychological conditions like Attention Deficit Hyperactivity Disorder (ADHD) and anxiety (particularly Obsessive Compulsive Disorder (OCD)) are known to affect between 50-70% of individuals with ASD
(Ghaziuddin & Zayfar, 2008), as illustrated in Figure 1.1. While little is known about the underlying basis of comorbidity, the presence of additional conditions cause the individual pronounced distress and impairment. For example, those with additional conditions are thought to have more severe symptoms, more pronounced social difficulties and are lower functioning that those with ASD alone (Kerns & Kendall, 2012).

![Venn diagram visualising the overlap in the three conditions, where ASD occurs with ADHD 28% of the time and anxiety 41% of the time (Siminoff, et al. 2008).]

Figure 1.1. Venn diagram visualising the overlap in the three conditions, where ASD occurs with ADHD 28% of the time and anxiety 41% of the time (Siminoff, et al. 2008).

1.6.1 The comorbidity debate

Few theories on the basis of comorbidity in ASD exist. However, researchers and practitioners are divided on determining true comorbidity from symptoms of ASD. That is, whether symptoms of ADHD and anxiety can be accounted for by the autism diagnosis or whether they are true co-existing conditions which warrant a self-standing diagnosis. Bradshaw’s frontostriatal model (2001) proposes that ASD, ADHD and anxiety all stem from a dysfunction in the frontostriatal system of the brain. The conditions seem separate as they each adopt different difficulties that stem from frontal lobe dysfunction (i.e., executive function deficits), but are essentially all caused by the same core deficit. This suggests that the conditions have the same origins and can be considered along the same spectrum of
disorders. However, given the general lack of research that directly addresses this uncertainty, there is currently no consensus on whether comorbid conditions are best conceptualised as part of the ASD diagnosis or are entirely separate.

When investigating comorbidity it is useful to first define what would constitute separate or comorbid conditions. Wood and Gadow (2010) outlined criteria for determining the validity of a comorbid diagnosis. If two conditions were truly comorbid we would expect to see the presentation of each disorder identical to its monomorbid form in the unaffected individual (i.e., anxiety, OCD or ADHD), or a condition phenotypically altered by ASD symptoms (an entirely different condition altogether). Alternatively, if the conditions are not truly comorbid, they could be better conceptualised as an aspect of the phenology of ASD (i.e., a behaviour or subtype of ASD), or simply due to inaccurate diagnosis. The overall aim of this thesis is to clarify the role that comorbid conditions play in ASD. The main focus is on two common coexisting conditions with ASD, anxiety disorders and ADHD.

1.6.2 Autism and comorbid ADHD

ADHD is characterised by a pattern of inattentive (e.g., failure to pay attention to tasks, difficulty organising tasks), hyperactive (e.g., excessive talking or fidgeting) or impulsive (e.g., inability to remain seated in appropriate situations) behaviour that results in difficulties in social, educational or work settings (APA, 2013). Behaviourally, ADHD is characterized by excessive activity, short attention span and impaired inhibitory control (Barkley, 1997). The full diagnostic criteria can be seen in Table 1.2. The worldwide prevalence of ADHD is estimated to be around 529/10,000 and is more common in males than females (Kessler et al., 2011).

One of the most contentious issues in comorbidity research is the validity of a dual diagnosis between ASD and ADHD. In fact, the Diagnostic and Statistical Manual of Mental
Disorders fourth edition (American Psychiatric Association, 1994) excluded the possibility of a co-diagnosis between the two. The issue at hand is whether the symptoms of ADHD are a behaviour of ASD itself, or a separate, self-standing condition (Nebel-Schwalm & Worley, 2014). Indeed there are many overlapping symptoms between the two disorders including: attention difficulties, hyperactivity, impulsivity (Hays, Reas, & Shaw, 2002), social skill deficits (Cervantes et al., 2013; Demopoulos, Hopkins, & Davis, 2013) and behavioural issues (Mayes, Calhoun, Mayes, & Molitoris, 2012). Research has also demonstrated that those with comorbid ASD and ADHD show more severe symptoms (more tantrum behaviours, anxiety and conduct disorder) than those with ASD or ADHD alone (J. Jang et al., 2013). In addition, both are associated with functional differences in the prefrontal cortex (Johnson, 2012). As such, there is a lack of agreement on whether these characteristics are simply a manifestation of ADHD-like symptoms or ADHD itself when they occur together with ASD.

However, while both groups show social deficits, those with ADHD are more socially motivated that those with ASD (Geurts, Luman, & Van Meel, 2008). In addition, neuropsychological research demonstrates differences in brain structure and function between those with ASD and ADHD (Taurines et al., 2012). In spite of some shared characteristics, the growing body of literature suggests that those with ADHD and ASD have different cognitive and neuropsychological profiles. Thus, in the most recent edition of the DSM, co-diagnosis of ASD and ADHD is permitted.
Table 1.2 DSM-V criteria for Attention Deficit Hyperactivity disorder

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):</td>
<td></td>
</tr>
</tbody>
</table>
| 1.                        | Inattention: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:  
Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).  
Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).  
Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).  
Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily side tracked).  
Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).  
Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).  
Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).  
Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).  
Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments). |
Often fidgets with or taps hands or feet or squirms in seat.

Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).

Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)

Often unable to play or engage in leisure activities quietly.

Is often “on the go,” acting as if “driven by a motor” (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).

Often talks excessively.

Often blurts out an answer before a question has been completed (e.g., completes people’s sentences; cannot wait for turn in conversation).

Often has difficulty waiting his or her turn (e.g., while waiting in line).

Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people’s things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

3. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

4. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

5. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

6. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).
1.6.3 Anxiety disorders and ASD as a comorbid condition.

Anxiety disorder is an umbrella term for which there are many sub-diagnoses, such as: generalised anxiety disorder (GAD), social phobia, OCD, post-traumatic stress disorder and panic disorder. The full diagnostic criteria can be seen in Table 1.3. The current thesis will concentrate on two particular subsets of anxiety: GAD and OCD. Particular focus was given to these two subsets as OCD has a phenotypical overlap with ASD and GAD is anxiety that is not linked to a particular object or situation (as is the case in social phobia, specific phobia or post-traumatic stress disorder).

GAD is characterised by excessive worry or anxiety about a variety of situations (American Psychiatric Association, 2013). GAD is a generalised type of anxiety, rather than having a specific cause or type of fear (whereas in social phobia, for example, anxiety is limited to social situations). As shown in Table 1.4, OCD is a debilitating condition characterised by obsessions (e.g., persistent thoughts, images, or impulses) that cause anxiety or distress and compulsions (e.g., repetitive behaviours or mental acts performed in response to obsessions) that reduce distress associated with a foreboding outcome (American Psychiatric Association, 2013). Lifetime prevalence of GAD is estimated at 3.7% of the typically developing population and OCD at 1.7% (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). GAD and OCD are both, in typically developing individuals, more common in girls than in boys (van Steensel, Francisca Johanna Arnoldina, Bögels, Magiati, & Perrin, 2014). The prevalence of OCD in ASD is estimated to be around 37% (Leyfer et al, 2006) and anxiety at around 40% (van Steensel, Francisca Johanna Arnoldina et al., 2014).

Generalised anxiety in ASD is common, and contributes to a reduced quality of life (Wood & Gadow, 2010). Despite the frequency of co-occurrence (estimated at 13.9%; Siminoff et al., 2008), the shared phenotype of GAD and ASD remains unclear. Anxiety does
not feature in the diagnostic criteria for ASD (see Table 1.1). Therefore, when anxiety does present together with ASD, it is treated as a self-standing comorbid condition. This suggests that the anxiety and ASD are independent of each other. However, it also seems plausible that those with ASD may experience anxiety as a by-product of their autism. For example, while anxiety in social situations may be shared by the two disorders, the term ‘anxiety’ when referring to those with ASD may not be caused by anxiety, but rather a lack of functional skills to be able to cope in a social situation (Wood & Gadow, 2010). Thus, if anxiety is caused by the characteristics of ASD (i.e., discomfort in social situations) the diagnostic criteria should account for anxiety that is typical for someone with ASD.

There are numerous similarities between OCD and ASD. Behaviours like repetition feature in the diagnostic criteria for both conditions (see Tables 1.1 and 1.4). People with OCD and ASD may both have obsessions about a particular event occurring (for example, repetition of certain numbers, like car registrations) (American Psychiatric Association, 2013). As a product of these obsessions, ritualistic behaviours that manifest as compulsions are performed to satisfy these obsessions (e.g., remembering all car registration numbers and repeating them). The critical distinction between these two is that, in OCD, these obsessions involve marked distress, while in ASD they are mostly harmonious with the individual’s goals (i.e., it is pleasurable) (Wood & Gadow, 2010). This suggests emotional reaction to repetitive behaviour in ASD may be the distinction between the two disorders.

Recent research has highlighted distinctions between OCD and ASD. One study by Ruzzano, Borsboom and Geurts (2015) found that while repetitive behaviour did occur in both disorders, the cluster of OCD symptoms (e.g., checking, hoarding or washing) and symptom connections within each disorder were distinct. Further, the common medical treatment of OCD is not effective in reducing repetitive behaviours in autism (King et al.,
2009), suggesting that the repetitive behaviour in each disorder may stem from different origins.

1.6.4 Summary of comorbid conditions in ASD

It is important to establish a difference between problematic behaviours in ASD that are manifestations of ASD itself or a comorbid condition. There are many overlapping symptoms between ASD, OCD, anxiety and ADHD, however it is unclear whether these overlapping symptoms are mutually exclusive. There is no treatment for ASD. However, there are well established treatments for conditions such as GAD, OCD or ADHD. Identifying behaviours that are manifestations of separate self-standing conditions will allow for appropriate treatment of these behaviours.

While observations of behaviour can give us important clues about the shared nature of the three disorders, it is also important to also investigate the underlying nature of these behaviours. It is possible that distinct neural networks give rise to similar symptomology in each condition.

Throughout this thesis, the terms “ASD group”, “ADHD group” and “anxiety group” will be used to label the broad diagnostic groups (i.e., those with and without comorbid conditions). When investigating comorbidity, the term “ASD pure” will be used to describe those with ASD only, “ADHD pure” for those with ADHD only and “anxiety pure” for those with anxiety only. The comorbid groups will be referred to as the “ASD and anxiety group” or the “ASD and ADHD group”. Alternately, “ASD comorbid group” is used to identify those with comorbid ASD and anxiety or ADHD, in the experiments where sample size did not allow for more specific analyses. The next section of this thesis will focus on the neural basis of the shared and distinct behaviour in each condition.
### Table 1.3 DSM-V criteria for Generalised Anxiety Disorder

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).</td>
</tr>
<tr>
<td>B.</td>
<td>The individual finds it difficult to control the worry.</td>
</tr>
<tr>
<td>C.</td>
<td>The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months): Note: Only one item is required in children.</td>
</tr>
<tr>
<td></td>
<td>1. Restlessness or feeling keyed up or on edge.</td>
</tr>
<tr>
<td></td>
<td>2. Being easily fatigued.</td>
</tr>
<tr>
<td></td>
<td>3. Difficulty concentrating or mind going blank.</td>
</tr>
<tr>
<td></td>
<td>4. Irritability.</td>
</tr>
<tr>
<td></td>
<td>5. Muscle tension.</td>
</tr>
<tr>
<td></td>
<td>6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).</td>
</tr>
<tr>
<td>D.</td>
<td>The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</td>
</tr>
<tr>
<td>E.</td>
<td>The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).</td>
</tr>
<tr>
<td>F.</td>
<td>The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder social phobia, contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder)</td>
</tr>
</tbody>
</table>
Table 1.4 DSM-V criteria for Obsessive Compulsive Disorder

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1.       | Presence of obsessions, compulsions, or both:  
           Obsessions are defined by (1) and (2):  
           1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.  
           2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).  
           Compulsions are defined by (1) and (2):  
           1. Repetitive behaviours (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.  
           2. The behaviours or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive. |
| 2.       | The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| 3.       | The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition. |
| 4.       | The disturbance is not better explained by the symptoms of another mental disorder |
CHAPTER ONE – GENERAL INTRODUCTION

1.7 Neuroimaging Research in ASD

Neuroimaging research provides valuable information about the underlying brain networks that drive our behaviour. Tools such as EEG provide information about the structure, organisation and function of brain networks. These tools will be described in detail in Chapter 2. The following summary of neuroimaging research related to ASD will be split into four broad sections: 1. language; 2. emotion recognition; 3. inhibitory control and 4. connectivity.

1.7.1 Language

Language is a social behaviour that structures our social conventions. As adults we use language to communicate with one another on a daily basis to share our thoughts and intentions in an effort to behave in a social manner (Tomasello, 1992). Accordingly, a properly developed language system in the human brain is vital for such social interactions. Speech recognition is associated with Wernicke’s area (left posterior temporal cortex), while speech production is associated with Broca’s area (left posterior frontal cortex) (Price, 2012), leading to a hypothesis of left-hemisphere dominance for language in neurotypical right-handed adults (Searleman, 1980). Dominance of one brain hemisphere over another is known as laterality (where a typical pattern of laterality for language is asymmetrical).

1.7.2 Language in ASD, ADHD and anxiety

Although difficulties with language are a core feature of autism, like the disorder itself, linguistic functioning can be highly variable within the disorder. Some children develop fluent speech while others never begin to speak at all. Linguistic difficulties in autism include difficulties in phonology (Schoen, Paul, & Chawarska, 2011); semantics (Brook & Bowler, 1992); syntax (Cantweil, Baker, & Rutter, 1978) and prosody (McCann, Peppè, Gibbon, O'Hare, & Rutherford, 2007). All of these difficulties would certainly contribute to divergent social functioning in autism.
There are fundamental neurophysiological differences that account for aberrant linguistic functioning in autism. Imaging studies show that individuals with autism produce more activation in the Wernicke’s area, but less in the Broca’s area than typically developing controls (Just, Cherkassky, Keller, & Minshew, 2004). The same study found that patterns of functional under-connectivity between cortical areas involved in language processing are significantly lower in autism than in typically developing controls. More recently, Lombardo and colleagues (2015) were able to predict language outcomes in adulthood using functional neuroimaging phenotypes taken in the first years of life. Specifically, areas in the superior temporal cortices were hypoactive in those with ASD who went on to have poor language outcomes, whereas those with ASD who went on to have good language outcomes demonstrated no differences in activation in the superior temporal cortices compared to neurotypical controls. Taken together, this evidence suggests dysfunctional integration of information related to language in autism.

Language deficits have also been reported in ADHD. Problems with social communication skills, reading and writing and expressive language (Bellani, Moretti, Perlini, & Brambilla, 2011; Bruce, Thernlund, & Nettelbladt, 2006) are associated with the core features of the disorder (e.g., hyperactivity, impulsivity). Those with ADHD show inappropriate behaviours in social conversations, which is also evident in ASD. One study by Guerts and Embrechts (2008) investigated the nature of these shared language profiles. They found that those with ASD and ADHD both had difficulties with pragmatics (social language skills), but for those with ADHD, language difficulties increase with the degree of impulsivity present. Difficulties in language in ADHD are associated with atypical hemispheric laterality (Rolfe, Hamm, & Waldie, 2008). One study demonstrated that, when compared to neurotypical controls, individuals with ADHD were impaired in discriminating words and nonwords, and this was mapped to reduced left hemisphere and increased right
hemisphere involvement during the task (Hale et al., 2005). To the best of knowledge, there are no known linguistic difficulties documented in those with anxiety.

1.7.3 Face processing

Broadly, face processing refers to an individual’s ability to understand and interpret the human face. Facial perception seems to be an innate ability, with babies preferring facial over other stimuli from birth (Farroni et al., 2005). In typically developing adults, preference for the eyes over other facial stimuli is also evident (Taylor, Edmonds, McCarthy, & Allison, 2001). Facial perception is associated with the fusiform gyrus and amygdala areas of the brain (Vuilleumier, Armony, Driver, & Dolan, 2001).

1.7.4 Face processing in ASD, ADHD and anxiety

There is great variability in symptom severity and intellectual functioning in ASD, but all individuals have difficulties in social interactions (e.g., eye contact, reciprocal interactions, responding to emotional cues). Unsurprisingly, the nature of face processing in autism differs vastly from their typically developing peers. In very young children, the ability to use facial information (e.g., engaging in joint attention) is considered a critical early marker of ASD (Barbaro & Dissanayake, 2013).

Many of these social difficulties seen in ASD stem from the inability to attend to and process information from faces. Children with ASD perform worse on face processing tasks, including face discrimination and face recognition, and perform comparably on tasks which require discrimination between face and non-face stimuli (where typically developing peers would easily discriminate faces) (for a review see Dawson, Webb & McPartland, 2005). In addition to the behavioural differences, those with ASD process faces using abnormal strategies. They pay less attention to core features of the face like the eyes and nose relative to typically developing adults (Joseph, Ehrman, McNally, & Keehn, 2008). Such
impaired have been mapped to specific brain networks. In ASD there is reduced activity in the fusiform gyrus and the amygdala (Harms, Martin, & Wallace, 2010), both areas heavily implicated in the processing of social information.

People with ADHD also suffer from a number of social and interpersonal problems, which may be in part caused by the patterns of hyperactivity and inattentiveness (Uekermann et al., 2010). These social problems may also be due to abnormal processing of emotion-related stimuli (particularly of the face). It could be that the dysfunctional fronto-temporal posterior systems (involved in regulating emotional function) in ADHD contribute to emotion-related deficits (Williams et al., 2008).

It is well documented that people with anxiety also have aberrant responses to emotional-based stimuli. Those with anxiety are faster and more accurate than typically developing controls at identifying fearful faces versus neutral faces (Surcinelli, Codispoti, Montebarocci, Rossi, & Baldaro, 2006), a response that is associated with altered activity in the amygdala (Easter et al., 2005). This demonstrates that those with anxiety may process threat-related stimuli more quickly than others, which may contribute to the diagnostic symptoms of anxiety (American Psychiatric Association, 2013).

1.7.5 Executive functioning

Executive functions include planning, working memory, attention, problem solving, verbal reasoning, inhibitory control, mental flexibility, task switching, and monitoring of actions. Inhibitory control is the component of executive functioning that allows individuals to withhold dominant responses or ignore distractor stimuli in order to give an appropriate response (Logan, Schachar, & Tannock, 1997). In real-world situations inhibitory control is important as it stops us from performing a potentially inappropriate action when given the urge (e.g., an extreme emotional outburst). Withholding inappropriate urges is vital in
performing socially appropriate behaviour (Adams & Jarrold, 2012). The dorsolateral frontal cortex has mainly been associated with executive functioning, whereas the orbitofrontal cortex is linked to socially appropriate behaviour (e.g., controlling impulses in social situations) (Alvarez & Emory, 2006). In addition, an fMRI study investigating functional connectivity found that executive dysfunction may be the result of frontal-parietal underconnectivity (Just et al, 2006).

1.7.6 Executive functioning in ASD, anxiety and ADHD

The evidence for inhibitory control deficits in ASD is mixed, with some research suggesting a deficit (Christ, Holt, White, & Green, 2007a) and others not (Kleinhans, Akshoomoff, & Delis, 2005). Recently, a large scale meta-analyses demonstrated that those with ASD do indeed show increased difficulties on response inhibition and interference control, but the variance between studies was large (Guerts, van den Bergh & Ruzzano, 2014). A DTI study investigating the relation of fronto-striatal circuitry to inhibitory control found that those with ASD had significantly different white matter tracts connecting the putamen and accumbens to the frontal cortical areas (Langen et al., 2014). Furthermore, behavioural performance on a go/no-go task was related to the organisation of the tracts in the ASD and control groups. Changes in the striatum and frontal cortex have been linked to repetitive behaviour seen in ASD (Langen et al., 2012). However, the most consistent findings suggest that difficulties with inhibitory control are correlated with repetitive behaviours. That is, performance on inhibitory control tasks becomes poorer as the amount of repetitive behaviour increases (Mosconi et al., 2009). In addition, while behavioural performance (i.e., accuracy) of participants with ASD on an inhibitory control task is similar to controls, the underlying neurology differs (participants with ASD show atypical left prefrontal networks; Schmitz et al, 2006). Therefore, the inhibitory control deficits in autism
CHAPTER ONE – GENERAL INTRODUCTION

may arise as a function of repetitive behaviour rather than as a defining characteristic of the disorder.

Difficulties with inhibitory control are well documented in OCD and ADHD (van Velzen, Vriend, de Wit, & van den Heuvel, 2014; Woltering, Liu, Rokeach, & Tannock, 2014). Brain imaging studies help to show which brain regions are linked to this deficit. Specifically, those with ADHD demonstrated significantly reduced brain activity in the right inferior prefrontal cortex during successful response inhibition and in the precuneus and posterior cingulate gyrus during inhibition failure (Rubia, Smith, Brammer, Toone, & Taylor, 2014). While the evidence for an inhibitory control deficit in children with ADHD is more consistent, the fronto-cortical abnormalities that underlie these deficits persist into adulthood (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Inhibitory control deficits in ASD and ADHD are outlined in an excellent review by Rommelse and colleagues (2011). Inhibitory control deficits seen in OCD are regulated by dysfunctional frontostriatothalamic brain regions necessary for inhibition (Woolley et al., 2008). There is also consistent support for the involvement of orbito-frontal striatal systems in OCD (Harrison et al., 2013) and in ADHD (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Performance on the stop-trial task, a good measure of inhibitory control, is impaired in children with ADHD (Overtoom et al., 2002) and in those with OCD (Lipszyc & Schachar, 2010).

Executive function deficits are often assumed to be a symptom of both ADHD and ASD (Johnson, 2012). However, research suggests that individuals with ADHD versus ASD behave differently on executive functioning tasks. One study by Sinzig and colleagues (2008) compared the profiles of children with ADHD alone, ASD alone and a comorbid ADHD and ASD group on an executive function task. The ADHD group displayed more deficits in inhibitory control and working memory, while the ASD group showed difficulties with planning and flexibility. The ASD and ADHD comorbid group showed more problems with
inhibitory control but not working memory deficits when compared to the ADHD only group. Furthermore, Barkley (1997) found that inhibitory control and sustained attention are affected in individuals with ADHD, but inhibitory control and sustained attention remains intact in ASD. In ASD, planning and attentional shifting have been found to be affected (Bühler, Bachmann, Goyert, Heinzel-Gutenbrunner, & Kamp-Becker, 2011; Gargaro, Rinehart, Bradshaw, Tonge, & Sheppard, 2011). This research suggests that those with ASD alone do not have marked deficits with executive function, but difficulties in inhibitory control do become more pronounced with a comorbid diagnosis (Bühler et al., 2011).

1.7.7 Connectivity

Brain connectivity is a broad term that describes the means in which the regions of our brain communicate with each other. Communication and integration of the segregated areas or networks of the brain is vital in order for the successful execution of cognitive and motor functions (Rubinov & Sporns, 2010). Functional connectivity describes the similarity of temporal characteristics of brain activity in different brain regions, whereas structural connectivity is the physical connections of regions (Vissers, Cohen & Geurts, 2012). For example, visual perception requires the recruitment of multiple brain regions that are structurally distinct, however we perceive the image as a cohesive whole. This cohesive image is possible as the specialised neuronal networks in each structure that are responsible for visual perception are connected via a network of anatomical pathways. Functional connectivity highlights the interrelationship between anatomical and dynamical processes throughout development (Sporns, Tononi & Edelman, 2000). Thus, increased connectivity demonstrates a more connected network, whereas decreased connectivity represents a more disconnected network.

The frequency of the electric brain signals shows the synchronisations of activation between locations. Using fMRI, functional connectivity can be examined by measuring
correlated fluctuations in BOLD (blood oxygen level dependent) signal over time during task performance (Biswal, Kylen, & Hyde, 1997). Structural connectivity can be examined using diffusion tensor imaging to look at white matter tracts (Vissers, Cohen & Geurts, 2012). Connectivity can also be measured using EEG to determine the correlation of neural activity (Handy, 2005).

1.7.8 Connectivity in ASD, anxiety and ADHD

Atypical patterns of connectivity can be seen in OCD, ASD and ADHD. In OCD, fMRI studies have demonstrated patterns of increased connectivity in the corticostriatal regions (Harrison et al., 2009). In ADHD, reduced connectivity manifests in the frontostriatal connections (Casey et al., 2007; Cubillo et al., 2010). In ASD however, altered patterns of connectivity are implicated in many brain regions and areas (Belmonte et al., 2004), the exact nature of which will be discussed later in the thesis.

1.7.9 Summary

There are similarities and differences in behaviour between ASD and GAD, OCD and ADHD. Difficulties with language are evident in both ASD and ADHD, but not in those with anxiety. Emotion processing difficulties are present in all three conditions. Inhibitory control deficits have been documented in OCD and ADHD with less convincing evidence for a deficit in ASD. Patterns of resting state brain activity are also different from neurotypical controls in the three conditions.

1.8 Rationale for the Current Research

The literature review presented above outlines core difficulties in those with ASD. These difficulties are brain-based and can be measured by atypical performance on cognitive and behavioural tasks when compared to neurotypical controls. These differences relate to the broad areas of: language; executive functioning; social interactions and overall brain
connectivity. Common co-existing conditions with ASD, such as anxiety and ADHD, share some of the difficulties seen in ASD, but not all. As the existing body of research typically studies these conditions separately; it remains unclear whether these overlapping behaviours can be accounted for through the ASD diagnosis, or whether they are separate behaviours altogether.

The current thesis will address these limitations by analysing data from experimental groups in three ways. Firstly, using the main diagnostic categories (i.e., ASD, ADHD and anxiety groups) which includes all participants recruited for the study and ignores any comorbidity. Secondly, in-depth comorbidity analyses will be conducted on those with ASD only (i.e., pure ASD group) versus those with comorbid ASD and ADHD or ASD and anxiety. Third, the current thesis has the added advantage of a behavioural profile for each participant. That is, their behavioural characteristics of ASD, ADHD, OCD and anxiety are measured using profiling tools (see Chapter 2 for a full description) that assess symptom severity. Using these continuous variables will enable us to measure the strength of relationship between a specific behaviour and performance on the tasks in the current study.

The current thesis will focus on the key difficulties, as reported in the DSM criteria, present in ASD and compare those with pure and comorbid ASD diagnoses. This will help to establish whether there is a different neuropsychological profile in those with pure versus comorbid ASD. This will help to determine whether, from a neuropsychological standpoint, ADHD and anxiety comorbid with ASD are in fact true separate conditions, or whether they are better conceptualised as part of the ASD diagnosis.

1.9 Aims and Objectives

The main objective of the thesis is to build a profile of the behavioural and brain basis of pure ASD, ADHD and anxiety. This is then compared to the profile of those with
comorbid ASD to determine whether they present with the same or different characteristics. The overall aim is to determine whether comorbid conditions in ASD are in fact true conditions that warrant their own diagnoses (i.e., are additive in nature), or whether they are simply symptoms of the ASD itself (i.e., are not “true” comorbid conditions).

The current thesis will use the guidelines on identifying comorbid conditions outlined by Wood and Gadow (2010) to determine whether the conditions are indeed separate. To summarise, a true comorbid condition is one in which either: the presentation of each disorder together with ASD is identical to its monomorbid form in the unaffected individual (i.e., anxiety, OCD or ADHD); or a condition phenotypically altered by ASD symptoms.

Therefore, when investigating the shared basis of comorbidity in the current thesis, we will determine whether the conditions are true comorbid conditions if the patterns of ERPs or behaviour between pure ASD and the comorbid ASD and anxiety or ADHD groups are significantly different from one another. To illustrate, when presented as a comorbid condition, if the ERPs take on specific characteristics of each condition (ADHD or anxiety) in its pure form, this suggests an additive effect. It is likely the conditions are separate. If the overall pattern of findings remains similar to that seen in ASD alone, and do not take on any characteristics of the ERPs seen in pure ADHD or anxiety, this suggests that the conditions are better conceptualised as part of the ASD diagnosis and the symptoms may have been misinterpreted.
CHAPTER TWO – GENERAL METHODOLOGY

This chapter describes the overall procedure and methods relevant to the five studies in this thesis. This includes, participant recruitment and screening, study design, demographics, behavioural profiling and electroencephalography (EEG) acquisition, as well as preliminary statistical analyses.

2.1 Participant Recruitment

2.1.1 Recruitment

All participants were recruited using advertisements placed around the University of Auckland City Campus and on a participant recruitment website. Participants were also recruited through organisations such as Altogether Autism, the Phobic Trust, the Parent and Family Centre and the ADHD Association using similar advertisements to those placed around the university. Participants were drawn from the New Zealand population. Participants responded to the advertisement by emailing the researcher directly to notify their interest in the study.

2.1.2 Participant screening

Once participants expressed interest in the study, they were given an initial questionnaire to ensure they fit the study criteria. The selection criteria were as follows: be between the ages of 16 and 45 years; no history of head injury; no history of comorbid depression or schizophrenia; be right-handed; have English as their first language and not be taking any psychoactive medication. If participants fit the initial criteria, there were invited to participate in the study. All participants were adults. Control participants consisted of mainly undergraduate students, recruited using flyers around the university, and had no history of any psychological illness (e.g., depression, anxiety). Experimental participants were required to have a diagnosis of ASD, ADHD or anxiety that was given by a registered medical
CHAPTER TWO – GENERAL METHODOLOGY

professional (i.e., not self-diagnosed). Diagnosis was not confirmed in the current study using clinical interviews, but by using behavioural profiling questionnaires, where the cutoffs for diagnosis used were the same as those recommended by the authors of each profiling measure. All participants had normal or corrected-to-normal vision and no history of head injury. Participants were given $20 in vouchers for each session they completed ($40 in total for attending both sessions).

2.2 Procedure

Participants were asked to come to the University of Auckland City Campus to attend two experimental sessions. These sessions were broadly split into the following two categories: the behavioural profiling session and the electroencephalography (EEG) session. Participants were asked to come in for the behavioural profiling session before the EEG session. Of the 83 participants who attended the first session, 8 decided not to return for the EEG session. This gives an overall retention rate of 96.38%. Ethical approval was provided by the University of Auckland Human Ethics Committee for the period of 16/12/12 – 16/12/15 reference number 8697 (see Appendix A for the documents relating to ethical approval).

2.2.1 Behavioural profiling

The overall aim of behavioural profiling was to gain as much information as possible about each participant and the behavioural phenotype of each disorder. Behavioural profiling measures participants’ characteristics on cognitive, social and motor tasks and builds a picture of behaviour specific to that individual which will be referred to as a behavioural phenotype throughout this thesis. During this session participants answered a number of questionnaires, performed the computer-based CPT task, and performed an IQ test. See appendices E-I for a copy of each profiling method.
The behavioural profiling session was always held in the same, minimally-decorated room in the Human Sciences Building at the University of Auckland. All questionnaires were given in paper-and-pen method, apart from the Continuous Performance Task (Sandford & Turner, 2004), which was run on a Toshiba notebook with a Windows 1998 operating system, with an 11.3 inch screen. This session also served as a screener for eligibility for the EEG session. If there was any reason why a participant should not do an EEG (e.g., found the EEG room too claustrophobic, low IQ) they were excluded from the next session.

2.2.2 Electroencephalography

The second session involved EEG recording of participants’ brain activity during task performance. Participants were asked to complete four tasks, plus a short resting-state task. This was conducted in the EEG lab at the University of Auckland City campus. EEG recordings took place in an electrically shielded room (Model L3000; Belling Lee, Enfield, England) using 128-channel Ag/AgCl EGI electrode nets (Tucker, 1993). Participants were seated 57 centimetres from the stimulus computer. The Geodesic sensor net distributes electrodes from nasion to inion and from left to right mastoids at uniform intervals (see Figure 2.1). EEG was recorded continuously (1000-Hz sample rate; 0.1–100 Hz analogue bandpass) with Electrical Geodesics Inc. amplifiers (300-MΩ input impedance). A Macintosh computer was used to acquire the data using NetStation software and this was then stored on the computer’s hard disk. Electrode impedances were kept below 40 kΩ, an acceptable level for this system (Tucker, 1993). An impedance check was always done after two of the five experiments to ensure that electrode impedance was below the threshold. Common vertex (Cz) was used as a reference, resulting in a total of 129 electrodes.
CHAPTER TWO – GENERAL METHODOLOGY

2.2.3 Final EEG data

One task was not included in the final analyses for this thesis due to technical difficulties and poor inter-rater reliability of the data. Outliers were excluded from analysis. Therefore, there were four tasks in the EEG session that are included in this thesis.

2.3 EEG as a Technique

EEG is a neuroimaging technique which measures the signals produced by electrical activity in the brain. Utilising methods such as EEG may be helpful in investigating the neural mechanisms behind specific cognitive functions (e.g., inhibitory control, decision making). EEG data is collected by placing electrodes coupled to high impedance amplifiers on the scalp. This reveals a pattern of variation in voltage over time. Precisely, the electrodes measure differences on the scalp resulting from ohmic currents induced by electrical activity in the brain (Handy, 2005). The most profound benefit of EEG imaging is extremely proficient temporal resolution. Manifestations in neural activity can be recorded at the millisecond they occur (Darvas, Pantazis, Kucukaltun-Yildirim & Leahy, 2004). However, the EEG electrodes are separated from the electrical signal by cerebrospinal fluid, skull and scalp resulting in poorer spatial resolution. High-resolution EEG addresses this limitation by estimating the signal from the inner skull surface to the scalp surface using an algorithm to obtain a more localised EEG signal (Handy, 2005). Spatial resolution is then measured by the distance between two electrodes at which the signals are identical and comparing this to separated electrodes. Despite this advance in EEG localisation, the signal produced when measuring cognitive processes can be generated from multiple brain regions (Nunez & Srinivasan, 2006), thus it is not possible to conclude with certainty spatial resolution from EEG alone.
2.4 Event-related Potentials

A common method in EEG research is the observation of event related potentials. Event related potentials (ERP’s) record the neurological activity in the brain associated with certain events. During the presentation of stimuli the neural activity is recorded. This neural activity is then time-locked to the presentation of the stimuli and averaged across a large number of trials to produce a waveform. As shown in Figure 2.2, this waveform consists of a series of peaks and troughs (positive and negative deflections) which reflect the sum of the underlying components (Handy, 2005). The measure of interest in ERP’s is the polarity of the waveform (i.e., negative or positive voltage) and its latency (i.e., how long after stimulus onset the waveform occurred), which is a measure of processing speed (Handy, 2005). The peak of each positive or negative waveform is the amplitude which measures the amount of neural resources devoted to a specific task at any one time (Dawson, Webb, & McPartland, 2005). Larger amplitudes reflect more neural activity and correlates to the amount of cognitive effort required (Spironelli & Angrilli, 2009).
2.5 ERP Components

Each ERP measures a different underlying summation of components typically labelled the N1, P1, P2 and so on (see Figure 2.2 for a simplified cartoon). One advantage of the ERP approach as that the waveform provides researchers with a measure of brain involvement during cognitive tasks. These components are understood to be related to different aspects of cognition. Overall, earlier components are involved in recognition of stimuli while later components are related to the processing of stimuli (Handy, 2005). Each component will be described in more detail in the experimental chapters of this thesis.

2.5.1 The P100 component

The P100 is an early ERP component that typically occurs between 70-100ms post stimulus. The P100 is involved in somatosensory processing (Desmedt, Huy, & Bourguet, 1983).
2.5.2 The N100 and the N170 components

The N1 component is event related negativity and occurs around 100ms after stimulus presentation. The N1 component is associated with target identification and categorisation (Rugg & Coles, 1995). ERP studies of face perception have revealed that, compared to objects, faces typically elicit a larger negative deflection at occipito-temporal sites approximately 170ms after stimulus onset. This component, which reflects perceptual processing of structural information from faces, is known as the N170 (Leppanen, Moulsen, Vogel-Farley & Nelson, 2007). The N170 differs as a function of emotional significance, reflective of the differential processing of emotionally significant stimuli. The N170 shows a larger negative deflection to fearful faces than neutral faces (Batty & Taylor, 2003; Leppanen et al, 2007) and responds primarily to the eyes within a face (Schyns et al, 2003).

2.5.3 N200

The N200 component, which occurs around 270ms after stimulus onset, reflects the activity in the brain when required to withhold a response. Jodo and Kayama (1992) measured ERP’s in a Go/ No-Go paradigm found increased amplitude in the N200 component in the fronto-central areas in the no-go trials.

2.5.4 The P250 and P300

The P250 is a positive component that closely follows the N170 (Marzi & Viggiano, 2007). This component is known to be involved in the late stages of analysing visual information and decision making (Spironelli & Angrilli, 2009). The P250 has been related to the processing of facial identity and familiarity (Marzi & Viggiano, 2007). The P300 component is a later component of the ERP waveform that occurs around 350-500ms post-stimulus (Basar, Basar-Eroglu, Rosen, & Schütt, 1984). This component is thought to reflect
‘cognitive function’ although the exact nature of this cognitive function is unclear (Intriligator & Polich, 1995).

2.5.5 Summary of ERP components

Studying specific ERP’s and how they differ in individuals with behavioural difficulties can give the researcher important information on how their brains are processing specific information. For example, earlier latencies reflect faster processing speed. Larger amplitudes of specific ERP components reflect the amount of neural activity associated with that task. As earlier components reflect object recognition and later components are involved in understanding and processing of stimuli, we are able to gauge the exact nature of the behavioural difficulties with which individuals present.

2.6 EEG Coherence

Another method used in EEG research is spectral coherence. Using EEG to measure functional connectivity involves examining phase- or spectral-coherence between oscillations in distant brain regions. The frequency of the electric brain signals shows synchronisation of activation between locations (Vissers, Cohen, & Geurts, 2012a). Coherence measures the relationship between different electrodes on the scalp. Unlike a simple correlation between electrodes, coherence analyses measures the correlation between two signals (e.g., a pair of electrodes) and then utilises a Fast Fourier Transform method to calculate the variation of this correlation as a function of time (Guevara & Corsi-Cabrera, 1996).

The EEG signal can be described in terms of broad frequency bands: delta (<4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma-band oscillations (30–70 Hz, centred at 40 Hz) (Taylor & Baldeweg, 2002). Coherence values are also related to power. Power refers to the amount of neurons that discharge in synchrony in each band (Klimesch, 1999). Different frequency bands are associated with different cognitive functions, for
example, the encoding of new information is reflected in theta oscillations, whereas alpha oscillations are associated with retrieval of long-term memories (Klimesch, 1999). Power is also associated with task demands. As opposed to task-related research, the power of alpha increases and theta decreases in resting state studies (Klimesch, 1999). Therefore, it is necessary to examine levels of coherence in the different frequency bands. Electrode pairs were selected using the international 10/20 system.

2.7 Measures

Each profiling method was carefully selected to gain the best representation of an individual’s behavioural phenotype (a quantifiable measure of characteristics that relate to behaviour, as mentioned previously). Each measure is described below. For the EEG section, each task was selected because of its relevance to ASD diagnostic criteria. There were four EEG tasks in total. 1. An emotion recognition task (to examine whether there is a link to the social difficulties evident in ASD). 2. An inhibitory control task (to examine whether there is a link to the executive functioning difficulties which may be evident in autism) 3. A lexical decision task (to examine whether there is a link to the language difficulties evident in autism) and 4. A resting state task (to examine whether there is differential resting-state brain activity between the groups).

2.8 Behavioural Measures

The reliability and validity of each measure are listed below, and summarised in Table 2.1. In addition, a copy of each profiling method can be seen in Appendices E-I.

2.8.1 The Integrated Visual and Auditory Continuous performance task

The Integrated Visual and Auditory Continuous Performance Task (CPT) was originally designed to test sustained attention to visual and auditory stimuli (Rosvold, Mirsky,
Sarason, Bransome Jr, & Beck, 1956). In the CPT a series of stimuli are presented on a computer screen (i.e., you will see or hear the number “1” and “2”). The aim of the task is to attend to one stimuli (i.e., click the mouse upon seeing or hearing a “1”) whilst simultaneously ignoring another (i.e., ignore seeing or hearing stimuli “2”) over a sustained period of time. Maintaining attention to this dull sequence of events over a prolonged period of time separates those with good and poor attentional capacity (Corkum & Siegel, 1993). Scores have been standardised to have a mean of 100 and a standard deviation of 15 (Rosvold et al., 1956).

The CPT consistently distinguishes those with a diagnosis of ADHD from typically developing controls, where those with ADHD perform significantly worse than controls (for a review see Losier, McGrath & Klein, 1996). In addition, the CPT has strong predictive power when discriminating between patients with ASD, ADHD and typically developing controls. A study utilising discriminate function analysis revealed CPT successfully discriminated between the three groups 75.6% of the time (Corbett & Constantine, 2006). Thus, the CPT is often used as a screening tool for ADHD.

2.8.2 Behavioural Inhibition Activation Scale

The Behavioural Inhibition/Activation Scale (BIS/BAS) designed by Carver and White (1994), is a questionnaire designed to identify patterns of behaviour in an individual’s personality. The questionnaire is measured on a 9-point Likert-scale where 4 is strongly agree and -4 is strongly disagree. The questionnaire consists of four subscales as theorised by Carver and White (1994). The subscales are: 1. Behavioural Inhibition (BIS) or punishment sensitivity scale. This measures an individual’s experience of anxiety in a situation where there are punishment cues (e.g., “I worry about making mistakes”); 2. Reward Responsiveness (BAS) measures positive responses in anticipation of a reward (e.g., “When
2.8.3 The Generalised Anxiety Disorder Scale

The Generalised Anxiety Disorder Scale (Spitzer, Kroenke, Williams, & Löwe, 2006) was designed as a brief clinical measure for generalised anxiety. The GAD is a 7-item questionnaire that asks about the major symptoms of anxiety (i.e., “feeling nervous, anxious or on edge”). Participants are asked to report how many days (from the past two weeks) they were bothered by each symptom i.e., none of the days; some of the days; most of the days; all of the days. The responses are marked on a scale of 0, 1, 2 or 3 respectively. The minimum score of the GAD is 0 with the maximum being 21.

2.8.4 The Obsessive Compulsive Inventory – Revised

The Obsessive Compulsive Inventory – Revised (OCI) is an 18-item questionnaire that measures OCD symptoms (Foa et al., 2002). The OCI includes statements such as; “I sometimes have to wash myself simply because I feel contaminated” and “I need things to be arranged in a particular way”. Participants are asked to report how distressed or bothered they are by each statement on a scale of 0 – 4 (with 0 being ‘not at all’, and 4 being ‘extremely’).
CHAPTER TWO – GENERAL METHODOLOGY

There is a minimum score of 0 and a maximum score of 72, with the mean being 28 for those with a diagnosis of OCD (Foa et al., 2002). The OCI consistently discriminates those with a diagnosis of OCD from those with GAD, or typically developing individuals (Huppert et al., 2007).

2.8.5 The Adult ADHD Self Report Symptom Checklist

The Adult ADHD Self Report Symptom Checklist (ASRS; (Kessler et al., 2005) is an 18-item self-report questionnaire which asks about clinical symptoms of ADHD as reported in the DSM-IV (e.g., “How often do you fidget or squirm when you have to sit down for long periods of time?”). Participants are asked to report how often they report each symptom on a scale of 0 – 4 (0 = never, 1 = rarely, 2 = sometimes, 3 = often or 4 = very often). As in the DSM-IV (American Psychiatric Association, 1994), the ASRS can be split into two subsections (hyperactive and inattentive) or combined into an overall score. For combined scores, the minimum score is 0 and the maximum score is 72.

2.8.6 The Autism Spectrum Quotient

The autism spectrum quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) is a 50-item self-report questionnaire that measures autistic-like traits in the typically developing population. The ASQ is scored on a Likert-type scale, however the general categories are “agree” or “disagree”. A score of around 10-21 is normal for the typically developing population, and a score of 32+ is the official criteria for autism (Baron-Cohen et al., 2001).

2.8.7 Wechsler Abbreviated Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI; (Wechsler, 1999)) is an abbreviated form of the Wechsler Adult Intelligence Scale that takes around 30 minutes to complete. The WASI is split into two sections; Performance IQ (which measures visuospatial
intelligence) and Verbal IQ (ability to solve problems using language-based reasoning). The WASI is standardised to have a mean of 100 and a standard deviation of 15.
<table>
<thead>
<tr>
<th>Task</th>
<th>Reference</th>
<th>Internal consistency</th>
<th>Test-retest reliability</th>
<th>Concurrent Validity</th>
</tr>
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<tbody>
<tr>
<td>The Adult Self Report Symptom</td>
<td>Adler, L. A., Spencer, T., Faraone, S. V., Kessler, R. C., Howes, M. J.,</td>
<td>α = 0.88</td>
<td>ADHD RS - r = 0.84 (p &lt; .001)</td>
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<td></td>
<td>report scale (ASRS) to rate adult ADHD symptoms. *Annals of Clinical</td>
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<td>Checklist</td>
<td>retest reliability of two patient-report measures for use in adults with</td>
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<tr>
<td>The Generalised Anxiety Disorder</td>
<td>Lowe, B., Decker, O., Muller, S., Brahler, E., Schellberg, D., Herzog, W.,</td>
<td>α = 0.89</td>
<td>PHQ-2 depression scale - r = 0.64</td>
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<tr>
<td>Scale</td>
<td>&amp; Herzberg, P. Y. (2008). Validation and standardization of the generalized</td>
<td></td>
<td>(p &lt; .001)</td>
<td>Rosenberg Self Esteem Scale r = -</td>
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<td></td>
<td>anxiety disorder screener (GAD-7) in the general population. *Medical</td>
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<td>0.43 (p &lt; .001)</td>
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<td></td>
<td>Care, 46(3), 266-274. doi:10.1097/MLR.0b013e318160d093</td>
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<td>The Obsessive Compulsive</td>
<td>Abramowitz, J. S., &amp; Deacon, B. J. (2006). Psychometric properties and</td>
<td>α = 0.89</td>
<td>Y-BOCS – r = 0.41 (p &lt; .01)</td>
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<tr>
<td>Inventory</td>
<td>construct validity of the Obsessive–Compulsive Inventory—Revised:</td>
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<td></td>
<td>Replication and extension with a clinical sample. *Journal of Anxiety</td>
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<td>Disorders, 20(8), 1016-1035.</td>
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<tr>
<td>The Obsessive Compulsive</td>
<td>Hajcak, G., Huppert, J. D., Simons, R. F., &amp; Foa, E. B. (2004). Psychometric</td>
<td>α = 0.88</td>
<td>MOCI – r = 0.65 (p &lt; .001)</td>
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<td>Inventory</td>
<td>properties of the OCI-R in a college sample. *Behaviour Research and</td>
<td>r = 0.70</td>
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<td></td>
<td>Therapy, 42(1), 115-123.</td>
<td></td>
<td></td>
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<tr>
<td>Intelligence</td>
<td>Wechsler abbreviated scale of intelligence and the Kaufman brief intelligence test among psychiatric inpatients. *Psychological Reports, 90(2), 355-359.</td>
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</tbody>
</table>
### CHAPTER TWO – GENERAL METHODOLOGY

<table>
<thead>
<tr>
<th>Test</th>
<th>Authors</th>
<th>Year</th>
<th>Description</th>
<th>Correlation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Abbreviated Scale of Intelligence</td>
<td>Abu-Hilal, M., Al-Baili, M., Saratawi, A., Abdelfattah, F., &amp; Qaryouti, I.</td>
<td>2011</td>
<td>Psychometric properties of the wechsler abbreviated scale of intelligence (WASI) with an Arab sample of school students. <em>Individual Differences Research, 9</em>(4), 219-230.</td>
<td><em>r</em> = 0.83-0.91 (<em>p</em> &lt; 0.001)</td>
</tr>
<tr>
<td>Behavioural Inhibition Activation Scale</td>
<td>Jorm, A. F., Christensen, H., Henderson, A. S., Jacomb, P. A., Korten, A. E., &amp; Rodgers, B.</td>
<td>1998</td>
<td>Using the BIS/BAS scales to measure behavioural inhibition and behavioural activation: Factor structure, validity and norms in a large community sample. <em>Personality and Individual Differences, 26</em>(1), 49-58.</td>
<td><em>BIS - α</em> = 0.76, <em>BAS - α</em> = 0.83 <em>WISC-IV - r</em> = 0.42 (<em>p</em> &lt; 0.001)</td>
</tr>
</tbody>
</table>
CHAPTER TWO – GENERAL METHODOLOGY

2.9 Neurophysiological Measures

The next set of tasks were conducted using concurrent EEG recording. For each task except the resting state task, ERP data was collected. For the resting state task, coherence measures were used. The order of the five EEG tasks were counterbalanced across participants as to minimize the potential effects of order (i.e., fatigue). In each EEG experiment, the order of the blocks (i.e., right hand first, eyes closed first) was also counterbalanced across participants. During data analysis, the researcher selected the amplitude and latencies of each ERP component by visual inspection. The researcher was blind to experimental group. The latency and amplitude of each ERP was also selected by a second coder. This reliability coder was also blind to experimental group. For each experiment the agreement of the latency and amplitude of each ERP component was above 90%. There was no reliability coding performed on the resting-state task as the pre-processing steps produced figures that were not subjective (i.e., there was no room for misinterpretation of the data).

Each EEG task will now be briefly described. A complete description of each ERP component and why they were selected can be found in the respective experimental chapters of this thesis.

2.9.1 The lexical decision task

The lexical decision task is a measure of visual word recognition and processing. In the current study, the lexical decision task will be used to investigate whether responses to word or nonword stimuli differs between experimental groups. Participants must make a decision if the word is a real word or a nonword (which is split into two sections, nonsense words or pseudowords). The lexical decision task used in the current study follows a basic
go/no-go paradigm (Perea, Rosa, & Gómez, 2002). Participants are asked to respond if they think the word is a real English word, and to do nothing if it is not a real English word.

For the lexical decision task, the variables of interest were: 1. Accuracy of response in the three conditions (word, nonword, pseudoword). 2. The P1 latency and amplitude for each condition in each hemisphere and 3. The N200 latency and amplitude for each condition in each hemisphere.

2.9.2 The stop signal task

Inhibitory control is the component of executive functioning that allows individuals to withhold dominant responses or ignore distractor stimuli in order to give an appropriate response. The stop signal task in the current study is modelled after Langenecker (2007) and is designed to specifically target inhibitory control. During the stop signal task, participants are rapidly presented with an array of letters of the alphabet. Participants must ignore all letters apart from the two designated target letters. Participants are asked to press a key each time they see a target letter. However, in some trials the target letters are followed immediately by a ‘stop’ signal. In these trials participants must withhold their desire to press the response key. Thus, in the stop signal task there are three conditions: 1. No-go trials (distracter letters to which participants do not respond), 2. Go trials (target letters to which participants respond) and 3. Stop trials (target letters followed by a stop signal, to which participants should withhold their response).

The measures of interest in the stop signal task were: 1. Accuracy of go, no-go and stop trials. 2. The N200 amplitude and latency for each condition and 3. The P300 amplitude and latency for each condition.
2.9.3 The reading the mind eyes task

The reading the mind eyes task is a measure of emotion recognition and facial expression processing. The experiment consists of pictures taken from the Mind Reading Emotions Library (Baron-Cohen, Hill, & Wheelwright, 2003), and the experimental procedure was modelled after that in O’Conner, Hamm and Kirk (2005). In this experiment participants are shown sections of the eye or mouth region that have either a sad or a neutral expression. Participants are asked to decide whether they judge the expression to be sad or neutral.

The measures of interest in the reading the mind eyes task were: 1. Accuracy and response time to each condition. 2. The latency and amplitude of the N170 component.

2.9.4 Resting state

EEG measures functional connectivity by examining phase- or spectral-coherence between oscillations in distant brain regions. The resting state task simply requires participants to sit still with their eyes either open or closed for two minutes during concurrent EEG recording. The resting state study measures resting state spectral coherence in the alpha and theta bands with eyes open and closed during rest. This is because different power bands are more evident with eyes open as opposed to closed.

2.10 Data Preparation and Statistical Analyses

2.10.1 Artefact removal

The EEG data were segmented as a function of trigger type for each experiment. This ensures that the conditions are kept separate. Data were filtered using a 30Hz Butterworth filter, re-referenced to average reference and segmented using in house software (WinView) into ERP waveforms (a specific time window for each ERP, called an epoch). Then artefacts
were removed on a trial-by-trial basis according to the guidelines set out in (Jervis, Nichols, Allen, Hudson, & Johnson, 1985). Any epochs that had eye blinks, eye movement or electrical noise were excluded from final data analysis using the Gratton et. al (2009) algorithm. There were no bad channels in the final data, as fastidious impedance checks were done during testing to ensure no loss of data.

2.10.2 Trigger insertion

The resting state task involved an additional step in processing of the data. In the resting state task, triggers were only sent at the beginning of the first block, at the end of the first block, and at the end of the experiment. This gave a total of three triggers which separated the eyes open and closed conditions. Additional triggers were required to increase the time-points in which to centre data collection. Triggers were manually inserted using in-house software (WinView) every 12000ms for each condition, giving a total of 10 triggers per condition.

2.11 Preliminary Analyses and Data Screening

All statistical analyses were conducted using SPSS version 20 software. All results were considered significant at the .05 level unless stated otherwise. Preliminary analyses were conducted on the data to see if there were any initial differences in gender split or IQ. Missing data values were also replaced using missing values analysis. In addition, full data screening of each profiling variable was conducted to investigate normal distribution of the data.

2.11.1 Gender

The overall gender split was 42 females, and 41 males. However, within each experimental group the gender split was not even, as shown in Table 2.2. A Pearson Chi Square test revealed that the gender of participants in each group did differ significantly by
gender, $\chi^2 (3, n = 83) = 8.96, p = .03$. There were more males than females in the ASD group, and more females than males in the anxiety group. This difference was expected and is in line with literature which suggests autism has a 4.3:1 ratio for males to females (Newschaffer et al., 2007), and anxiety is much more common in females than males (Lowe et al., 2008; Matza, Van Brunt, Cates, & Murray, 2011).

2.11.2 Age and IQ

A one-way ANOVA was conducted to investigate whether there were any differences in age or IQ between groups. This is important as some of the EEG tasks are relatively difficult, and participants must be able to understand each task. The results revealed no significant differences between groups on measures of age, $F (3, 79) = .434, p > .05$ or IQ, $F (3, 74) = 2.712, p > .05$. These results suggest that any differences in results cannot be accounted for by participants’ intelligence, or differences age.

Table 2.2. Gender distribution and mean age of the participants in the study.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Gender</th>
<th>Age</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Mean</td>
</tr>
<tr>
<td>ADHD</td>
<td>23</td>
<td>9</td>
<td>14</td>
<td>27.21</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12</td>
<td>3</td>
<td>9</td>
<td>25.99</td>
</tr>
<tr>
<td>ASD</td>
<td>25</td>
<td>18</td>
<td>7</td>
<td>25.69</td>
</tr>
<tr>
<td>Control</td>
<td>23</td>
<td>11</td>
<td>12</td>
<td>24.43</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>41</td>
<td>42</td>
<td>25.81</td>
</tr>
</tbody>
</table>

2.11.3 Missing values analysis

From the 83 subjects, two were missing data for the “Drive” and “Fun seeking” values, and four were missing data for the continuous performance task. Analysis showed these cases to be missing completely at random from the study population (that is, they were
CHAPTER TWO – GENERAL METHODOLOGY

no more likely to come from one experimental group than another). Subjects were grouped according to their condition and then missing values were completed using the mean of the surrounding data points (i.e., mean of experimental group). This avoids rejection of an entire subject due to absence of data for one random measure (as would be the case in listwise deletion), whilst preserving variance between groups (Acock, 2005).

2.11.4 Data screening

Data were screened prior to analysis to investigate normality. The full list of all skewness and kurtosis values are listed in Appendix J. There are notable violations of normality in skewness values for the CPT and the OCI. This is expected when dealing with atypical populations as those with ADHD would have scored very poorly compared to the other experimental groups on the CPT, and those with OCD would have scored very highly on the OCI compared to other participants. While ANOVA is robust to violations of normality, the data for these two tasks must be interpreted with caution.
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

3.1 Study Overview

The study in Chapter 3 builds a profile of behaviour in ASD, ADHD and anxiety when the conditions occur alone as well as when they occur together as a comorbid condition with ASD. This is part of a larger research effort to establish the nature of co-existing conditions in ASD and to determine whether they are separate conditions or whether they can be accounted for through the ASD diagnosis. A number of questionnaires and a computer-based task were used, which asked about symptoms of ASD, ADHD and anxiety as well as overall adaptive functioning, to determine this profile. The results demonstrate that each condition in its pure form can be easily differentiated from one another, and from neurotypical controls, using these profiling tools. Further analysis revealed that when ASD occurs together with anxiety, the conditions have different behavioural profiles and can be easily discriminated from one another. This suggests that anxiety is a separate condition when it occurs together with ASD. On the contrary, there is no clear behavioural profile for when ASD and ADHD occur together. The results of the current study suggest that there might be some degree of overlap when the two present as a comorbid condition. This information will be important not only to healthcare practitioners when administering a diagnosis to these individuals, but also to therapists who need to apply evidence-based treatment to specific conditions.

3.2 Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition for which there is no known cause or cure (see Chapter 1 for full diagnostic criteria). Autism is a highly variable condition, the most prominent difficulties of which include aberrant behaviour, poor social skills and disrupted communication skills (American Psychiatric
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

Association, 2013). The prevalence of ASD is estimated to be 60 in 10,000 (0.6%) (Fombonne, 2005) and is more common in males than females, with a ratio of 4.3:1 (Newschaffer et al, 2007). Although this suggests an x-linked condition, the data is inconclusive (Muhle, Trentacoste & Rapin, 2004). The prevalence of ASD appears to be steadily rising (over a ten-year period, from 4.4/1000 to 9 – 11/10,000; Fombonne, 2003), and this has led to widespread speculation and research concerning the cause(s) of the condition. In part, the increase in prevalence is due to an increase in awareness, diagnosis at an earlier age and widening of diagnostic criteria. Nonetheless, a legitimate rise in prevalence is also likely (see Matson & Kozlowski, 2011 and Rubenstein & Merzenich, 2003 for reviews). Following about 50 years of intensive study, researchers now believe that autism is a complex condition whose core aspects have distinct causes that often co-occur.

3.3 Coexisting Conditions in ASD

Psychiatric comorbidity is defined as the co-occurrence of two or more conditions in the same individual (American Psychiatric Association, 1994). Additional conditions like Attention Deficit Hyperactivity Disorder (ADHD) and anxiety (particularly Obsessive Compulsive Disorder (OCD)) are known to affect between 50-70% of individuals with ASD (Ghaziuddin & Zayfar, 2008). While little is known about the underlying basis of comorbidity, the presence of these additional conditions causes the individual pronounced distress and impairment. For example, those with additional conditions are thought to have more severe ASD symptoms, more pronounced social difficulties and are lower functioning than those with ASD alone (Kerns & Kendall, 2012). Note, however, that there is ongoing debate as to whether true comorbidity exists in ASD (for a review see Taurines et al., 2012). Are additional conditions true independent conditions with their own behavioural profile (and therefore warrant a separate diagnosis), or are these behaviours simply characteristics of the ASD itself (and can be accounted for by the diagnosis of ASD)? Until recently, each
condition has been typically studied separately and compared to each other in statistical
analyses. Although this provides researchers with valuable information about, for example,
the epidemiology and pathology of each condition, what remains unclear is the behavioural
and cognitive characteristics of each condition within the ASD spectrum.

3.3.1 ASD and ADHD

Approximately 28% of those with ASD have an additional diagnosis of ADHD (Simonoff
et al., 2008). ADHD is characterised by a pattern of inattentive (e.g., failure to pay attention
to tasks, difficulty organising tasks), hyperactive (e.g., excessive talking or fidgeting) or
impulsive (e.g., inability to remain seated in appropriate situations) behaviour that results in
difficulties in social, educational or work settings (APA, 2013). Behaviourally, these
symptoms manifest as excessive activity, short attention span and impaired inhibitory control
(Barkley, 1997). There are many overlapping symptoms between ADHD and ASD including:
attention difficulties, hyperactivity, impulsivity (Hays et al., 2002); social skill deficits
(Cervantes et al., 2013; Demopoulos et al., 2013) and behavioural problems (Mayes et al.,
2012). Executive function deficits are often assumed to be a symptom of both conditions,
which may be associated with functional differences in the prefrontal cortex (Johnson, 2012).
Research has also demonstrated that those with comorbid ASD and ASD show more severe
symptoms (more tantrum behaviours, anxiety and conduct disorder) than those with ASD or
ADHD alone (J. Jang et al., 2013).

3.3.2 ASD and anxiety

Both OCD and GAD are common in ASD. The prevalence of OCD in ASD is estimated
to be around 37% (Leyfer et al, 2006) and GAD at around 40% (van Steensel, Francisca
Johanna Arnoldina et al., 2014). GAD is characterised by excessive worry or anxiety about a
variety of situations (American Psychiatric Association, 2013). GAD is a generalised type of
anxiety, rather than having a specific cause or type of fear (whereas in social phobia, for example, anxiety is limited to social situations). Despite the frequency of co-occurrence, the shared phenotype of GAD and ASD remains debatable. For example, while anxiety in social situations may be shared by the two conditions, the term ‘anxiety’ when referring to those with ASD may not be caused by anxiety per se, rather a lack of functional skills to be able to cope in a social situation (Wood & Gadow, 2010). Anxiety does not feature in the diagnostic criteria for ASD (see Chapter 1 for full diagnostic criteria). Therefore, when anxiety does present together with ASD, it is treated as a self-standing comorbid condition.

Obsessive Compulsive Disorder is a debilitating condition characterised by obsessions (e.g., persistent thoughts, images, or impulses) that cause anxiety or distress and compulsions (e.g., repetitive behaviours or mental acts performed in response to obsessions) that reduce distress associated with a foreboding outcome (American Psychiatric Association, 2013). There are numerous similarities between OCD and ASD. Behaviours like repetition feature in the diagnostic criteria for both conditions (see Chapter 1 for full diagnostic criteria). Difficulties with inhibitory control are well documented in OCD (Bannon et al., 2002; Enright & Beech, 1993). The evidence for inhibitory control deficits autism is mixed, with some research suggesting a deficit (Christ et al., 2007a) and others not (N. Kleinhans et al., 2005). The shared nature of deficits in ASD and anxiety remains unclear.

3.3.3 Summary of common co-existing conditions in ASD

Taken together, research suggests there is indeed a link in the behavioural phenotype between ASD, ADHD and OCD. This is supported by research that demonstrates ASD, ADHD and OCD all involve some form of executive functioning deficit (Bradshaw & Sheppard, 2000), and are associated with differences in frontal lobe anatomy or functioning (E. L. Hill, 2004). Another body of research suggests that all three conditions involve basal
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

ganglia deficits and are thus part of a group of conditions caused by faulty basal ganglia networks (Palumbo, Maughan, Kurlan, 1997). One aim of the current study is to address the issue of whether each condition has its own defining characteristics on which they can be differentiated.

3.4 Aims and Hypotheses

The debate about the validity of comorbidity in autism is ongoing. Researchers need to clarify the phenotypes of each condition when they occur together in ASD, rather than compare them separately. Currently, there is little research on how comorbid ASD and anxiety, or ASD and ADHD should present as a comorbid condition. It is important for researchers and practitioners to identify the role that coexisting diagnoses play when examining conditions like ASD. Firstly, for the impact on research outcomes and secondly, the importance to healthcare practitioners. While there is currently no cure for ASD, there are pharmacological and behavioural treatments for anxiety, OCD and ADHD. Treating these additional conditions could have benefits for the ASD child in regards to their adaptive functioning at school, and in everyday situations.

The current study has three main aims: 1. To investigate the psychometric properties of each scale on a New Zealand population in distinguishing the conditions; 2. To investigate to what extent that ASD, ADHD and anxiety share specific behaviours, and how these change when presented as a comorbid condition; 3. To clarify if comorbid conditions, when presented together with ASD, are separate conditions that warrant their own diagnosis, or whether they are simply characteristics of the ASD itself.

Given that the behavioural measures used in the current study are thought to have sound validity and reliability, we expect those with ASD, ADHD, anxiety and neurotypical controls to be significantly different from one another on each scale.
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

Secondly, if the behaviour of anxiety or ADHD when presented together with ASD is simply a characteristic of the ASD itself, we expect those with comorbid ASD to have higher severity of ASD (i.e., more symptoms) than those without singular ASD. This is because increased symptoms of anxiety or ADHD should be accounted for by increased ASD symptoms, if they are indeed misinterpretations of ASD behaviour.

If these conditions are indeed separate, we expect to see no significant differences in ASD symptom severity between those with singular or comorbid ASD. However, we would expect to see a difference in these groups on measures of anxiety and ADHD. This would suggest that the comorbid conditions are not a behaviour of the ASD alone, and can be accounted for by independent difficulties with anxiety or ADHD.

3.5 Methods

3.5.1 Participants

The initial sample included 84 subjects. One participant was excluded due to incompletion of questionnaires. The remaining 83 participants formed the final sample. The participants were split into the following groups: ADHD ($n = 23$); anxiety ($n = 12$); ASD ($n = 25$); and controls ($n = 23$). Overall, the final sample consisted of 41 males and 42 females. However, within each group the gender ratio was not evenly split (see Table 3.1). This is inevitable as literature suggests autism has a 4.3:1 ratio for males to females (Newschaffer et al., 2007), and anxiety is much more common in females than males (Lowe et al., 2008; Matza et al., 2011). The mean age of all participants was 25.8 years ($SD = 8.20$), with a range of 16.5 years to 54.2 years.
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

Table 3.1. Gender and age of participants in each experimental group in the behavioural profiling study

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Gender</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>ADHD</td>
<td>23</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>ASD</td>
<td>25</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Control</td>
<td>23</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>41</td>
<td>42</td>
</tr>
</tbody>
</table>

3.5.2 Recruitment

Subjects were recruited using advertisements placed around the University of Auckland City Campus and on a participant recruitment website. Subjects were also recruited through organisations such as Altogether Autism, the Phobic Trust, the Parent and Family Centre and the ADHD Association. Once subjects contacted the researcher with their interest in the study, they were given an initial questionnaire to ensure they fit the study criteria. The selection criteria were as follows: no history of head injury; no history of comorbid depression or schizophrenia; be right-handed; have English as their first language. Control subjects consisted of mainly undergraduate students who had no history of any psychological illness (e.g., depression, anxiety). Experimental participants were required to have a diagnosis of ASD, ADHD or anxiety that was given by a registered medical professional (i.e., not self-diagnosed). From the 23 subjects in the ADHD group, five had an additional diagnosis of anxiety. In the ASD group, seven subjects had a diagnosis of high functioning autism with no coexisting conditions; 12 had a diagnosis of high functioning autism and coexisting anxiety or OCD; and the remaining six had a diagnosis of coexisting high functioning autism and ADHD. The anxiety group included those with a diagnosis of anxiety or OCD. All subjects
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

had normal or corrected-to-normal vision and no history of head injury. Participants were given $20 in vouchers for their participation in this study.

3.5.3 Medication

From the total sample, 30 participants were taking psychoactive medication (Ritalin \((n = 14)\); Concerta \((n = 11)\); Fluoxetine \((n = 5)\)). As Ritalin (a methylphenidate) has a short half-life of approximately three hours (Shaywitz et al., 1982), the medication was out of participants’ systems at the time of participation. Unfortunately Concerta is long-acting in nature (Coghill et al., 2013). While every effort was made to ensure maximum time from dose to participation, there may have been some affect of this drug on participants performance. This is a noted limitation.

3.6 Procedure

Participants were asked to come into the University of Auckland city campus for the study. All participants were tested in the same, minimally decorated room in the Human Sciences Building at the University of Auckland. Before participation, the researcher explained the study procedure thoroughly and informed consent was gained from each participant. Participants were then asked to answer a number of self-report questionnaires, perform a computer-based task and complete intelligence testing.

3.6.1 Equipment

The Continuous Performance Task (Sandford & Turner, 2004) was run on a Toshiba notebook with a Windows 1998 operating system, with an 11.3 inch screen. All other questionnaires were in pen and paper format.
3.7 Measures

Each profiling measure used in the behavioural profiling study will now be discussed in turn. See Chapter 2 for a full description of the reliability and validity of each measure.

3.7.1 The Integrated Visual and Auditory Continuous performance task

The Integrated Visual and Auditory Continuous Performance Task (CPT) was originally designed to test sustained attention to visual and auditory stimuli (Rosvold et al., 1956). In the CPT a series of stimuli are presented on a computer screen (i.e., you will see or hear the number “1” and “2”). The aim of the task is to attend to one stimuli (i.e., click the mouse upon seeing or hearing a “1”) whilst simultaneously ignoring another (i.e., ignore seeing or hearing stimuli “2”) over a sustained period of time. Maintaining attention to this dull sequence of events over a prolonged period of time separates those with good and poor attentional capacity (Corkum & Siegel, 1993). Scores have been standardised to have a mean of 100 and a standard deviation of 15 (Rosvold et al., 1956). The CPT is a reliable ($\alpha = 0.69$) and valid ($r = 0.42$) measure (Arble, Kuentzel, & Barnett, 2014).

The CPT consistently distinguishes those with a diagnosis of ADHD to typically developing controls, where those with ADHD perform significantly worse than controls (for a review see Losier, McGrath & Klein, 1996). In addition, the CPT has strong predictive power when discriminating between patients with ASD, ADHD and typically developing controls. A study utilising discriminate function analysis reveals CPT successfully discriminated between the three groups 75.6% of the time (Corbett & Constantine, 2006). Thus, the CPT is often used as a screening tool for ADHD.
3.7.2 Behavioural Inhibition Activation Scale

The Behavioural Inhibition/Activation Scale (BIS/BAS) designed by Carver and White (1994), is a questionnaire to identify patterns of behaviour in an individual’s personality. The questionnaire is measured on a 9-point Likert-scale where 4 is strongly agree and -4 is strongly disagree. The BIS and BAS scales are reliable (BIS = 0.76, BAS = 0.83; Jorm et al., 1998) and valid (BIS $r = 0.66$, Response Reward $r = 0.59$, Fun Seeking $r = 0.69$ and Drive $r = 0.66$) (Jorm et al., 1998). The questionnaire consists of four subscales as theorised by Carver and White (1994). The subscales are: 1. Behavioural Inhibition (BIS) or punishment sensitivity scale. This measures an individual’s experience of anxiety in a situation where there are punishment cues (e.g., “I worry about making mistakes”); 2. Reward Responsiveness measures positive responses in anticipation of a reward (e.g., “When good things happen to me, it affects me strongly”); 3. Drive measures an individual’s pursuit of desired objects (e.g., “I go out of the way to get things I want”) and; 4. Fun Seeking, which measures the willingness to approach new events which may give a reward (e.g., “I am always willing to try something new if I think it might be fun”). The BIS scales are found to relate to neuroticism and negative affect (and are higher in females), while the BAS scales are related to extraversion and positive affect (Jorm et al., 1998). Outward display of aggression is also positively related to BAS, and negatively to BIS (Smits & Kuppens, 2005).

Accordingly, the BIS/BAS scales are not designed to measure atypical behaviour related to developmental disabilities but rather as a measure of personality characteristics.

3.7.3 The Generalised Anxiety Disorder Scale

The Generalised Anxiety Disorder (GAD) Scale (Spitzer et al., 2006) was designed as a brief clinical measure for generalised anxiety. The GAD is a 7-item questionnaire that asks about the major symptoms of anxiety (i.e., “feeling nervous, anxious or on edge”).
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

Participants are asked to report how many days they were bothered by each symptom i.e., none of the days; some of the days; most of the days; all of the days. The responses are marked on a scale of 0, 1, 2 or 3 respectively. The minimum score of the GAD is 0 with the maximum being 21. The GAD is a reliable ($\alpha = 0.89$) and valid ($r = 0.64$) measure (Lowe et al., 2008).

3.7.4 The Obsessive Compulsive Inventory – Revised

The Obsessive Compulsive Inventory – Revised (OCI) is an 18-item questionnaire that measures OCD symptoms (Foa et al., 2002). The OCI includes statements such as; “I sometimes have to wash myself simply because I feel contaminated” and “I need things to be arranged in a particular way”. Participants are asked to report how distressed or bothered they are by each statement on a scale of 0 – 4 (with 0 being ‘not at all’, and 4 being ‘extremely’). There is a minimum score of 0 and a maximum score of 72, with the mean being 28 for those with a diagnosis of OCD (Foa et al., 2002). The OCI consistently discriminates those with a diagnosis of OCD from those with GAD, or typically developing individuals (Huppert et al., 2007) and is a valid ($\alpha = 0.89$) and reliable ($r = 0.41$) measure (Abramowitz & Deacon, 2006).

3.7.5 The Adult ADHD Self Report Symptom Checklist

The Adult ADHD Self Report Symptom Checklist (ASRS; (Kessler et al., 2005) is an 18-item self-report questionnaire which asks about clinical symptoms of ADHD as reported in the DSM-IV (e.g., “How often do you fidget or squirm when you have to sit down for long periods of time?”). Participants are asked to report how often they report each symptom on a scale of 0 – 4 (0 = never, 1 = rarely, 2 = sometimes, 3 = often or 4 = very often). As in the DSM-IV (American Psychiatric Association, 1994), the ASRS can be split into two subsections (hyperactive and inattentive) or combined into an overall score. For combined
scores, the minimum score is 0 and the maximum score is 72. The ASRS is a valid ($\alpha = 0.80$) and reliable ($r = 0.84$) measure (Adler et al., 2006)

3.7.6 The Autism Spectrum Quotient

The autism spectrum quotient (Baron-Cohen et al., 2001) is a 50-item self-report questionnaire that measures autistic-like traits in the typically developing population. The ASQ is scored on a Likert-type scale, however the general categories are “agree” or “disagree”. A score of around 10-21 is normal for the typically developing population, and a score of 32+ is the official criteria for autism (Baron-Cohen et al., 2001). The ASQ is a valid, ($\alpha = 0.67$) (Hurst, Mitchell, Kimbrel, Kwapiil, & Nelson-Gray, 2007) and reliable ($r = 0.78$) measure (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005).

3.7.7 Wechsler Abbreviated Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) is an abbreviated form of the Wechsler Adult Intelligence Scale that takes around 30 minutes to complete. The WASI is split into two sections; Performance IQ (which measures visuospatial intelligence) and Verbal IQ (ability to solve problems using language-based reasoning). The WASI is standardised to have a mean of 100 and a standard deviation of 15.

3.8 Statistical Analyses

All analyses were conducted using SPSS version 20 (SPSS, 2011). The main analyses used were discriminant function analyses, ANOVA, Mann Whitney-U and Kruskall Wallis. In all analyses, effects were deemed significant if the p-value was less than .05, unless otherwise specified. All follow-up analyses to ANOVAs were conducted with a Bonferroni post hoc correction. A series of one-way ANOVAs were also conducted that are exploratory
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

in nature given the uneven sample sizes of the experimental groups. Results of these analyses should therefore be interpreted with caution.

3.9 Results

3.9.1 Discriminant function analysis

The primary question of interest in this set of analyses is whether we could predict group membership based on participants responses to the questionnaires. Group membership analyses are detailed in Table 3.2. Discriminate function analysis also identified the best predictor for distinguishing each experimental group from the control participants.

Table 3.2. Discriminant function analysis reveals the percentage of predicted vs. actual group membership of study participants

<table>
<thead>
<tr>
<th>Actual group membership (%)</th>
<th>Predicted Group Membership (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADHD</td>
<td>Anxiety</td>
</tr>
<tr>
<td>ADHD</td>
<td>87.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>66.7</td>
</tr>
<tr>
<td>ASD</td>
<td>4.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Control</td>
<td>4.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

a. 75.9% of original grouped cases correctly classified.

3.9.1.1 ADHD versus controls

Discriminant function analysis revealed that the best predictor of ADHD was the ASRS (see Figure 3.1), Multivariate Wilks’ Lambda = 0.285, $p < .001$. 

67
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

![Histogram showing the scores of participants in the control and ADHD groups on the ASRS](image)

**Figure 3.1.** Histogram showing the scores of participants in the control and ADHD groups on the ASRS

3.9.1.2 ASD versus controls

As shown in Figures 3.2 and 3.3, the best predictor of ASD was the autism spectrum quotient, Multivariate Wilks’ Lambda = 0.453, $p < .001$, and the BIS scale, Multivariate Wilks’ Lambda = 0.399, $p < .001$.

![Histogram showing scores on the ASQ for the ASD vs control groups](image)

**Figure 3.2.** Histogram showing scores on the ASQ for the ASD vs control groups
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

![Figure 3.3 Histogram showing scores on the drive scale for the ASD vs control groups](image)

3.9.1.3 Anxiety versus controls

The best predictors of anxiety group were the GAD, Multivariate Wilks’ Lambda = 0.523, \( p < .001 \) and the drive scores, Multivariate Wilks’ Lambda = 0.430, \( p < .001 \) (as shown in Figure 3.4).
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

Figure 3.4 Scatter plot showing that the two best predictors of differentiating controls from the anxiety group are the “Drive” and the GAD measures.

3.9.2 ANOVA analyses

A Multivariate ANOVA (MANOVA) was conducted to investigate the effect of gender (two levels: male, female) and experimental group (four levels: ADHD; ASD; anxiety and controls) on profiling tasks (i.e., BIS/BAS, ASRS, ASQ, GAD, OCI). There was a significant main effect of the following profiling measures: Continuous Performance Task, $F(3, 74) = 4.89, p = .004$; Behavioural Inhibition Scale, $F(3, 74) = 5.96, p = .001$; Drive, $F(3, 74) = 3.07, p = .033$; Fun Seeking, $F(3, 74) = 10.36, p < .001$; Generalised Anxiety Disorder Scale, $F(3, 74) = 4.28, p = .008$; ASRS, $F(3, 74) = 24.33, p < .001$; the Autism Spectrum Quotient, $F(3, 74) = 16.57, p < .001$ and the Obsessive Compulsive Inventory, $F(3, 74) = 3.69, p = .016$. The effect of response reward was approaching significance, $F(3, 74) = 2.64, p = .056$. Follow-up tests for each of these measures are listed below. All means and standard deviations are listed in Table 3.3.
There was also a significant main effect of gender, $F(9, 66) = 2.28, p = .027$, where females scored higher than males on both the Behavioural Inhibition Scale, $F(1, 74) = 5.96, p = .001$, and the Generalised Anxiety Disorder Scale, $F(1, 74) = 7.18, p = .009$. There was also an interaction between experimental group and gender on profiling tasks, $F(9, 68) = 2.35, p = .023$, where for males only, the anxiety group had higher drive scores than neurotypical controls, $F(1, 74) = 2.79, p = .046$. There were no other significant effects or interactions (all $p > .05$).

Table 3.3. Means and standard deviations of each experimental group for each profiling scale

<table>
<thead>
<tr>
<th></th>
<th>ADHD Mean</th>
<th>ADHD SD</th>
<th>Anxiety Mean</th>
<th>Anxiety SD</th>
<th>ASD Mean</th>
<th>ASD SD</th>
<th>Control Mean</th>
<th>Control SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural Inhibition Scale</td>
<td>21.77</td>
<td>4.11</td>
<td>23.33</td>
<td>3.17</td>
<td>22.04</td>
<td>3.31</td>
<td>18.74</td>
<td>3.31</td>
</tr>
<tr>
<td>Response Reward</td>
<td>17.14</td>
<td>2.36</td>
<td>17.08</td>
<td>1.73</td>
<td>15.28</td>
<td>2.46</td>
<td>15.57</td>
<td>2.41</td>
</tr>
<tr>
<td>Drive</td>
<td>10.46</td>
<td>2.56</td>
<td>11.08</td>
<td>2.58</td>
<td>10.33</td>
<td>2.71</td>
<td>9.14</td>
<td>2.25</td>
</tr>
<tr>
<td>Fun Seeking</td>
<td>13.19</td>
<td>2.52</td>
<td>9.75</td>
<td>2.49</td>
<td>9.21</td>
<td>2.64</td>
<td>10.64</td>
<td>1.50</td>
</tr>
<tr>
<td>Generalised Anxiety</td>
<td>6.86</td>
<td>4.69</td>
<td>11.17</td>
<td>5.39</td>
<td>8.32</td>
<td>5.41</td>
<td>4.22</td>
<td>2.56</td>
</tr>
<tr>
<td>Obsessive Compulsive Inventory</td>
<td>17.91</td>
<td>9.72</td>
<td>31.42</td>
<td>18.97</td>
<td>23.12</td>
<td>15.5</td>
<td>14.22</td>
<td>5.71</td>
</tr>
<tr>
<td>Adult Self-Report ADHD scale</td>
<td>49.61</td>
<td>7.99</td>
<td>32.42</td>
<td>10.01</td>
<td>33.64</td>
<td>10.6</td>
<td>26.96</td>
<td>7.19</td>
</tr>
<tr>
<td>Autism Spectrum Quotient</td>
<td>20.78</td>
<td>7.54</td>
<td>23.33</td>
<td>6.919</td>
<td>32.16</td>
<td>6.97</td>
<td>16.70</td>
<td>7.40</td>
</tr>
</tbody>
</table>

3.9.2.1 BIS scores

A 2 (Gender: male or female) by 4 (experimental group: ADHD; ASD; anxiety; control) ANOVA was performed to investigate the effect of gender and experimental group on the Behavioural Inhibition Scale. There was a significant main effect of gender on BIS scores, $F(1, 82) = 10.69, p = .002$, where females ($M = 22.26, SD = 3.92$) scored significantly
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

higher than males ($M = 20.15$, $SD = 3.83$) (see Figure 3.6). There was also a significant main effect of experimental group on BIS scores, $F(3, 82) = 5.96$, $p = .001$, where the control group scored significantly lower than the ADHD group ($p = .019$), the anxiety group ($p = .001$) and the ASD group ($p = .006$). This effect is shown in Figure 3.5. Means and standard deviations are listed in Table 3.3.

Figure 3.5. Main effect of experimental group on behavioural inhibition scores

Figure 3.6. Main effect of gender on behavioural inhibition scores
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

3.9.2.2 Fun Seeking Scores

A univariate ANOVA was conducted to investigate the effect of experimental group on fun seeking scores. As shown in Figure 3.7, a significant main effect of experimental group was found, $F(3, 83) = 14.06, p < .001$. The ADHD group scored significantly higher on fun seeking than the anxiety group ($p < .001$), the ASD group ($p < .001$), and the control group ($p = .001$).

![Figure 3.7. Main effect of experimental group on fun seeking scores.](image)

3.9.2.3 Drive Scores

A 2 (Gender: male, female) x 4 (Experimental Group: ADHD; ASD; anxiety; control) ANOVA was conducted on drive scores to investigate the significant main effects and interaction between gender and experimental group. As shown in Figure 3.8, there was a significant main effect of experimental group on drive scores, $F(3, 83) = 3.10, p = .032$. Despite this, follow up analyses show that there were no significant differences between groups (all $p > .05$). The interaction between gender and experimental group was approaching significance, $F(3, 83) = 2.68, p = .053$ (see Figure 3.8). Post hoc tests reveal that for males
only, the control group \((M = 8.85, SD = 1.96)\) scored significantly lower than the anxiety group \((M = 13.67, SD = 1.53, p = .027)\).

3.9.2.4 Response reward

A univariate ANOVA was conducted to investigate the effect of experimental group on response reward scores. A significant main effect was found, \(F(3, 82) = 3.61, p = .017\) (see Figure 3.9). The ADHD group scored significantly higher on response reward than the ASD group \((p = .047)\).
3.9.2.5 GAD scores

A 2 (gender: male, female) by 4 (experimental group: ADHD; ASD; anxiety; control) ANOVA was conducted to investigate the effect of gender and experimental group on GAD scores. As shown in Figure 3.11, there was a main effect of gender on GAD scores, $F(1, 83) = 7.34, p = .008$, where females ($M = 8.09, SD = 5.27$) had significantly higher anxiety scores than males ($M = 6.24, SD = 4.60$). There was also a main effect of experimental group on GAD scores, $F(3, 83) = 4.33, p = .007$ (see Figure 3.10). The control group scored significantly lower on the GAD than the anxiety group ($p < .001$) and the ASD group ($p = .010$). Also, the ADHD group had significantly lower GAD scores than the anxiety group ($p = .039$).
3.9.2.6 CPT Scores

A univariate ANOVA was conducted to investigate the effect of experimental group on the CPT. A significant main effect was found, $F(3, 83) = 5.18, p = .003$ (see Figure 3.12). The ADHD group had significantly lower scores on the CPT than the ASD group ($p = .028$), and the control group ($p = .003$). The ADHD group also scored lower than the anxiety group ($p = .065$).
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

3.9.2.7 ASRS scores

A univariate ANOVA was conducted to investigate the effect of experimental group on the ASRS. A significant main effect was found, $F(3, 83) = 26.53, p < .001$ (see Figure 3.13). The ADHD group had significantly higher scores on the ASRS than the anxiety group ($p < .001$), the ASD group ($p < .001$), and the control group ($p < .001$).

Figure 3.13. Main effect of experimental group on ASRS scores
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

3.9.2.8 ASQ scores

A univariate ANOVA was conducted to investigate the effect of experimental group on the ASQ. A significant main effect was found, $F(3, 83) = 19.74, p < .001$ (see Figure 3.14). The ASD group had significantly higher scores on the ASQ than the ADHD group ($p < .001$), the anxiety group, ($p = .005$), and the control group ($p < .001$).

![Figure 3.14](image)

*Figure 3.14. Main effect of experimental group on ASQ scores*

3.9.2.9 OCI scores

A one-way ANOVA was conducted to investigate the effect of experimental group on the OCI. As shown in Figure 3.15, a significant main effect was found, $F(3, 83) = 5.60, p = .002$. The anxiety group score significantly higher than the ADHD group ($p = .021$) and controls ($p = .001$).
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

3.9.3 Non-parametric tests

Initially, a Kruskall-Wallis was conducted to identify if there were any significant differences on the profiling tasks when the groups were split by their comorbid conditions (seven groups: control; ADHD; ADHD/anxiety; anxiety; ASD; ASD/anxiety and ASD/ADHD). A Kruskall-Wallis test demonstrated significant difference between groups on measures of: CPT, $\chi^2(6) = 20.60, p = .002$, BIS, $\chi^2(6) = 21.70, p = .001$, response reward, $\chi^2(6) = 13.70, p = .031$, fun seeking, $\chi^2(6) = 29.41, p < .001$, GAD, $\chi^2(6) = 24.69, p < .001$, OCI, $\chi^2(6) = 14.92, p = .021$, ASRS, $\chi^2(6) = 41.21, p < .001$ and the ASQ, $\chi^2(6) = 36.25, p < .001$. These effects can be visually inspected in Figures 3.16 – 3.23.
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

**Figure 3.16.** ASQ scores of groups when split by comorbid condition

**Figure 3.17.** GAD scores of groups when split by comorbid condition

**Figure 3.18.** ASRS scores of groups when split by comorbid condition

**Figure 3.19.** OCI scores of groups when split by comorbid condition
3.9.3.1 Comorbid ASD and ADHD

A Mann-Whitney U test was conducted to follow up on the significant Kruskall Wallis test, to see whether the ASD group differed from the ADHD group or the ASD and ADHD comorbid group on the behavioural measures. The ADHD pure group had significantly lower CPT scores than the ASD pure group \((U = 22.00, p = .012)\). The ADHD also had significantly higher response reward scores then the ASD only group \((U = 19.50, p = .010)\). The ASD and ADHD group had lower response reward scores than the ADHD group.
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

($U = 24.50, p = .060$). The ASD group had significantly lower fun seeking scores than the ADHD group ($U = 8.50, p = .001$). The ASD and ADHD had significantly lower ASRS scores than the ADHD group ($U = 18.00, p = .016$). The ASD group also had significantly lower ASRS scores than the ADHD groups, ($U = 14.50, p = .003$). The ASD group had significantly higher ASQ scores than the ADHD groups, ($U = 8.00, p = .001$). The ASD and ADHD group also had higher ASQ scores than the ADHD group ($U = 14.00, p = .008$).

Means and standard deviations are listed in Table 3.4. There were no other significant effects (all $p > .05$).

Table 3.4. Means and SD for each ADHD pure, ASD pure and comorbid ASD + ADHD on each profiling measure.

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th></th>
<th>ASD</th>
<th></th>
<th>ASD + ADHD</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Behavioural Inhibition Scale</td>
<td>21.41</td>
<td>4.52</td>
<td>22.14</td>
<td>3.02</td>
<td>19.00</td>
<td>3.52</td>
</tr>
<tr>
<td>Response Reward</td>
<td>17.65</td>
<td>1.87</td>
<td>14.86</td>
<td>2.12</td>
<td>15.17</td>
<td>3.13</td>
</tr>
<tr>
<td>Drive</td>
<td>10.71</td>
<td>2.71</td>
<td>9.86</td>
<td>2.27</td>
<td>9.83</td>
<td>3.82</td>
</tr>
<tr>
<td>Fun Seeking</td>
<td>13.31</td>
<td>2.60</td>
<td>8.43</td>
<td>1.81</td>
<td>10.83</td>
<td>3.82</td>
</tr>
<tr>
<td>Generalised Anxiety Disorder</td>
<td>5.76</td>
<td>4.60</td>
<td>4.86</td>
<td>3.85</td>
<td>8.50</td>
<td>5.58</td>
</tr>
<tr>
<td>Obsessive Compulsive Inventory</td>
<td>16.61</td>
<td>8.30</td>
<td>16.14</td>
<td>15.38</td>
<td>19.83</td>
<td>12.61</td>
</tr>
<tr>
<td>Adult Self-Report ADHD scale</td>
<td>49.39</td>
<td>7.57</td>
<td>31.29</td>
<td>11.79</td>
<td>37.67</td>
<td>10.05</td>
</tr>
<tr>
<td>Autism Spectrum Quotient</td>
<td>19.44</td>
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<td>33.29</td>
<td>6.34</td>
<td>31.50</td>
<td>9.03</td>
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<tr>
<td>Continuous performance task</td>
<td>59.00</td>
<td>31.50</td>
<td>88.00</td>
<td>14.52</td>
<td>76.67</td>
<td>26.77</td>
</tr>
</tbody>
</table>

3.9.3.2 Comorbid ASD and anxiety

A Mann-Whitney U test was conducted to follow up on the significant Kruskall Wallis test, to see whether the ASD group differed from the anxiety group or the ASD and anxiety comorbid group on the behavioural measures. The anxiety group had significantly lower CPT scores than the ASD and anxiety group, ($U = 37.00, p = .043$). The ASD group had significantly lower response reward measures than the anxiety group, ($U = 16.50, p =
The ASD groups have significantly lower GAD scores than the anxiety group, \((U = 15.00, p = .022)\). The ASD and anxiety groups also have significantly higher GAD scores than the ASD group, \((U = 16.50, p = .031)\). The anxiety group had higher OCI scores than the ASD group, \((U = 20.00, p = .062)\). The ASD and anxiety groups also had higher OCI scores than the ASD group, \((U = 20.00, p = .063)\). The ASD group had significantly higher ASQ scores than the anxiety group, \((U = 15.50, p = .025)\). The ASD and anxiety groups also had significantly higher ASQ scores than the anxiety group, \((U = 28.00, p = .011)\). Means and standard deviations are listed in Table 3.5. There were no other significant effects (all \(p > .05\)).

Table 3.5. Means and SD for each anxiety pure, ASD pure and comorbid ASD + anxiety on each profiling measure.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Anxiety</th>
<th>ASD</th>
<th>Anxiety + ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Behavioural Inhibition Scale</td>
<td>23.55</td>
<td>3.23</td>
<td>22.14</td>
</tr>
<tr>
<td>Response Reward</td>
<td>17.00</td>
<td>1.79</td>
<td>14.86</td>
</tr>
<tr>
<td>Drive</td>
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<td>2.68</td>
<td>9.86</td>
</tr>
<tr>
<td>Fun Seeking</td>
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<td>8.43</td>
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<tr>
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<td>Obsessive Compulsive Inventory</td>
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<tr>
<td>Adult Self-Report ADHD scale</td>
<td>33.36</td>
<td>9.92</td>
<td>31.29</td>
</tr>
<tr>
<td>Autism Spectrum Quotient</td>
<td>23.27</td>
<td>7.25</td>
<td>33.29</td>
</tr>
<tr>
<td>Continuous performance task</td>
<td>87.60</td>
<td>7.85</td>
<td>88.00</td>
</tr>
</tbody>
</table>

### 3.10 Discussion

The current study aimed to investigate the psychometric properties of a number of profiling measures on a New Zealand population. This is part of a larger aim to investigate what extent ASD, ADHD and anxiety share specific behaviours, and how these change when presented as a comorbid condition. Finally, the study aimed to clarify if comorbid conditions,
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

when presented together with ASD, are separate conditions that warrant their own diagnosis, or whether they are simply characteristics of the ASD itself.

We expected that the four experimental groups would score significantly different from one another on each profiling method, given that the ASQ, ASRS, GAD, OCI and the CPT have all been found to be valid and reliable at discriminating those with a condition from neurotypical controls (Abramowitz & Deacon, 2006; Adler et al., 2006; Arble et al., 2014; Lowe et al., 2008). Results from the discriminate function analyses reveal that this is indeed the case. The best predictor of distinguishing ASD from neurotypical controls was the ASQ. For ADHD, the ASRS was the best predictor. For those with anxiety the GAD and the “drive” section of the BIS/BAS were best at distinguishing the condition. ANOVA analyses confirmed these results by showing that the experimental groups were significantly different from one another on each measure. On the CPT, those with ADHD had lower scores than the anxiety, ASD and control groups. Those with ADHD had higher scores on the ASRS than the anxiety, ASD and control groups. Those with ASD had higher scores than the anxiety, ADHD and control groups on the ASQ.

Previous literature suggests that ADHD and ASD, in particular, share much of the same behaviour. These overlapping symptoms between ADHD and ASD include: attention difficulties, hyperactivity, impulsivity (Hays et al., 2002); social skill deficits (Cervantes et al., 2013; Demopoulos et al., 2013) and behavioural problems (Mayes et al., 2012). This has caused an ongoing debate as to whether diagnostic criteria should allow a dual diagnosis on the basis that characteristics of ADHD when presented together with ASD are simply misinterpreted symptoms that do not warrant their own diagnosis. Some researchers suggest that ASD and ADHD should be considered along a spectrum of one overarching condition (van der Meer et al., 2012). The evidence above, however, demonstrates that ASD and ADHD have distinct behavioural profiles from which they can be reliably discriminated from
one another. This is not to say that some behaviours may overlap between conditions, but rather, the two conditions should not be thought of as stemming from the same origin. This finding is supported by neuropsychological evidence which demonstrates differences in brain structure and function between those with ASD and ADHD (Taurines et al., 2012).

To investigate the effects of comorbidity in the current study, non-parametric tests were conducted between those with ASD only and those with ASD and anxiety. If ASD and anxiety were separate conditions, we expected to see similar ASQ scores in those with ASD and ASD with anxiety, and higher GAD or OCI scores in those with ASD with anxiety versus those with ASD only. This is exactly what was found. Previous literature states that co-existing anxiety in ASD would compound overall social impairment in ASD (White, Oswald, Ollendick, & Scwhill, 2009). However, the current data suggests that anxiety, when presented together with ASD, does not impact affect ASD symptoms, but rather adds an independent set of challenges to the individual. Anxiety cannot be accounted for by severity of ASD symptoms, when they occur together. To further this point, those with ASD and anxiety had significantly higher scores on both the GAD and the OCI scales than those with ASD alone. If anxiety was a symptom of ASD, we would expect those with ASD alone to have similar anxiety levels to those with ASD with anxiety, or those with anxiety alone. Indeed, literature suggests that there is no true comorbidity if the levels of anxiety present in the comorbid individual are similar to those with a pure form of the condition (Wood & Gadow, 2010). Accordingly, as levels of anxiety are significantly higher in those with ASD with anxiety versus ASD alone, the administration of a second, dual diagnosis, is warranted.

The current research suggests that anxiety should not be conceptualised as part of the ASD diagnosis but rather as a set of common, but independent, difficulties. Establishing the distinct behavioural profiles between the two conditions is only a small step in determining why they so often co-occur. It does, however, demonstrate that misinterpretation of anxiety
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

that can be accounted for by the ASD diagnosis is not the cause for high comorbidity rates. Future research needs to focus on determining why this high prevalence exists by investigating the brain and genetic makeup of affected individuals.

On the contrary, the results of the non-parametric tests for the ADHD comorbid results are in line with what we would expect to see if ADHD behaviour, when presented together with ASD, is a characteristic of the ASD itself. Firstly, the ASD and ADHD group show significantly higher ASQ scores than the ASD only group, indicating more severe ASD in this group. Secondly, the ASD and ADHD group show significantly lower scores on the ASRS than the ADHD alone group, but not the ASD only group. If these conditions were indeed separate, we would expect higher ASRS scores in the comorbid group than the ASD only group, but the ASD scores between those with ASD only and ASD and ADHD should remain similar. Instead, our results indicate that ADHD can be conceptualised within the ASD diagnosis as those with both conditions have more symptoms of ASD but not ADHD.

A lack of distinction between the two conditions when presented as a comorbid condition, as demonstrated in the current study, was used as the basis to preclude a dual diagnosis between the two in a previous edition of the DSM (American Psychiatric Association, 1994). This finding is also line with previous research that supports the hypothesis that, to some extent, the cognitive and behavioural difficulties that are present in ASD and ADHD may stem from one overarching disorder (van der Meer et al., 2012). However, should this be the case, the profiling methods comparing the groups in their pure form would have been less accurate at distinguishing between the conditions. It is possible, that given the confusion surrounding the shared nature of behaviour in ASD and ADHD, the results could be explained by misdiagnosis. That is, individuals are incorrectly assigned a dual diagnosis of ASD and ADHD when the symptoms could simply be accounted for by the ASD.
CHAPTER 3 - STUDY ONE: BEHAVIOURAL PROFILING

As mentioned previously, while the behavioural similarities between the two conditions are unclear, recent research demonstrates distinct cognitive and neuropsychological profiles between the two conditions (Gargaro et al., 2011). It is possible that while the two conditions share a behavioural basis, symptoms are given rise by distinct neural networks. Thus, further research is needed to determine the shared basis of ADHD and ASD.

The ANOVA results from the BIS/BAS scaled revealed that, on the BIS scale, the neurotypical controls score significantly lower than the ASD, anxiety and ADHD groups. Previous studies have demonstrated that high BAS scores are associated with externalising conditions, drug and alcohol abuse, psychopathy and hyperactive ADHD, whereas high BIS scores are associated with inattentive ADHD (Hundt, Kimbrel, Mitchell, & Nelson-Gray, 2008; Johnson, Turner, & Iwata, 2003). However, there is little existing research on the nature of BIS/BAS qualities in ASD or anxiety. This interesting finding suggests that the BIS section of the BIS/BAS scale may be a good overall measure of overall adaptive functioning as it discriminates between those that have a neurobehavioural condition and their neurotypical peers. Including the BIS/BAS when investigating a diagnosis could provide medical professionals with useful information about overall adaptive functioning.

The anxiety scales were less sensitive at discriminating the groups from one another. Controls had lower scores than the ASD and anxiety groups on the GAD, in addition, those with ADHD had lower GAD scores than the anxiety group. On the OCI, those with anxiety scored higher than the ADHD and control groups, but not the ASD group. Taken together, this evidence suggests that the OCI and GAD are good measures to discriminate those with anxiety from their neurotypical peers and those with ADHD, but are not good at discriminating those with ASD from those with anxiety. Anxiety does not feature in the diagnostic criteria for ASD (American Psychiatric Association, 2013). Therefore, when
anxiety does present together with ASD, it is treated as a self-standing comorbid condition. Quantifying the amount of anxiety that is typical in an individual with ASD is challenging, with some research suggesting anxiety should be part of the diagnostic criteria, and others demonstrating no link between symptoms of ASD and anxiety (Kerns & Kendall, 2012). The results of the current study may suggest that some level of anxiety in those with ASD is typical. However as the ASD group included those with a comorbid anxiety diagnosis, it is likely that the lack of distinction between these two groups simply reflects the anxiety diagnosis of those participants.

Taken together, the results of the behavioural testing give us interesting and important information about the nature of neurodevelopmental conditions in New Zealand. Firstly, the profiling tools used in the current study are good at distinguishing different conditions from each other and are can be extended to a New Zealand population. Secondly, to the best of our knowledge, this study is the first to investigate the nature of coexisting conditions in ASD in a New Zealand population. The current behavioural data suggest that while anxiety may not be a characteristic of ASD, behaviour of ADHD may indeed be a characteristic of ASD. However, this information does little to explain the underlying nature of the symptoms, and what brain systems may be moderating them. It is possible that despite the behavioural profile of these conditions suggesting these links, neuroimaging research that investigates the brain basis of these behaviours may demonstrate different profiles altogether.

3.10.1 Limitations

Some limitations of the current study warrant consideration. Firstly, due to small sample sizes, some analyses performed were targeted to specific groups (i.e., comparing ADHD, ASD and ADHD + ASD). Larger sample sizes would have given the statistical power to perform a full scale comparative analysis of all experimental groups when split by
their comorbid conditions. Second, males were over-represented in the ASD group and females were over-represented in the anxiety group, due to the uneven gender balance in the prevalence of these conditions. Gender was included in the statistical analyses and all significant effects were reported accordingly. Lastly, the main profiling techniques used were questionnaires. Clinical interviews would have been preferable, as they give a more objective account of behavioural difficulties. However, given the resources available for the current study, questionnaires were determined to be the best available option for measuring behaviour.

3.10.2 Conclusions

The results of the current study suggest that the ASRS, OCI, GAD, CPT and the ASQ are good measures of discriminating those with the condition it aims to detect against neurotypical controls and against those with another condition. In addition the BIS/BAS may be a good measure of adaptive functioning as it discriminates those with a condition (of either ADHD, ASD or anxiety) from neurotypical controls. The results of the current analysis also suggest that when anxiety presents as a comorbid condition with ASD it is indeed a separate condition. However, the current study also suggests that perhaps ADHD is a behaviour of the ASD when the two conditions present together, rather than being a separate condition.

These findings are particularly important for researchers when recruiting participants. Researchers need to ensure they properly screen for additional conditions in ASD so the results of their research are not misinterpreted due to comorbidity. In addition, this information is also important to medical professionals when dealing with an ASD client. While there are no known cures for ASD there are well established treatments, both behavioural and pharmalogical, for ADHD and anxiety and administering these could greatly reduce the impact on those with ASD.
CHAPTER FOUR – STUDY TWO: EMOTION PROCESSING AND EEG

4.1 Study Overview

Difficulties with social functioning, including emotion recognition, are a core feature of ASD. The current study investigated emotion processing, using an emotion recognition task with concurrent EEG recording, in ASD alone versus those with comorbid ASD and ADHD or anxiety. In this task participants were asked to decide whether an image of eyes or mouth displayed a neutral or a sad emotion. This study is part of a larger research effort to establish the nature of co-existing conditions in ASD and to determine whether they are separate conditions or whether they can be accounted for through the ASD spectrum diagnosis. Contrary to our expectation, there were no group differences in the latency or amplitude of the N170 found in the current study. There were however, group differences in the amplitude of the P250. Those with ASD showed a different P250 profile from the ADHD group in response to sad and neutral stimuli. Together, this suggests that initial recognition of emotions is intact in both ASD and ADHD, but further processing of emotion-based stimuli (as reflected in later ERP components) is differently affected in the two groups. In addition, there was a trend for those with anxiety to be slower to respond to the emotion portrayed (which was also reflected in the latency of the P250). This may reflect the automaticity for those with anxiety to view stimuli as threatening. Finally, the amplitude of the N170 was larger in those with ASD only versus those with ASD and anxiety or ADHD. Taken together, the results of the current study suggests that ADHD and anxiety are indeed separate from ASD, and warrant their own diagnoses.

4.2 Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition for which there is no known cause or cure. Autism is a highly variable disorder, the most
prominent difficulties of which include aberrant behaviour, poor social skills and disrupted communication skills (American Psychiatric Association, 2013). There is great variability in symptom severity and intellectual functioning in ASD, but all individuals have difficulties in social interactions (e.g., eye contact, reciprocal interactions, responding to emotional cues). In particular, the nature of face processing in autism differs from their typically developing peers. In very young children, the ability to use facial information (e.g., engaging in joint attention) is considered a critical early marker of ASD (Dawson et al., 2004a).

4.2.1 Common co-occurring conditions in ASD

Additional neuropsychological conditions like Attention Deficit Hyperactivity Disorder (ADHD) and anxiety (particularly Obsessive Compulsive Disorder (OCD)) are known to affect between 50-70% of individuals with ASD (Ghaziuddin & Zayfar, 2008). ADHD is characterised by a pattern of inattentive (e.g., failure to pay attention to tasks, difficulty organising tasks), hyperactive (e.g., excessive talking or fidgeting) or impulsive (e.g., inability to remain seated in appropriate situations) behaviour that results in difficulties in social, educational or work settings (American Psychiatric Association, 2013). Anxiety is an umbrella term for which there are many sub-diagnoses, such as: generalised anxiety disorder (GAD), social phobia, obsessive compulsive disorder (OCD), post-traumatic stress disorder and panic disorder (American Psychiatric Association, 2013). Difficulties in processing social information are also evident in these conditions, and will be discussed in detail below.

4.2.2 Brain basis of social processing difficulties in ASD, anxiety and ADHD

The social difficulties seen in ASD may stem from the inability to attend to, or process, information from faces. Children with ASD perform worse on face processing tasks, including face discrimination or recognition, and perform comparably on tasks which require
discrimination between face and non-face stimuli (where typically developing peers would easily discriminate faces) (Dawson et al., 2005). In addition to behavioural differences when responding to faces, those with ASD process faces using abnormal strategies. They typically pay less attention to core features of the face, like the eyes and nose, relative to neurotypical adults (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004). These difficulties have been mapped to certain brain regions. There is reduced activity in the fusiform gyrus and the amygdala (Harms et al., 2010), both areas involved in the processing of social information. Difficulties processing social information in autism are not just limited to facial stimuli. Research suggests that those with ASD also process emotion-based words differently to typically developing controls (Lartseva, Dijkstra, Kan, & Buitelaar, 2014). It is likely that impairments in emotion-based processing contribute to the dysfunction of brain systems seen in ASD.

Clinically, ADHD, anxiety and ASD all share difficulties in social interactions. In ADHD, these social difficulties may be due to abnormal processing of emotion-related stimuli. It is possible that the dysfunctional fronto-temporal posterior systems (involved in regulating emotional function) contribute to these emotion-related deficits (Williams et al., 2008). It is also well documented that people with anxiety also have atypical responses to emotional-based stimuli. Those with anxiety are faster and more accurate than controls at identifying fearful faces versus neutral faces (Surcinelli et al., 2006), a response that is associated with altered activity in the amygdala (Easter et al., 2005). This suggests that those with anxiety have a predisposition to quickly interpret negative versus positive emotions. Taken together, the current literature suggests that anxiety, ADHD and ASD have diagnostic overlap in behaviour, and share emotion recognition difficulties.

Despite these shared characteristics, there is debate in the literature surrounding the validity of coexisting conditions in ASD. One school of thought is that comorbidity in ASD
does not exist. That it, traits of ADHD or OCD behaviour in ASD can be attributed to the ASD itself rather than a true coexisting condition. Whereas other research has demonstrated functional and structural differences in those with pure ASD and coexisting ASD, suggesting a dual diagnosis is warranted (see Taurines et al., 2012 for a review). Further research is therefore needed to clarify the shared basis of coexisting conditions. Investigating the shared nature of social processing difficulties in the three disorders will help to identify whether coexisting conditions in ASD stem from the same basis (i.e., ADHD or anxiety behaviours are simply characteristics of the ASD itself), or are entirely separate conditions (i.e., the coexisting conditions are true separate conditions).

4.2.3 Social information processing and EEG

A common approach used to investigate how the brain processes stimuli is through the use of electroencephalography (EEG). The event related potentials (ERPs) that are recorded using EEG give information about the speed in which certain stimuli are processed. A typical ERP consists of a waveform of positive and negative deflections which are labelled according to their presentation after stimulus onset. The peak of each positive or negative waveform is the amplitude which measures the amount of neural resources devoted to a specific task at any one time (Dawson et al., 2005). Larger amplitudes reflect more neural activity and correlates to the amount of cognitive effort required (Spironelli & Angrilli, 2009). The onset of each peak after stimulus onset is the latency, and measures processing speed (Handy, 2005).

In typically developing individuals, the N170 (a negative component that typically occurs about 170ms after stimulus onset) differs as a function of emotional expression. The latency of the N170 toward sad versus neutral face stimuli is shorter and the amplitude larger in fearful faces versus neutral faces (Batty & Taylor, 2003). In addition, typically developing
adults prefer the eyes over other facial stimuli (Taylor et al., 2001). The P250 is a positive component that closely follows the N170 (Marzi & Viggiano, 2007). This component is known to be involved in the late stages of analysing visual information and decision making (Spironelli & Angrilli, 2009). The P250 has been related to the processing of facial identity and familiarity (Marzi & Viggiano, 2007). In addition, the amplitudes of both the N170 and the P250 have been found to differentiate neutral and emotive stimuli (DaSilva, Crager & Puce, 2015). These two components are an appropriate focus of this chapter given that together they provide information about the recognition and processing of facial information, and differentiate between neutral and emotive expressions. ERP waveform in response to faces provides researchers with important information about how the brain processes emotion-based stimuli.

**4.2.4 Social information processing in ASD, ADHD and anxiety using EEG**

In addition to the shared behavioural characteristics presented above, EEG research has demonstrated aberrant neurophysiological responses to emotion-based stimuli in ASD, ADHD and anxiety. Firstly, those with ASD show longer latencies (which reflects slower processing speed) and reduced amplitude (which reflects fewer neural resources devoted to the process) in both early (N170) and late ERP (N400) components. These components reflect both the structural encoding and recognition memory stages of processing facial stimuli respectively (Dawson et al., 2005). Similarly, an EEG study investigating ERP response to sad, neutral and happy facial stimuli found that adults with autism were found to exhibit delayed P1 and N170 latencies and smaller N170 amplitudes in comparison to control subjects for all expressions (O’Connor et al., 2005). Additionally, those with ASD do not show a different neurophysiological response to fearful versus neutral faces (i.e., the amplitudes were not significantly different from one another) (Dawson et al., 2004a), a pattern that is expected in typically developing individuals. However, a study by Wong,
Fung, Chua and McAlonan (2008) failed to find any differences in the N170 between those with ASD and typically developing controls. Thus, there are some inconsistencies in the literature on whether the N170 amplitude is affected in those with ASD. In addition it is uncertain whether earlier (e.g., N100) or later (e.g., P300) ERP components are affected.

In those with anxiety, EEG studies show enhanced early negativity (i.e., a larger negative waveform with an earlier latency) in response to emotional stimuli (Mühlberger et al., 2009). However, another study investigating the perception of fearful or happy faces using ERP’s in those with anxiety demonstrated that early components (P100, N170) of facial processing are left intact, while later components (P300) are altered (Rossignol, Philippot, Douilliez, Crommelinck, & Campanella, 2005). Thus, there is currently no clear consensus on which ERPs are altered during face processing in anxiety.

In ADHD, EEG recordings show a pronounced reduction in latency and amplitude in the occipital area during the early stages of emotional expression encoding (Williams et al., 2008). However, recent research has shown an opposite pattern. Since this thesis began, a study with very similar methodology to the current study was published (Tye et al., 2014), where researchers attempted to differentiate ASD and ADHD based on their neurophysiological reaction to emotion based stimuli. An EEG investigation by Tye and colleagues (2014) investigated the N170 and P400 components in response to emotional stimuli (i.e., images of faces with disgust, fear, anger, joy or neutral expressions) in children with ASD, ADHD and coexisting ASD and ADHD. They found that, while the ASD and ADHD children had different neurophysiological profiles in response to the stimuli, those with coexisting ASD and ADHD showed unique deficits of each disorder. Specifically, the N170 amplitude was reduced in the ASD group and ASD with ADHD group (particularly to ‘fear’ expressions), while in ADHD (and ADHD + ASD) the N400 was reduced. This suggests an additive effect (given that the two conditions have different profiles when
presented alone), but appear to adopt characteristics of each disorder when presented as a comorbid condition.

4.3 Aims and Hypotheses

An emerging body of research that investigates coexisting conditions in developmental disorders is certainly helping to understand the underlying nature of comorbidity. However, research in autism as a coexisting condition is not well established. It remains unclear whether emotion processing in anxiety or ADHD is different from that of ASD. In addition, there are still inconsistencies in the literature regarding which ERPs are atypical in ASD and anxiety. The current study aims to clarify these uncertainties by: 1). Investigating whether social processing, measured by the N170 and the P250, is atypical in each of the disorders (ASD, ADHD and anxiety); and, 2). investigating whether the N170 or the P250 are the same in single ASD versus ASD and ADHD or anxiety.

Overall, we expect to see shorter N170 latencies toward sad versus neutral stimuli, and larger P250 amplitudes toward sad versus neutral stimuli in neurotypical controls. In addition, we expect latencies toward mouth stimuli to be shorter than toward the eye stimuli in neurotypical controls, given the research highlighted above.

We also expect to see differences in the latency or amplitude of the N170 and the P250 between the ASD, ADHD and anxiety group versus the neurotypical controls, if a social processing deficit exists in these groups. Specifically, we expect to see a pattern of earlier N170 latencies and lower amplitudes in the ASD group (particularly for the ‘eye’ stimuli), given the research outlined above, but we do not expect to see the same effect for the P250 component. We expect to see a reduction in the overall latency and amplitude of the P250 toward the stimuli in the ADHD group versus neurotypical controls, but not the N170. Finally, we expect to see a difference in the latency or amplitude of the N170 or P250 in
those with anxiety, but given the existing body of research does not establish firm ERP patterns in those with anxiety it is unclear where those differences will lie. If these ERP differences are evident in the N170 component, this suggests there is aberrant structural encoding and recognition memory mechanisms. If the ERP differences are evident in the P250 component, then this suggests differences in the analysis and decision making of the facial stimuli.

The overall aim on the thesis is to investigate ASD as a comorbid condition. Thus, if social difficulties are a common feature of all three conditions that have a shared neural basis, then we would expect to see no significant differences in the latency or amplitude of the N170 or the P250 between the ASD pure group and the ASD comorbid groups. However, if these social difficulties stem from different neural networks (suggesting that the disorders are separate conditions) then we would expect to see significant differences in the latency or amplitudes of the N170 or P250 between the ASD pure and the ASD comorbid groups.

4.4 Methods

4.4.1 Subjects

The initial sample consisted of 83 subjects. There were 9 subjects that were excluded from the final analyses: electrical noise \( n = 1 \); incompletion of task \( n = 6 \); extreme outliers \( n = 2 \). The final sample consisted of 74 subjects and were split into experimental groups according to their diagnosis given by a registered medical professional (ADHD \( n = 22 \); anxiety \( n = 12 \); ASD \( n = 20 \); control \( n = 20 \)). All subjects had normal or corrected-to-normal vision and no history of head injury. The overall sample consisted of 38 females and 36 males. However, within each group the gender ratio was not evenly split (see Table 4.1). This is in line with literature which suggests autism has a 4.3:1 ratio for males to females (Newschaffer et al., 2007), and anxiety is much more common in females than males (Lowe
et al., 2008; Matza et al., 2011). The mean age of all participants was 25.88 years, with a range from 16.3 years to 54.2 years.

Table 4.1. Mean age, IQ and gender distribution, with standard deviations, for each experimental group in the social information processing study.

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Anxiety</th>
<th>ASD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>26.72</td>
<td>(7.81)</td>
<td>25.99</td>
<td>(8.13)</td>
</tr>
<tr>
<td>IQ</td>
<td>117.95</td>
<td>(8.20)</td>
<td>117.3</td>
<td>(8.46)</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

4.4.2 Recruitment

Participants were recruited by using advertisements placed around the University of Auckland City Campus and on a participant recruitment website. Subjects were also recruited through organisations such as Altogether Autism, the Phobic Trust, the Parent and Family Centre and the ADHD Association. Participants must have no history of head injury, no history of coexisting depression or schizophrenia, be right-handed and have English as their first language. Participants were given $20 in vouchers for their participation in this study.

4.4.3 Diagnoses

Control subjects consisted of mainly undergraduate students and had no history of any psychological illness (e.g., depression, anxiety). Experimental participants were required to have a diagnosis of ASD, ADHD or anxiety that was given by a registered medical professional (i.e., not self-diagnosed). From the 22 subjects in the ADHD group, four had an additional diagnosis of anxiety. In the ASD group, six subjects had a diagnosis of high functioning autism with no coexisting conditions; 10 had a diagnosis of high functioning
autism and coexisting anxiety or OCD, and the remaining four had a diagnosis of coexisting high functioning autism and ADHD. The anxiety group included those with a diagnosis of anxiety or OCD.

4.5 Measures

4.5.1 Behavioural measures

Participants were asked to answer questionnaires that measured specific behaviours. The questionnaires included: 1). The Generalised Anxiety Disorder Scale (Spitzer et al., 2006), which is a brief clinical measure for generalised anxiety; 2). The Obsessive Compulsive Inventory – Revised (OCI), an 18-item questionnaire that measures OCD symptoms (Foa et al., 2002); 3). The Adult ADHD Self Report Symptom Checklist (ASRS; Kessler et al., 2005), an 18-item self-report questionnaire which asks about clinical symptoms of ADHD as reported in the DSM-IV (e.g., “How often do you fidget or squirm when you have to sit down for long periods of time?”); and 4). The autism spectrum quotient (Baron-Cohen et al., 2001) is a 50-item self-report questionnaire that measures autistic-like traits in the typically developing population. See Chapter 2 for a full description of the psychometric properties of each measure.

4.5.2 Stimuli

Stimuli consisted of 105 x 47 pixel images from the Mind Reading Emotions Library (Baron-Cohen et al., 2003). Images were sections of the eye or mouth regions and were presented in black and white form (see Figure 4.1). Stimuli were presented using E-prime version 2.0 software (Schneider, Eschman, & Zuccolotto, 2002) and were displayed on a colour computer monitor with a screen resolution of 800 x 600 pixels. E-Prime also recorded the percent correct and response time information from each participant. Participants with a
accuracy rate of less than 60% were excluded from analysis. Overall, participants responded with the correct response 72.47% of the time.

Figure 4.1. An example of stimuli presented for the social information processing experiment. The sad stimuli are above, with the neutral stimuli below.

### 4.6 Procedure

The paradigm used in the current study was modelled after that in O’Connor, Hamm and Kirk (2005). The total experiment consisted of three trial blocks plus one practice block. Each block consisted of 56 trials (14 for each condition), making the total number of trials for each participant 168. Initially, a white screen with a black fixation cross in the centre of the screen appeared at a varying interval of 600-1000ms. The stimulus then appeared in the centre of the screen with a white background for 600ms. This was followed by a 700ms inter-stimulus interval (a blank white screen), then the response slide was displayed that prompted participants to respond. Only sad and neutral emotions were selected for use, as mentioned in above, sad faces elicit a strong emotional response in an individual, whereas a neutral face is emotionless. Participants responded by pressing the “1” key if they thought the expression was sad, or the “2” key if they judged the expression to be neutral. This screen was only terminated upon detection of a response from participants.
CHAPTER FOUR – STUDY TWO: EMOTION PROCESSING AND EEG

4.6.1 EEG acquisition

EEG recordings were conducted in an electrically shielded room (Model L3000; Belling Lee, Enfield, England) using 128-channel Ag/AgCl electrode nets (Tucker, 1993). The Geodesic sensor net distributes electrodes from nasion to inion and from left to right mastoids at uniform intervals. EEG was recorded continuously (1000-Hz sample rate; 0.1–100 Hz analogue bandpass) with Electrical Geodesics Inc. amplifiers (300-MΩ input impedance). A Macintosh computer was used to acquire the data using NetStation software and this was then stored on the computer’s hard disk. Electrode impedances were kept below 40 kΩ, an acceptable level for this system (Tucker, 1993). Common vertex (Cz) was used as a reference, resulting in a total of 129 electrodes.

Triggers were programmed into E-Prime and synchronised with the EEG acquisition software via a parallel port. Triggers were sent as a function of stimulus type (four types: eyes sad, eyes neutral, mouth sad, mouth neutral) at stimulus onset, and again upon response (two types: correct, or incorrect). This resulted in two triggers per trial.

4.6.2 EEG processing

Data was segmented using in-house software (WinView) into ERP waveforms with any artefacts removed according to the guidelines set out in (Jervis et al., 1985). EEG data was segmented as a function of trigger type. Data included both correct and incorrect trials to increase power (results were not significantly different when incorrect trials were omitted). Each epoch was centred on the stimuli trigger (i.e., the trigger that was sent when the stimuli was displayed). Each epoch was 100ms pre stimulus and 500ms post-stimulus giving a total epoch segments of 600ms. Artefact rejection was done on a trial-by-trial basis. Any epochs with bad channels, eye blinks, too much drift or noise were discarded from analyses using the parameters described in Gratton and colleagues (2008). From the 168 trials for each
participant, 152.33 epochs on average were accepted. Epochs were re-referenced to average reference as a function of expression (sad, neutral) and area (mouth, eyes) giving a total of four ERP’s. These ERP’s were then grand-averaged and filtered using a 30-Hz low-pass Butterworth Filter (Alarcon, Guy, & Binnie, 2000).

4.6.3 ERP analysis

The four grand averaged waveforms for each participant were visually inspected for the N170 and the P250 components. As noted earlier, the N170 is a large negative deflection at occipito-temporal sites approximately 140 - 190ms after stimulus onset (Eimer, 2000). The N170 differs as a function of emotional significance, reflective of the differential processing of emotionally significant stimuli. The P250 is a positive ERP component that follows the N170 at about 200-300ms post stimulus (Marzi & Viggiano, 2007). The P250 involved in the late stages of analysing visual information and decision making (Mikhailova & Davydov, 1999). The electrodes selected were 58, 59, 64, 65, 69, 70, 90, 91, 92, 95, 96 and 97. A montage of electrodes can be seen in Chapter 2, Figure 2.1. These electrodes are located in the occipito-temporal region and are consistent with the electrodes used in similar research (e.g., McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; O’Connor et al., 2005). From each ERP the amplitude and latency of the N170 (i.e., the first, most negative, deflection between 140-190 ms) and the P250 (i.e., the first positive component following the N170, 200-300ms after stimulus onset) was collected for each participant. These peaks were selected by visual inspection of the ERP waveform.

4.6.4 Statistical analysis

Data were analysed using SPSS version 20 software. All alpha levels were set at the .05 level, unless otherwise stated. The main statistical techniques used were ANOVA (with Bonferroni post hoc tests), t-tests and Pearson correlations. Initial data screening revealed
violations of skewness and kurtosis for latencies only (See Appendix J for a full description of data screening). Removal of extreme outliers ($n = 2$) put the skewness and kurtosis values within an acceptable range (Field, 2013).

4.7 Results

4.7.1 Behavioural data

Data collected from the E-prime files gave information on the percentage of correct judgements (i.e., correct identification of the expression, sad or neutral) and the time taken to respond. All means and standard deviations are listed in Table 4.2.

A one-way ANOVA was conducted to see if mean percent accuracy (for each region and overall) differed between experimental groups (four levels: ADHD; anxiety; ASD and controls). The effect of group on overall accuracy was approaching significance, $F(3,70) = 2.31, p = .084$. The ADHD group was less accurate than the control group ($p = .098$).

A one-way ANOVA was conducted to see if mean response time (for each region and overall) differed between experimental groups (Four levels: ADHD; anxiety; ASD and controls). There were significant effects for: sad mouth, $F(3,70) = 4.37, p = .007$; neutral mouth, $F(3,70) = 3.91, p = .012$; eyes neutral, $F(3,70) = 2.95, p = .039$; eyes sad, $F(3,70) = 5.50, p = .002$ and overall response time, $F(3,70) = 4.54, p = .006$.

For the mouth sad region the control group were faster to respond than the ADHD group ($p = .021$), and the anxiety group ($p = .017$). For the mouth neutral region, the control group were faster to respond than the ADHD group ($p = .042$), and the anxiety group ($p = .022$). For the eyes neutral region the control group were faster to respond than the anxiety group, ($p = .048$). For the eyes sad region the control group, was faster to respond to the anxiety group, ($p = .004$), the ASD group ($p = .011$). In addition, the control group were
faster than the ADHD group ($p = .052$). For overall response time, the control group was faster to respond than the ADHD group ($p = .034$), and the anxiety group, ($p = .009$).

4.7.2 EEG analyses

Mixed ANOVAs were used to investigate if there were differences in latency or amplitude of the N170 between or within groups, area (i.e., eyes or mouth) or expression (i.e., sad or neutral). A second, mixed ANOVA was conducted to investigate if there were differences in the P250 between or within groups. Both the latency and amplitudes for each group, in each condition, can be seen in Figures 4.2-4.5.

Gender could not be included as an independent variable in the main analyses due to small samples. Preliminary analysis using a 2 (gender) x 2 (area: eyes, mouth) x 2 (expression: sad, neutral) mixed ANOVA found that gender was only involved in a significant main effect, $F(1,65) = 8.80, p = .004$, where females ($M = 173.46, SE = 2.41$) had shorter overall latencies than males ($M = 184.28, SE = 2.73$). Importantly, no interaction effects were found; therefore, we felt it was acceptable to leave gender out of the main analyses.

To investigate comorbidity, exploratory t-tests were conducted. This was due to small samples sizes in each of the groups. Due to the exploratory nature of these tests, results of these analyses must be interpreted with caution.
Table 4.2. Means and standard deviations of accuracy and response time, for each experimental group, in each condition.

<table>
<thead>
<tr>
<th>Area</th>
<th>ADHD</th>
<th>ADHD</th>
<th>ASD</th>
<th>ASD</th>
<th>Control</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Mouth Sad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>514.23</td>
<td>270.62</td>
<td>554.90</td>
<td>248.97</td>
<td>446.63</td>
<td>171.84</td>
</tr>
<tr>
<td>Accuracy</td>
<td>50.43</td>
<td>17.24</td>
<td>59.52</td>
<td>17.05</td>
<td>49.56</td>
<td>17.90</td>
</tr>
<tr>
<td>Mouth Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>487.48</td>
<td>239.11</td>
<td>535.67</td>
<td>252.37</td>
<td>446.78</td>
<td>178.51</td>
</tr>
<tr>
<td>Accuracy</td>
<td>85.06</td>
<td>10.60</td>
<td>81.94</td>
<td>8.70</td>
<td>84.64</td>
<td>13.26</td>
</tr>
<tr>
<td>Eyes Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>525.08</td>
<td>268.22</td>
<td>606.30</td>
<td>341.13</td>
<td>509.25</td>
<td>242.23</td>
</tr>
<tr>
<td>Accuracy</td>
<td>69.51</td>
<td>27.04</td>
<td>68.45</td>
<td>18.64</td>
<td>76.43</td>
<td>22.78</td>
</tr>
<tr>
<td>Eyes Sad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>467.10</td>
<td>183.44</td>
<td>553.52</td>
<td>258.11</td>
<td>503.52</td>
<td>195.69</td>
</tr>
<tr>
<td>Accuracy</td>
<td>75.78</td>
<td>19.76</td>
<td>85.05</td>
<td>8.74</td>
<td>75.60</td>
<td>17.20</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response time</td>
<td>498.47</td>
<td>220.68</td>
<td>562.60</td>
<td>250.89</td>
<td>476.55</td>
<td>188.47</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>70.20</td>
<td>8.10</td>
<td>73.74</td>
<td>6.90</td>
<td>71.56</td>
<td>5.12</td>
</tr>
</tbody>
</table>

105
Figure 4.2. Grand average ERP waveform for each experimental group toward the sad eye stimuli. The N170 and the P250 components are labelled.

Figure 4.3. Grand average ERP waveform for each experimental group toward the neutral eye stimuli.

Figure 4.4. Grand average ERP waveform for each experimental group toward the sad mouth stimuli.
4.7.3 Latency

A 4 (experimental group: ADHD; anxiety; ASD; control) x 2 (area eyes, mouth) x 2 (expression: sad or neutral) mixed ANOVA was conducted to investigate whether there was an effect on the latency of the N170. There was a significant main effect of area on latencies, $F(1, 69) = 151.08, p < .001$. Latencies to the eye area stimuli were significantly shorter ($M = 174.50, SE = 1.77$) than the mouth area ($M = 182.44, SE = 1.79$). There was also a significant effect of expression, $F(1, 69) = 17.96, p < .001$, where latencies were shorter to neutral expressions ($M = 177.71, SE = 1.72$) than sad expressions ($M = 179.22, SE = 1.79$).

There was a significant interaction between area and expression, $F(1, 69) = 25.81, p < .001$. Latencies to sad eyes ($M = 176.29, SE = 1.78$) were longer than toward neutral eyes ($M = 172.70, SE = 1.81$), but not between the mouth areas. In addition, latencies were significantly longer toward the mouth ($M = 182.15, SE = 1.88$) than the eyes ($M = 176.29, SE = 1.78, p < .001$) for the sad stimuli. Latencies were also significantly longer toward the mouth ($M = 182.72, SE = 1.74$) than the eyes ($M = 172.70, SE = 1.81, p < .001$) for the neutral stimuli, as seen in Figure 4.6.

Figure 4.5. Grand average ERP waveform for each experimental group toward the neutral mouth stimuli.
Figure 4.6. Significant interaction between area and expression of the N170.

A 4 (experimental group: ADHD; anxiety; ASD; control) x 2 (area: eyes or mouth) x 2 (expression: sad or neutral) mixed ANOVA was conducted on the latency of the P250. There was a significant main effect of area on latencies, $F(1, 70) = 12.21, p = .001$. Latencies toward the mouth stimuli ($M = 245.09, SE = 3.11$) were significantly longer than toward the eye stimuli ($M = 239.16, SE = 2.76, p = .001$). There was a significant interaction between area and expression, $F(1, 70) = 16.56, p < .001$. Latencies toward the neutral stimuli ($M = 248.42, SE = 3.13$) were significantly longer than to sad stimuli ($M = 241.75, SE = 3.36, p < .001$) in the mouth area, but not the eye area (see Figure 4.7). In addition, latencies toward eye stimuli ($M = 237.80, SE = 2.91$) were significantly lower than toward mouth stimuli in the neutral condition ($M = 248.42, SE = 3.13, p = .001$), but not the sad condition.
There was also an interaction between area and experimental group, $F(3, 70) = 2.20, p = .096$. Latencies toward the mouth stimuli were significantly longer than toward eye stimuli in the control ($p = .040$), ASD, ($p = .002$) and approaching in the anxiety groups ($p = .088$), but not in the ADHD group (see in Figure 4.8). In addition, the difference between the ADHD and anxiety group toward eye stimuli was approaching significance ($p = .073$). Means and standard errors are listed in Table 4.3.
Table 4.3. Means, with standard errors, of latencies toward the eye and mouth stimuli for each experimental group.

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Mean (SE)</th>
<th>ADHD</th>
<th>Mean (SE)</th>
<th>ADHD</th>
<th>Mean (SE)</th>
<th>ADHD</th>
<th>Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250.93</td>
<td>4.92</td>
<td>anxiety</td>
<td>229.58</td>
<td>6.67</td>
<td>ASD</td>
<td>242.65</td>
<td>5.17</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td></td>
<td>233.46</td>
</tr>
<tr>
<td>Mouth</td>
<td>250.48</td>
<td>5.54</td>
<td></td>
<td>236.67</td>
<td>7.50</td>
<td></td>
<td></td>
<td>240.09</td>
</tr>
</tbody>
</table>

4.7.4 Amplitude

A 4 (experimental group: ADHD; anxiety; ASD; control) x 2 (area: eyes or mouth) x 2 (expression: sad or neutral) mixed ANOVA was conducted on the amplitude of the N170. As shown in Figure 4.9, the results show a main effect of area, $F(1, 69) = 4.48, p = .038$, where amplitudes to mouth stimuli ($M = -2.84, SE = .44$) were significantly smaller than amplitudes to eye stimuli ($M = -3.13, SE = .42$). There were no other significant effects.

**Figure 4.9.** Significant main effect of latencies toward mouth and eye areas of the N170.

A 4 (experimental group: ADHD; anxiety; ASD; control) x 2 (area: eyes or mouth) x 2 (expression: sad or neutral) mixed ANOVA was conducted on the amplitude of the p250.
There was a significant main effect of expression on amplitudes, $F(1, 70) = 34.63, p < .001$, where amplitudes to the neutral stimuli ($M = 4.24, SE = .335$) were significantly larger than toward sad stimuli, ($M = 3.66, SE = .35$). There was also an interaction between area and experimental group, $F(3, 70) = 6.58, p = .001$. The ASD group had significantly larger amplitudes toward the mouth than the eye stimuli ($p = .003$) (see Figure 4.10). The ADHD group had significantly larger amplitudes toward the eye than the mouth stimuli ($p = .004$). Amplitudes toward the eye or mouth stimuli were no different in the anxiety or control groups (both $p > .05$). In addition, amplitudes toward mouth stimuli were approaching significance between the ASD and ADHD groups ($p = .055$). Means and standard errors are listed in Table 4.4.

Figure 4.10. Significant interaction between area and experimental group, where the ADHD and ASD groups had significantly different amplitudes of the P250, but not the anxiety or control groups.
Table 4.4. Means, with standard errors, of amplitudes toward the eye and mouth stimuli for each experimental group.

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Anxiety</th>
<th>ASD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Eyes</td>
<td>3.27</td>
<td>0.61</td>
<td>3.53</td>
<td>0.82</td>
</tr>
<tr>
<td>Mouth</td>
<td>2.66</td>
<td>0.61</td>
<td>3.21</td>
<td>0.83</td>
</tr>
</tbody>
</table>

4.7.5 t-tests

An independent samples t-test was conducted to investigate whether amplitudes of the N170 differed within subjects with ASD, depending on if they had pure ASD or coexisting ASD. Given the small sample size in the comorbid group, there was not enough statistical power to separate those with coexisting ADHD or anxiety. This limitation is mentioned in the discussion. The results revealed that within the ASD group, those with ASD only (\(M = -5.37, SD = 2.85\)) had significantly larger N170 amplitudes to the neutral eye stimuli than those with comorbid ASD, (\(M = -1.72, SD = 3.11, t(18) = 2.46, p = .024\)). Those with ASD only (\(M = -5.07, SD = 3.91\)) had larger amplitudes to the sad eyes stimuli than the ASD coexisting group (\(M = -1.77, SD = 3.27, t(18) = 1.95, p = .067\)), an effect that was approaching significance. These effects are shown in Figures 4.11 and 4.12.
Figure 4.11 Grand average waveform of the ASD pure and comorbid groups in the eyes sad condition. The difference in the N170 between groups is significant.

Figure 4.12 Grand average of the ASD pure and comorbid groups in the eyes neutral condition. The difference between groups on the N170 component is significant.

An independent samples t-test was conducted to investigate whether amplitudes of the P250 differed within subjects with ASD, depending on if they had pure ASD or coexisting ASD. The results revealed that there were no significant differences between groups in any condition (all $p > .05$).

4.7.6 Correlations

Pearson’s correlations were run between the profiling measure and the latencies and amplitudes of the eyes task to determine whether there was a relationship between these
variables. As there were multiple correlations conducted we do need to be mindful of a Type 1 Error. Therefore, the following results must be interpreted with caution. For the amplitudes, there was only significant negative correlation between scores on the OCI and amplitudes toward the neutral eye stimuli and the sad mouth stimuli. For the latencies, there was only a significant negative correlation between scores on the ASRS and sad eye stimuli. A full list of correlation coefficients can be seen in Tables 4.5 and 4.6.
### Table 4.5. Correlations between the N170 amplitudes of each condition and the profiling measures.

<table>
<thead>
<tr>
<th></th>
<th>Generalised Anxiety Disorder</th>
<th>Obsessive Compulsive Inventory</th>
<th>Adult Self-Report ADHD scale</th>
<th>Autism Spectrum Quotient</th>
<th>Eyes Sad</th>
<th>Eyes Neutral</th>
<th>Mouth sad</th>
<th>Mouth Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised Anxiety Disorder</td>
<td>1</td>
<td>.65**</td>
<td></td>
<td>.35**</td>
<td>.29**</td>
<td>-0.14</td>
<td>-0.15</td>
<td>-0.16</td>
</tr>
<tr>
<td>Obsessive Compulsive Inventory</td>
<td>1</td>
<td>.24*</td>
<td>.29**</td>
<td>-0.21</td>
<td>-.24*</td>
<td>-.25*</td>
<td>-.17</td>
<td>-.15</td>
</tr>
<tr>
<td>Adult Self-Report ADHD scale</td>
<td>1</td>
<td>0.08</td>
<td>-0.17</td>
<td>-0.15</td>
<td>-0.18</td>
<td>-0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism Spectrum Quotient</td>
<td>1</td>
<td></td>
<td>-0.10</td>
<td>-0.10</td>
<td>-0.11</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes Sad</td>
<td>1</td>
<td>.96**</td>
<td></td>
<td>.94**</td>
<td>.92**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes Neutral</td>
<td>1</td>
<td></td>
<td>.93**</td>
<td>.91**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth sad</td>
<td></td>
<td>1</td>
<td></td>
<td>.92**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth Neutral</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
Table 4.6. Correlations between the N170 latencies in each condition and the profiling measures.

<table>
<thead>
<tr>
<th></th>
<th>Eyes Sad</th>
<th>Eyes Neutral</th>
<th>Mouth Sad</th>
<th>Mouth Neutral</th>
<th>Generalised Anxiety Disorder</th>
<th>Obsessive Compulsive Inventory</th>
<th>Adult Self-Report ADHD scale</th>
<th>Autism Spectrum Quotient</th>
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</thead>
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<td>.93**</td>
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<td>.91**</td>
<td>-0.16</td>
<td>-0.16</td>
<td>.24*</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
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<td>-0.11</td>
<td>0.21</td>
<td>0.19</td>
<td>0.12</td>
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</tr>
<tr>
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<td></td>
<td>0.15</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td>.65**</td>
<td>.35**</td>
<td>.29**</td>
<td></td>
</tr>
<tr>
<td>Obsessive Compulsive Inventory</td>
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<td>.24*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.29**</td>
<td></td>
</tr>
<tr>
<td>Adult Self-Report ADHD scale</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td></td>
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<tr>
<td>Autism Spectrum Quotient</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
4.8 Discussion

The overall aim of the study was to investigate whether those with ASD, ADHD and anxiety have brain-based differences in social information processing. In addition, we sought to understand whether this deficit was shared by those with coexisting ASD and ADHD or anxiety versus those with pure ASD. In general, we expected to see longer ERP latencies toward the mouth stimuli than for eye stimuli for controls. We also expected shorter N170 latencies toward sad versus neutral stimuli, and larger P250 amplitudes toward sad versus neutral stimuli in neurotypical controls. This is because the mouth is a less salient feature of the face than the eyes (Riby, Doherty-Sneddon, & Bruce, 2009), and therefore is more difficult to decipher the emotions portrayed. We are also faster to recognise sad versus neutral emotions (Taylor et al., 2001), and sad emotions require a higher level of processing than neutral emotions (Blair, Morris, Frith, Perrett, & Dolan, 1999).

We also expected to see differences between experimental groups versus controls, particularly with the ASD group. Earlier research has demonstrated that those with ASD do not show a different response to fearful versus neutral facial stimuli, as seen in neurotypical controls (Dawson et al., 2004a), and aversion to eye gaze is part of the diagnostic criteria for the condition (American Psychiatric Association, 2013). Additionally, those with anxiety show earlier N170 latencies and smaller amplitudes toward emotion-based stimuli than neurotypical controls (Mühlberger et al., 2009), and those with ADHD may show a reduction in latency and amplitude toward emotional based stimuli in early ERP components, as opposed to neurotypical controls (Rossignol et al., 2005; Tye et al., 2014).

4.8.1 The P250 component

The most interesting ERP finding in the present study was in the analysis of the P250 component. The latencies of the ASD and control groups were significantly longer toward
mouth versus eye stimuli, but this ‘face’ effect was not present in the ADHD group. In addition, there was a pattern of longer latencies toward mouth versus eye stimuli in the anxiety group that was approaching significance. This suggests that there is faster processing for eye over mouth stimuli in the ASD and control groups (and probably the anxiety group), but not the ADHD group.

We expected to see an “eye preference” in neurotypical controls, reflected by the latency of the P250. This finding is in line with previous literature that demonstrates that the eyes are the most salient in portraying different moods and thus are processed more quickly in emotion processing tasks (Batty & Taylor, 2003). However, we did not expect that the ASD group would share this early processing for the eyes over the mouth, given that those with ASD have an aversion to eye contact (Tottenham et al., 2014), and show specific deficits when manipulating information related to the eyes rather than the mouth area (Riby et al., 2009). Research has demonstrated that those with high functioning autism demonstrate hypersensitivity, as measured by P50 latencies (which reflects early visual and sensory processing of information) to visual stimuli (Baruth, Casanova, Sears, & Sokhadze, 2010). While this effect is usually present in earlier ERP components, it is possible that in the current study, the early latencies toward eye stimuli reflect the hypersensitivity associated with ASD. The behavioural aversion to eye contact in ASD may be driven by a hypersensitivity to eye stimuli.

A lack of differentiation between the eye and mouth stimuli for the P250 latency was observed in the ADHD group but not in the neurotypical controls. One reason for this might be because those with ADHD have difficulties in their attentional capacity (American Psychiatric Association, 2013), which may be extended to areas of the face. An EEG study investigating the N170 toward facial stimuli in those with ADHD found that, while the component was sensitive in neurotypical controls toward facial stimuli versus non-facial
stimuli, this effect was not present in those with ADHD (Ibáñez et al., 2011). Thus, it is possible that the attentional difficulties in ADHD preclude preferential processing of the eye versus mouth stimuli as seen in neurotypical controls.

We also found that the ASD and ADHD groups had opposite profiles on the amplitude of the P250. Those with ASD had larger amplitudes toward mouth stimuli than eye stimuli and those with ADHD had larger amplitudes toward eye stimuli toward mouth stimuli. This is in line with previous ERP literature that has differentiated those with ASD and ADHD using an emotion processing task (Tye et al., 2014). While previous research has investigated the N170 and the P300 components in-depth, there is relatively little research on the P250 component. The results of the current study demonstrate that the P250 is an important component in face processing. The P250 is specifically associated with the analysis and decision making (e.g., what emotion the stimuli is displaying) of facial stimuli (Spironelli & Angrilli, 2009). As mentioned earlier, larger amplitudes reflect more neural resources being devoted to that specific process (Barcelo, Suwazono, & Knight, 2000; Dawson et al., 2005), and are associated with a higher amount of cognitive effort. Therefore, the current study differentiates those with ASD and ADHD using the P250 component. Those with ASD devote less neural resources to the analysis of eye stimuli, and those with ADHD devote less neural resources to the analysis of mouth stimuli. The findings for each group will now be elaborated on.

Those with ASD had larger amplitudes toward mouth versus eye stimuli. This fits with the behaviour of those with ASD, which includes an aversion to eye contact (American Psychiatric Association, 2013). It is also in line with research showing lower amplitudes for later ERP components during facial recognition tasks in those with ASD (Dawson et al., 2005). However, the ASD group displayed a pattern of latencies toward the eye stimuli similar to that of neurotypical controls. Together, this suggests that although those with ASD
were sensitive to the recognition of eye stimuli, the amount of neural resources dedicated
toward the analysis of the eye stimuli was much less than controls. These results fit with the
hypersensitivity hypothesis discussed above, where those with ASD have faster latencies
toward eye stimuli but do not devote neural resources to process this stimuli, which might
result in a behavioural aversion to eye contact.

An opposite profile was found in the ADHD group, where amplitudes were higher
toward eye than mouth stimuli. This finding is in line with a study by Da Fonseca et al., who
found an overall deficit for emotion processing in ADHD (Da Fonseca, Seguier, Santos,
Poinsot, & Deruelle, 2009). Larger amplitudes may reflect the greater amount of attention
needed to process information from the eyes, given that those with ADHD have well
documented deficits in attentional capacity (American Psychiatric Association, 2013). As
there is more mood and emotion portrayed through the eyes than other facial features (Riby et
al., 2009), it is plausible that those with attentional difficulties require a higher level of
concentration and cognitive effort to process this information and make a decision on the
emotion portrayed. Therefore, deficits in emotional processing in ADHD may be explained
by a lack of attention to the cues given from faces. To this end, research has shown that
forced eye contact in those with ADHD improved compliance with parental command
(Kapalka, 2004). This demonstrates that assisting those with attentional difficulties to pay
attention to the cues given from the eyes (e.g., I am angry with you, I am sad) helps to reduce
core behavioural difficulties in ADHD.

4.8.2 The N170 component

The ERP analysis did not reveal differences between those with ADHD, ASD, anxiety
or controls on the latencies or amplitudes for the N170. This finding was unexpected, given
that other studies have demonstrated a smaller and earlier N170 in those with ASD compared
to controls (O’Connor et al., 2005; Tye et al., 2014). The discrepancies in these findings might be explained by the pool of participants used in the current study. For example, an EEG study using a mismatch negativity paradigm (measuring a deviant stimulus in amongst a sequence of ‘standard’ stimuli) found that higher scores on the Autism Spectrum Quotient was also related to lower amplitudes for happy, but not sad emotional stimuli (Gayle, Gal, & Kieffaber, 2012). Given that the participants in the current study had high functioning autism, it is possible that the N170 effects were not apparent given the milder nature of their ASD symptoms.

It is also possible that this unexpected finding is due to our small sample size. Visual inspection of the ERP waveforms do hint that a group difference in the N170 may have been evident with a larger sample size. Therefore, this unexpected finding may be due to lack of statistical power. However, if this is a true effect then together with the results of the P250 analyses discussed earlier, the results of the current study suggest that those with ASD and ADHD do not differ in their ability to detect emotion based stimuli (reflected by the N170). Instead, those with ASD and ADHD process emotion-related information given by faces differently to neurotypical controls, and to each other.

Overall, N170 latencies were shorter to eye than to mouth stimuli, and shorter to neutral rather than sad expressions. This finding was in line with what we expected, given the following findings: shorter latencies to eye stimuli have been posited to reflect automaticity of processing for the eye stimuli over other facial features (O’Connor et al., 2005); sad expressions take longer to process than a neutral expression (given the time taken to process the mood); and that positive emotions are processed more quickly than negative emotions (e.g., Batty & Taylor, 2003; Leppänen & Hietanen, 2004). Finally, latencies are shorter in females than males. It is well established that females have a processing advantage over males for recognising both positive and negative emotions (e.g., Hampson, van Anders, &
Mullin, 2006; Schirmer, Kotz, & Friederici, 2002). While these findings do not answer the current research question, findings consistent with previous literature demonstrate that the methods used in the current are an appropriate measure of emotion recognition.

### 4.8.3 Behavioural analyses

The behavioural results of the current study showed that, while there are no differences in accuracy between the four experimental groups (which relates to recognition of the different emotions), the control group was significantly faster at responding to each emotion. This effect was most evident between the control group and the ADHD group and anxiety group, less so with the ASD group. This finding is supported by results from the correlational analyses that showed associations between symptoms of ADHD and OCD and amplitudes or latencies of the N170 toward the stimuli. These results will now be discussed in turn.

While those with anxiety were slower at recognising then deciding the emotion, the results of the behavioural analysis revealed that they were no less accurate at recognising the emotions from one another. This finding is consistent with previous research demonstrating that adults with anxiety are not prone to misinterpreting facial expressions (McClure, Pope, Hoberman, Pine, & Leibenluft, 2014). McClure et al., however, did not measure response time. The current study found that those with anxiety may take longer to correctly decipher the emotion. It is well documented that those with anxiety have a bias toward threatening versus neutral facial expressions (e.g., Bradley, Mogg, Falla, & Hamilton, 1998). Therefore, those with anxiety may need longer to process information about emotions as they may have a predisposition to interpret the stimuli as threatening.

The slower response time in those with ADHD may simply be explained by their attentional difficulties (American Psychiatric Association, 2013). It may take longer to decide
on the emotion given that they first need to overcome a predisposition toward inattention to stimuli.

4.8.4 Comorbidity investigation

The second aim of the current study was to investigate whether any potential differences in emotion processing are different when ASD occurs on its own versus together with ADHD or anxiety. This was done by specifically comparing the ERP waveform of those with ASD only versus those with ASD and comorbid ADHD or anxiety. The results revealed larger and earlier amplitudes and latencies of those with ASD only on the N170, but not the P250 toward eye stimuli. This suggests that the early recognition of eye stimuli (as measured by the N170) requires more cognitive effort (as measured by higher amplitude), but this effect is associated specifically with characteristics of ASD (and not ASD or anxiety). This finding is in line with the literature discussed above which shows a similar effect in those with ASD alone. This finding demonstrates the importance of properly screening for comorbid conditions in research studies, as the addition of comorbid conditions washed out this “N170 effect” that would have otherwise been present.

In support of the theory that comorbid conditions wash out any potential effects, correlations conducted on participants’ behavioural characteristics (i.e., scores on the GAD, OCI, ASRS and the ASQ) and their amplitudes show that there is some association between amplitudes and symptoms of OCD, where higher OCD scores (i.e., more OCD symptoms) are associated with lower amplitudes toward the stimuli. This association is the opposite effect of what was found in those with ASD only (where larger amplitudes of the N170 were found in those with pure ASD). Thus, the addition of OCD in ASD lead to lower amplitudes toward the eye stimuli, a neurological profile that is separate from the one demonstrated in pure ASD.
The current data do not support this hypothesis that the behaviour of ADHD or anxiety, when presented as a comorbid condition with ASD, are simply a characteristic of the ASD itself. Should this be true we would have expected to see either no difference between the ASD and ASD comorbid group, or a pattern of ERP’s that are enhanced in the comorbid group versus the pure group (which would suggest more severe ASD). This suggests that additional conditions, when they occur together with ASD, have their own distinct profile rather than being an exaggerated version of ASD.

4.8.5 Potential application of findings

The current study provides researchers with important information about the nature of social information processing in the developmental conditions studied. The current study suggests that it is the processing of emotion-based stimuli that is more affected than the recognition of such stimuli in ADHD and ASD. This information is useful not only for researchers, but also practitioners who can target behavioural therapies to the specific deficits of each condition. For example, teaching children with ASD to process information given by the eye area (i.e., to elaborate on why a person would be showing such an emotion), rather than to simply recognise an emotion (i.e., what emotion is this), could help to improve eye contact in these children. This may in turn lead to better overall social functioning. In addition, training those with ADHD to pay attention to the eye area may reduce behavioural difficulties as they may not be attending to the social cues given by others. Thus, treatments for difficulties identifying social information can be targeted accordingly in young children with the condition.

4.8.6 Limitations

Unfortunately, the current study had a relatively small sample size. An increased sample size would have resulted in more statistical power. This, in turn, may have revealed
differences between the groups in the main ANOVA analysis. As such, interpretations based on the results of the analyses should be treated with some caution. Secondly, the participants in the current study had a diagnosis of high functioning autism. As those with high functioning autism typically show less severe symptoms of autism, it is possible that this ‘weakened’ symptomology was also reflected in brain activity, and contributed to the lack of group differences.

It is possible that some participants in this study were not able to hold their attention for the duration of the experiment, given the nature of their difficulties. To address this possibility, the current study recorded correct versus incorrect responses. The analysis revealed no differences in the means for each group, indicating that all groups paid enough attention to the stimuli to answer correctly the same amount of time. Those with a percentage of correct responses at the chance level were also excluded from analysis. In addition, the number of trials was carefully selected to give the maximum balance between maintaining the attention of participants with known attentional difficulties, and maintaining statistical power. Given the smaller number of trials, it was decided to only focus on two emotions. While this still provides important information about emotion processing, a larger-scale study with a wider range of emotions would have provided more in-depth findings. While the relatively small number of trials for an ERP study may have contributed to less overall power, we believe that it was not plausible to ask participants to complete more trials, given the nature of their difficulties.

Finally, EEG recording gives researchers valuable information about the temporal resolution of brain activity, but less information about the spatial resolution. While event-related potentials can give us information about processing speed and the size of an effect, it gives us less information about the brain structures driving this effect. Therefore, while we can conclude that a difference in brain activity exists, we cannot determine with certainty the
anatomical structures involved in this effect. Future research investigating the nature of coexisting conditions could utilise both structural and functional imaging methods simultaneously to better understand the brain basis of these conditions.

4.8.7 Summary and future directions

The results of the current study did not find differences in the recognition of emotion-based stimuli in ADHD, anxiety and comorbid ASD, compared to neurotypical controls as measured by the N170. Instead, later ERP components (the P250) reveal that those with ASD and ADHD show a different profile to neurotypical controls, and to each other, on the encoding and decision making process in emotion processing tasks. Firstly, this demonstrates the importance of the P250 component in emotion processing literature, especially with atypical subjects. Secondly, this finding gives us a basis on which to distinguish the difficulties evident in ASD and ADHD. While no differences were found in the large group analysis of the N170, this component was altered when investigating those with pure ASD versus those with comorbid ASD. This differential neurological profile of those with pure versus comorbid ASD suggests that comorbid with ADHD and anxiety with ASD are separate conditions. However, a larger scale study is needed to fully confirm these suspicions.

While ERP’s provide information about the amount and timing of neural resources involved in a task, they do not tell us enough about the underlying brain structures involved. Future research utilising both EEG and neuroimaging methods (such as fMRI) concurrently would provide such information. Further research into the treatment of emotion processing deficits in ADHD and ASD would also help to improve social functioning in those affected, which may in turn improve their day-to-day functioning.
5.1 Study Overview

This study sought to clarify the nature of lexical decision making information processing, using a lexical decision paradigm, in four groups: ASD; ADHD; anxiety; and neurotypical controls, when they occur alone versus together as a comorbid condition. This is part of a larger research to clarify to nature of comorbidity in ASD. The lexical decision paradigm used in the current study was a basic go / no-go task where participants had to choose whether a word presented on screen was a real English word or a non-word (or pseudoword). The main technique used in the current study was ERP analysis using EEG. The P100 and the N170 ERP components were the focus of the analyses. Overall, we found larger P100 amplitudes in the right (relative to the left) hemisphere in neurotypical controls. This early ERP component likely reflects pre-linguistic processing (e.g., the sorting of nouns into categories) at a stage before the left hemisphere, which is specialised for language, takes over. We also found that those with ADHD had longer P100 latencies than both the anxiety and ASD groups towards all lexical stimuli. The ADHD group also showed smaller amplitudes toward word stimuli than toward pseudowords and nonwords. The ASD and ADHD group had significantly longer latencies towards pseudowords than the pure-ASD group. A unique pattern of ERPs was therefore observed in the comorbid group, which suggests that the two conditions are separate. This finding is in accord with the latest revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

5.2 Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition for which there is no known cause or cure. Autism is a highly variable disorder, the most prominent difficulties of which include aberrant behaviour, poor social skills and disrupted
communication skills (American Psychiatric Association, 2013). Difficulties in social communication and interaction feature in the diagnostic criteria for ASD (American Psychiatric Association, 2013). While language difficulties are a core characteristic of autism, like the disorder itself, linguistic functioning can be highly variable within those on the spectrum. Some children develop fluent speech while others never begin to speak at all. Verbal and nonverbal communications are vital the formation of social interactions (Cicourel, 1974), and thus, any investigation into the nature of linguistic difficulties in ASD may help us to further understand basis of the condition.

5.2.1 Language difficulties in ASD, ADHD and anxiety

Interestingly, impediments in linguistic information processing have also been documented in ADHD (Carter & Scherer, 2013), a condition that commonly occurs together with ASD. Investigating the shared nature of linguistic processing difficulties (if any) in conditions that commonly occur together will contribute to a larger research effort to identify whether coexisting conditions in ASD stem from the same basis (i.e., are additional conditions simply characteristics of the ASD itself), or are entirely separate conditions (i.e., the coexisting conditions are true separate conditions).

Difficulties with language in ASD may be driven by poor language acquisition and processing. These include problems with phonology (Schoen et al., 2011); semantics (Brook & Bowler, 1992); syntax (Cantweil et al., 1978) and prosody (McCann et al., 2007). Those with ADHD (see Chapter 2 for full diagnostic criteria) are known to have pragmatic language deficits and are significantly more likely to have a language disorder such as Specific Language Impairment or dyslexia (Camarata & Gibson, 1999), a profile that is also seen in ASD (Geurts & Embrechts, 2008). These difficulties contribute to problems with academic achievement and cognition in ADHD (Cohen et al., 2000). To the best of our knowledge,
there are no known deficits in linguistic information processing in those with generalised anxiety disorder. ADHD and anxiety commonly occur together with ASD as a comorbid condition (Simonoff et al., 2008). Exploration of a core deficit evident in both conditions will assist to further investigate the shared nature of these conditions when they occur together.

5.2.2 Brain networks involved in language difficulties

While language difficulties in ASD are well documented, there are no clear links to underlying the brain networks involved. fMRI studies show that individuals with autism produce more activation in the Wernicke’s area (located in the superior temporal gyrus and involved in the understanding of speech and language), but less in the Broca’s area (located in the frontal lobe and involved in the production of speech and language) than typically developing controls (Just et al., 2004). This evidence suggests dysfunctional integration of information related to language in autism.

In ADHD, difficulties may be driven by atypical hemispheric laterality. Most right-handed neurotypical adults have left hemisphere dominance for language (Knecht et al., 2000), therefore a more symmetrical pattern of activation or a dominant right hemisphere, is considered atypical. One study demonstrated individuals with ADHD to be impaired in discriminating words and nonwords compared to typically developing controls on a lexical decision task. This impairment was mapped to reduced left hemisphere, and increased right hemisphere involvement during the task compared to neurotypical controls (Hale et al., 2005). A finding that has been replicated using a line bisection task (Rolfe et al., 2008). Research has also found atypical lateralisation of language in those with ASD (Kleinhans, Müller, Cohen, & Courchesne, 2008).
5.2.3 Measuring language difficulties using EEG

A common approach used to investigate how the brain processes stimuli is through the use of electroencephalography (EEG). The event related potentials (ERPs) that are recorded using EEG give information about the speed in which certain stimuli are processed. A typical ERP consists of a waveform of positive and negative deflections which are labelled according to their presentation after stimulus onset. The amplitude at the peak of each positive or negative waveform is argued to index the neural resources devoted to a specific task at any one time (Dawson et al., 2005). Larger amplitudes reflect more neural activity and is correlated with the amount of cognitive effort required (Spironelli & Angrilli, 2009). The onset of each peak after stimulus onset is the latency, and is argued to measure processing speed (Handy, 2005). Early ERP components, such as the N150 which occurs 130-150ms post stimulus, mark the automatic lexical classification of a word (Spironelli & Angrilli, 2009). Late ERP components like the N300 or the N400 are related to phonological and semantic processing, respectively (Grodzinsky, Shapiro, & Swinney, 2000).

ASD children with very disrupted linguistic functioning show markedly smaller N1 amplitudes in response to auditory evoked stimuli than neurotypical controls (Bruneau, Roux, Adrien, & Barthélémy, 1999). Another study which investigated semantic processing in ASD by measuring the N400 component, found that the N400 was significantly higher in neurotypical controls versus those with autism in response to musical or linguistic stimuli (Ribeiro, Valasek, Minati, & Boggio, 2013). Therefore, while there has been research to demonstrate altered N1 and N400 ERPs in autism in response to various auditory stimuli, it is unclear whether the ERP waveform will differ from neurotypical controls in response to a lexical decision task.
In ADHD, ERP research in the absence of specific language impairment is rare. A study that investigated laterality by measuring ERPs in each hemisphere during a simple reaction time experiment found that those with ADHD demonstrated that compared with controls, attention-deficit/hyperactivity disorder-combined participants demonstrated significantly faster left-to-right transfer, whereas attention-deficit/hyperactivity disorder-inattentive participants had significantly slower right-to-left transfer (Rolfe, Kirk, & Waldie, 2007). More information is needed to establish the nature of ERP’s with specific relation to lexical stimuli in ADHD without specific language impairment.

5.3 Aims and Hypotheses

The current study aimed to determine whether there is an underlying neurological difference in the processing of lexical information in any of the three experimental groups compared to neurotypical controls, using a lexical decision paradigm. Additionally, the current study aims to further investigate any shared nature of this difference when looking at those with singular versus those with multiple conditions.

Firstly, we expect to see the shortest latencies and/or larger amplitudes in the left hemisphere for the word condition in the neurotypical controls, given that the left hemisphere is specialised for language processing. We also expect to see shorter latencies and/or larger amplitudes in the right hemisphere, relative to the left, for the ADHD group, given that language previous research has demonstrated that language may not be typically lateralised in ADHD. If language is typically organised in ASD and anxiety then we also would expect to see shorter latencies and/or larger amplitudes in one or more of these groups.

Second, we expect to see shorter latencies for word over nonword stimuli in neurotypical controls. In addition, we expect the P100 and the N170 to be larger in the left hemisphere for word over nonword stimuli. This is because the left hemisphere is specialised
for language processing and therefore real language should show a left preference over nonwords. Given that language is not typically organised in ADHD, we do not expect to see this left hemisphere preference for words over nonwords. Again, if language is typically organised ASD and anxiety then we also would expect to see shorter latencies and/or larger amplitudes in the left hemisphere for word over nonword stimuli in one or more of these groups.

Third, if the comorbid group is better conceived of as one condition and not two, we would expect no significant group differences in either the hemisphere, latency, or the amplitude of the N170 or the P100 (between the ASD-pure and ASD-comorbid groups).

5.4 Methods

5.4.1 Subjects

The initial sample consisted of 83 subjects. There were 10 subjects that were excluded from the final analyses: English not first language $n = 1$; dyslexia $n = 1$; not enough correct trials $n = 8$. The final sample consisted on 73 subjects and were split into experimental groups (ADHD $n = 21$; anxiety $n = 12$; ASD $n = 20$; control $n = 20$). All subjects had normal or corrected-to-normal vision and no history of head injury. The overall sample consisted of 37 females and 36 males. However, within each group the gender ratio was not evenly split (see Table 5.1). This imbalance is in line with literature which suggests autism has a 4.3:1 ratio for males to females (Newschaffer et al., 2007), and anxiety is much more common in females than males (Lowe et al., 2008; Matza et al., 2011). The mean age of all participants was 25.86 years, with a range from 16.3 years to 54.2 years.
Table 5.1. Mean age, IQ and gender distribution for each experimental group in the lexical decision study.

<table>
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<td>26.11</td>
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<td>111.37</td>
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<td>(11.84)</td>
<td>(12.24)</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
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<td>5</td>
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<tr>
<td>Male</td>
<td>9</td>
<td>3</td>
<td>15</td>
<td>20</td>
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5.4.2 Recruitment

Subjects were recruited using advertisements placed around the University of Auckland City Campus and on a participant recruitment website. Subjects were also recruited through organisations such as Altogether Autism, the Phobic Trust, the Parent and Family Centre and the ADHD Association. Once subjects contacted the researcher with their interest in the study, they were given an initial questionnaire to ensure they fit the study criteria. Participants must have no history of head injury, no history of comorbid depression or schizophrenia, be right-handed and have English as their first language. Participants were given $20 in vouchers for their participation in this study.

5.4.3 Diagnoses

Control subjects consisted of mainly undergraduate students and had no history of any psychological illness (e.g., depression, anxiety). Subjects who fell into the experimental groups were diagnosed with their respective conditions by a registered medical professional prior to participation. From the 21 subjects in the ADHD group, four had an additional diagnosis of anxiety. In the ASD group, six subjects had a diagnosis of high functioning autism with no coexisting conditions; 10 had a diagnosis of high functioning autism and
coexisting anxiety or OCD; and the remaining four had a diagnosis of coexisting high functioning autism and ADHD. The anxiety group included those with a diagnosis of anxiety or OCD.

5.5 Measures

5.5.1 Stimuli

Stimuli consisted of black words, or nonwords. The nonword condition was split into two types, legitimate nonwords (i.e., nonwords that follow English language rules) and illegitimate nonwords (i.e., words that do not follow English language rules), as shown in Table 5.2. Thus, there were three conditions in the experiment: real words, pseudowords and nonwords. All words were generated using the MRC Psycholinguistic Database (Wilson, 1998), and consisted of common English nouns. All nonword stimuli were presented using the ARC nonword database (Rastle, Harrington & Coltheart, 2002). All words were either 4 or 5 letters long. Words were presented in black Times New Roman Font point-size 72 in the centre of a blank screen on E-prime software (Schneider et al., 2002) and were displayed on a colour computer monitor with a screen resolution of 800 x 600 pixels. Overall, participants responded with the correct response 94.17% of the time.
Table 5.2. Examples of the stimuli used for each condition in the lexical decision experiment.

<table>
<thead>
<tr>
<th>Real word condition</th>
<th>Pseudoword condition</th>
<th>Nonword condition</th>
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</thead>
<tbody>
<tr>
<td>fruit</td>
<td>whols</td>
<td>cauv</td>
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<tr>
<td>pansy</td>
<td>clett</td>
<td>esuyp</td>
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<td>pizza</td>
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<td>mango</td>
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<td>thumb</td>
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5.6 Procedure

The total experiment consisted of two trial blocks plus one practice block. Each block consisted of 120 trials, making the total number of trials for each participant 240. Participants were asked to respond with a different hand for each block (either left or right hand) and the hand for the first block was counterbalanced among participants (i.e., either respond with left or right hand first). The stimuli appeared on the screen for 800ms and was followed by a 1500ms inter-stimulus interval. The study design followed a ‘go no-go’ paradigm, where participants were asked to respond by pressing the space bar if they thought the word was a real English word, and to not respond if it was a nonword.

5.6.1 EEG acquisition

EEG recordings were conducted in an electrically shielded room (Model L3000; Belling Lee, Enfield, England) using 128-channel Ag/AgCl EGI electrode nets (Tucker, 1993).
CHAPTER FIVE - STUDY THREE: LEXICAL DECISION

The Geodesic sensor net distributes electrodes from nasion to inion and from left to right mastoids at uniform intervals. EEG was recorded continuously (1000-Hz sample rate; 0.1–100 Hz analogue bandpass) with Electrical Geodesics Inc. amplifiers (300-MΩ input impedance). A Macintosh computer was used to acquire the data using NetStation software and this was then stored on the computer’s hard disk. Electrode impedances were kept below 40 kΩ, an acceptable level for this system (Tucker, 1993). Common vertex (Cz) was used as a reference, resulting in a total of 129 electrodes.

Triggers were programmed into E-Prime and synchronised with the EEG acquisition software via a parallel port. Triggers were sent as a function of word type and hand (six in total: real words, pseudowords and nonwords for left and right hands) at stimulus onset, and again upon response (two types: correct, or incorrect), thus resulting in two triggers per trial.

5.6.2 EEG processing

Data was segmented using in house software (WinView) into ERP waveforms with any artefacts removed according to the guidelines set out in (Jervis et al., 1985). EEG data was segmented as a function of trigger type. Data included both correct and incorrect trials to increase power (results were not significantly different when incorrect trials were omitted). Each epoch was centred around the stimuli trigger (i.e., the trigger that was sent when the stimuli was displayed). Each epoch was 100ms pre stimulus and 500ms post-stimulus giving a total epoch segments of 600ms. Artefact rejection was done on a trial-by-trial basis. Any epochs with bad channels, eye blinks, too much drift or noise were discarded from analyses using the parameters outlined by Gratton and colleagues (2008). From the 237 trials for each participant, 217.93 epochs on average were accepted. Epochs were collapsed across hand and re-references to the average as a function of word type (Real word, Pseudoword and nonword) giving a total of three ERPs. These ERPs were then grand-averaged and filtered.
using a 30-Hz low-pass (high pass 0.1) Butterworth Filter (Alarcon et al., 2000). Amplitudes and latencies were selected by visual inspection of the waveform.

5.6.3 ERP analysis

The three grand averaged waveforms for each participant were visually inspected for the P100 and N170 component. The N170 is a large negative deflection at occipito-temporal sites approximately 140 - 190ms after stimulus onset (Eimer, 2000). The electrodes selected for 59, 64, 65, 66, 68, 69, 70, 83, 84, 89, 90, 91, 94 and 95. These electrodes are located in the occipito-temporal region and are consistent with the electrodes used in similar research (e.g., Barber & Carreiras, 2003; Segalowitz & Zheng, 2009). From each ERP the amplitude and latency of the P100 (i.e., the first most positive peak). For the N170, the amplitude and latency of the first most negative peak (i.e., the most negative deflection) was collected for each participant, for each hemisphere (left and right).

5.6.4 Statistical analyses

Data were analysed using SPSS version 20 software. All p-values were considered significant at the .05 level, unless otherwise stated. The main statistical technique used was ANOVA. Initial multivariate analyses showed no significant main effects or interactions with gender. Therefore, analyses were collapsed across this dimension to increase statistical power. All follow-up analyses were conducted with a Bonferonni correction.

5.7 Results

5.7.1 Behavioural analyses

A one way ANOVA was conducted to investigate if there were any differences in accuracy in the three conditions (real word, pseudoword and illegitimate word) for each experimental group. The results show there are no significant differences in accuracy between any of the experimental groups (all $p > .05$).
CHAPTER FIVE - STUDY THREE: LEXICAL DECISION

5.7.2 EEG analyses

Two separate 4 (group) x 2 (hemisphere: left or right) x 3 (condition: pseudoword; real word; illegitimate word) repeated measures ANOVA were conducted on the latency and amplitude of the N170. Results show there are no significant main effects or interactions on either the latency or amplitude of the N170 (all \( p > .05 \)). Grand averaged ERPs for each condition and hemisphere are illustrated in Figures 5.1 – 5.6.

Figure 5.1. Left hemisphere grand averaged ERPs for each experimental group in the real word condition.

Figure 5.2. Right hemisphere grand averaged ERPs for each experimental group in the real word condition.

Figure 5.3. Left hemisphere grand averaged ERPs for each experimental group in the pseudo word condition.

Figure 5.4. Right hemisphere grand averaged ERPs for each experimental group in the pseudo word condition.
A 4 (group) x 2 (hemisphere: left or right) x 3 (condition: pseudoword; real word; illegitimate word) repeated measures ANOVA was conducted on the latency of the P100. There was a main effect of experimental group, $F(3,67) = 3.44, p = .022$. The ADHD group had overall longer latencies of the P100 ($M = 106.08, SE = 2.61$) than the anxiety ($M = 96.14, SE = 2.61, p = .046$) and the ASD groups ($M = 94.35, SE = 3.37, p = .054$), as shown in Figure 5.7. There were no other significant effects or interactions.

A 4 (group) x 2 (hemisphere: left, right) x 3 (condition: pseudoword, real word, illegitimate word) repeated measures ANOVA was conducted on the amplitude of the P100.
CHAPTER FIVE - STUDY THREE: LEXICAL DECISION

There was a significant main effect of hemisphere, $F(1,67) = 7.08, p = .010$, where overall amplitudes were larger in the right ($M = 3.48, SE = .22$) than left hemisphere ($M = 3.05, SE = .21$), as shown in Figure 5.8.

![Bar chart showing significant main effect of hemisphere for amplitudes of the P100.](image)

*Figure 5.8. Significant main effect of hemisphere for amplitudes of the P100.*

There was also a significant main effect of condition, $F(2,67) = 6.75, p = .002$. The amplitude of the P100 was significantly larger in the pseudoword condition ($M = 3.46, SE = .20$) than in the word condition ($M = 3.12, SE = .20, p = .001$) and the nonword condition ($M = 3.21, SE = .22, p = .047$), as shown in Figure 5.9.
There was also an interaction between condition and experimental group that was approaching significance, $F(6,67) = 1.93, p = .081$. For the ADHD group only, amplitudes toward word stimuli ($M = 2.51, SE = .37$) were significantly smaller than toward pseudowords ($M = 3.16, SE = .37, p = .001$) and nonwords ($M = 3.12, SE = .41, p = .004$), as shown in Figure 5.10.
There was also an interaction between hemisphere and experimental group that was approaching significance, $F(3,67) = 2.13, p = .105$. For the control group only, amplitudes in the right hemisphere ($M = 3.89, SE = .42$) were significantly larger than in the left hemisphere ($M = 3.04, SE = .39, p = .007$), as shown in Figure 5.11.

Figure 5.11. Interaction between experimental group and hemisphere of the amplitude of the P100.

### 5.7.3 Comorbidity

With regard to comorbidity, one-way ANOVAs were conducted on the latency of the P100 in each condition separately. In the real word condition, there was a significant effect of group, ($F(2,26) = 6.81, p = .005$), where the ADHD group had significantly longer latencies than the ASD only group, ($p = .003$), as shown in Figure 5.12.
As shown in Figure 5.13, in the Pseudoword condition there was also a significant main effect of group, \( F(2,26) = 4.48, p = .022 \), where the ADHD group had significantly longer latencies than the ASD group, \( p = .050 \), and the ASD and ADHD group had significantly longer latencies than the ASD only group \( p = .039 \).

**Figure 5.12.** Significant difference between the latency of the P100 in the ADHD and ASD group in the real word condition.

**Figure 5.13.** Significant differences in the latency of the P100 in the pseudoword condition between the ASD and ADHD groups, and the ASD and ASD + ADHD groups.
In the nonword condition, there was a significant effect of group, \( F(2,23) = 4.85, p = .019 \), where the ADHD group had significantly longer latencies than the ASD group \( p = .020 \) (see Figure 5.14).

One-way ANOVA’s were conducted to investigate if there were any differences between the ASD pure, anxiety pure and the ASD and anxiety comorbid groups on the latency of each condition of the P100. There were no significant effects between the groups in any condition (all \( p > .05 \)).

One-way ANOVAs were also conducted to investigate if there were differences between the comorbid versus pure groups on the latency or amplitude of the N170 in each condition. There were no significant effects in any condition.

*Figure 5.14. Significant difference between the ADHD and ASD groups of latency the P100 in the illegitimate nonword condition.*
5.8 Discussion

The main aim of the current study was to investigate whether there are neurophysiological differences in lexical information processing between ASD, ADHD, anxiety and neurotypical controls, as measured by ERPs and using a lexical decision paradigm. The second aim of the current study was to investigate the role of comorbidity in ASD by determining whether any differences in lexical information processing are altered when examining the pure conditions versus comorbid conditions (i.e., ASD + ADHD). Overall, we expected to see larger P100 or N170 amplitudes and shorter P100 or N170 latencies in the left hemisphere for the control group. If lexical processing deficits were present in ADHD, ASD and/or anxiety, then we expected to see a different pattern of amplitudes and latencies to the control group.

5.8.1 Hemispheric differences of the P100

We expected to see a pattern of left hemisphere specialisation, measured by shorter latencies and larger amplitudes, for the control group in particular given previous research demonstrating this effect (e.g., Knecht et al., 2000). Our results demonstrate the exact opposite, where P100 amplitudes were larger in the right hemisphere and there were no significant differences between latencies for the control group. This right-sided dominance was not shared, to the same extent, by the ASD, anxiety or ADHD groups.

There are three main possibilities for this finding. It is most likely that the P100 component reflects pre-lexical processing, whereas later components reflect lexical processing. A study investigating early and late ERP components in lexical decision making found significantly larger ERPs in the right over the left hemisphere in the P100 component, with left hemisphere specialisation only occurring in later components (Jordan, Fuggetta, Paterson, Kurtev, & Xu, 2011). This suggests that the left hemisphere does not take over the
processing of lexical information until 200-300ms after stimulus presentation. Later ERP components reflect processing of lexical information, rather than recognition (Grodzinsky et al., 2000). This theory is supported by the fact that the electrodes at which the maximal P100 is seen in the current study are located over the occipito-temporal region of the brain, an area responsible for early visual processing (Catani, Jones, Donato, & Ffytche, 2003). Further support for this theory will be outlined with reference to the N170 component later in the discussion.

The second possibility is closely related to the first. It is possible that the P100 reflects participants’ organisation of the stimuli into categories rather than the processing of this information. One body of research suggests the role of the right hemisphere in language is underestimated. The right hemisphere may be involved in categorisation and recognition of language, whereas the left hemisphere is involved in the processing and production of lexical information (Federmeier, Wlotko, & Meyer, 2008). To illustrate, one study found larger N170 components in the right over the left hemisphere when categorising objects in your area of expertise (e.g., knowledge of dogs or cats) (Tanaka & Curran, 2001). The words used in the current study ‘English condition’ were nouns. Participants may have visualised the object being named and used a ‘sorting technique’ to classify it as a real English word, rather than process the lexical information. Thus, the larger P100 ERP in the right hemisphere could reflect neural activity involved in sorting, rather than analysing the lexical value of the stimuli when using nouns.

Third, smaller latencies of the P100 in the left hemisphere could reflect a more streamlined neural process for the recognition of lexical stimuli. That is, the left hemisphere does not need to exert cognitive effort at this early stage, which only involves recognition of the stimuli. The amplitudes are therefore larger in the right hemisphere as more cognitive effort is required to process the information. In support of this hypothesis, EEG studies have
demonstrated that the amplitude of the P100 in lexical decision tasks is modulated by word length, that is shorter words have a smaller P100 than larger words (Hauk, Pulvermüller, Ford, Marslen-Wilson, & Davis, 2009; Hauk, Davis, Ford, Pulvermüller, & Marslen-Wilson, 2006). As the words in the current study were 4-5 letters in length, it is possible that little cognitive effort was required to recognise these words and thus a smaller amplitude was produced. However, given the established body of research demonstrating left-hemisphere dominance for lexical processing, this ‘streamlined theory’ is perhaps less likely that those suggested above.

The ASD, anxiety and ADHD group did not show the same extent of right hemisphere specialisation as seen in the control group. In these groups, there were no significant differences between the left and right hemispheres in the amplitude or latency of the P100. Given that this pattern of ERPs is not as strong as that seen in neurotypical controls, it is likely that there is a dysfunction in the recognition of lexical stimuli present in these groups. This is in line with previous literature that has demonstrated patterns of atypical laterality for those with ADHD (Rolfe et al., 2008) and ASD (Kleinhans et al., 2008). An overall dysfunction of brain systems may contribute to this atypical pattern of brain activity. If the P100 should be right hemisphere specialised for pre-linguistic processing, and this is not evident in ADHD, this may explain the high rate of language impairment seen in ADHD (Camarata & Gibson, 1999). A lack of differentiation between the right and left hemisphere in the P100 suggests that the ADHD brain may not recruit specialised brain networks for non-linguistic versus linguistic processes.

Visual inspection of the ERPs and means demonstrate a similar pattern to that of neurotypical controls in the ASD and anxiety groups. As some participants in the ASD group had a comorbid diagnosis of ADHD the atypical pattern of lateralisation may, in part, be explained by the addition of ADHD. However, it is also possible that there is a specific
deficit in the P100 associated with ASD only. This will be discussed in more detail in a later section of this discussion. While no significant differences were found in the anxiety group, it is possible that this can be explained by lack of statistical power, rather than a true effect given that the anxiety group had a relatively small sample size.

5.8.2 Additional P100 findings

In addition, analysis of the P100 revealed an overall longer latency for the ADHD group as opposed to the ASD and anxiety groups. Slow processing speed, defined as the overall speed of completing a task while maintaining accuracy, is a core deficit in those with ADHD and significantly impacts reading fluency (Jacobson et al., 2011). The overall later latencies shown by those with ADHD would certainly reflect this slower processing speed.

There was also an overall effect for larger amplitudes toward pseudowords than nonwords or real words. This finding fits with the current theory that larger amplitudes reflect higher cognitive effort. It is relatively easy to distinguish real English words and nonwords (that have a non-typical structure) from one another, but distinguishing a pseudoword (a nonword that has a typical English language structure) is more difficult. Research has demonstrated that the recognition of pseudowords produces significantly more brain activation than real words (Price, Wise, & Frackowiak, 1996). The overall larger amplitudes toward pseudowords likely reflects the effort required to process the information and assign the word a correct classification.

An interaction effect revealed the effect of smaller P100 amplitudes toward the word stimuli as opposed to the nonword or pseudoword stimuli was strongest in the ADHD group (where those with ADHD has significantly smaller P100 amplitudes toward word versus nonword and psuedoword stimuli). This could suggest a specific deficit in the recognition of linguistic stimuli over other visual stimuli. As previously stated, smaller amplitudes likely
CHAPTER FIVE - STUDY THREE: LEXICAL DECISION

reflect a lower amount of neural activity dedicated to that process (Dawson et al., 2005). An inability to devote neural resources in the pre-linguistic processing stage, would certainly have lead-on effects for when more effortful linguistic processing systems were to take over. Thus contributing to an overall pattern of lexical difficulties in those affected.

5.8.3 Comorbidity analysis

The comorbidity analysis revealed significantly longer latencies of the P100 in the ADHD pure group compared to the ASD pure group in all three conditions. This indicates that ADHD and ASD have different ERP profiles evoked in the recognition of lexical information. While both conditions are associated with lexical processing difficulties, these difficulties stem from different origins. Recent research has shown that it is not uncommon for the same phenotype (e.g., difficulties with language) to be driven by different cognitive difficulties in individuals with developmental disorders (Ozonoff & Jensen, 1999). Lexical decision processing deficits in ADHD are associated with longer latencies, which is associated with slower processing speed, whereas this slow processing speed was not evident in ASD. This finding is in line with previous literature that demonstrates slow processing speed as a core deficit in those with ADHD (Jacobson et al., 2011), and hypersensitivity to stimuli as a key characteristic of those with ASD (Baruth et al., 2010). The phenotype of linguistic difficulties, while shared by both conditions, stems from distinct underlying neurological deficits in each condition.

Visual inspection of the latency of the P100 in each condition are line with what we would expect if ASD and ADHD are indeed separate conditions. Because there are significant differences between the ASD and ADHD pure groups in each condition (suggesting different neuropsychological profiles), we also expect to see significant differences between the ADHD and ASD + ADHD groups if ADHD is simply an aspect of
ASD. However, this is not what is visually demonstrated in the ERPs. These findings demonstrate a similar conclusion to the findings in Chapter Four. This is in line with the theory proposed by Wood and Gadow (2010), and the overall hypothesis of this thesis, that if ERPs take on specific characteristics from each condition in its pure form, this suggests they are additive in nature.

5.8.4 N170 analysis

There were no significant effects or interactions on the N170 latency or amplitude toward any condition, for any of the experimental groups. This is unexpected given that ERP components such as the N170 reflect lexical classification of a word, have found that this is affected in ADHD and ASD in particular (Bruneau et al., 1999; Kuperman et al., 1996). Visual inspection of the ERP waveforms (and means and standard deviations for each experimental group) do show potential differences in this component. These differences may have not reached significance due to low statistical power. For example, for neurotypical controls, the latency of the N170 was visually earlier in the left then the right hemisphere for the word condition only. As this hemispheric specialisation was evident in the word condition only and not the pseudoword or nonword conditions, this suggests that the left hemisphere is beginning to take over lexical processing at this point. This finding supports the theory outlined above that lexical processing is not immediate, and rather happens later (e.g., reflected by later ERP components).

The current findings also suggests that when ASD and ADHD present together, they are indeed separate conditions (see Wood & Gadow, 2010), and early lexical processing is differentially affected in this group versus those with a pure version of each condition. Therefore, interventions targeted to those with comorbid ASD and ADHD need to be aware that a treatment plan that is appropriate for those with ASD or ADHD alone may not be
appropriate or effective in this population. For example, children with a comorbid ADHD + ASD diagnosis may benefit from the same behavioural interventions to improve linguistic functioning as those with ADHD alone. Similarly, therapies that improve overall processing speed may be beneficial for those with a comorbid diagnosis, even though slower processing is not a core deficit of those with ASD alone.

5.8.5 Limitations

The most important limitation of the current study is the small sample sizes of each group, particularly the comorbid ASD and anxiety group. This likely contributed to non-significant effects on the N170 component due to lack of statistical power. A larger scale study may have allowed for a more robust statistical analysis.

The current study also has a number of strengths. Firstly, the use of concurrent EEG during lexical decision making allowed us to measure the underlying neurological activity in millisecond timing. We found, for example, that the right hemisphere is involved in very early lexical processing. However, our task was not designed to specifically manipulate the conditions. Future research into the exact function of early ERP components is needed to establish whether these components are indeed involved in pre-lexical processing, and to clarify the role of the right hemisphere involved in this processing.

5.8.6 Practical implications

This study demonstrates the importance of measuring factors related to pre-linguistic processing in those with a neurodevelopmental condition. If very early processing is altered in those with ADHD and ASD, then treatments targeted to improve linguistic functioning need to take this into account. Specifically, language deficits may not be associated with the processing of the lexical stimuli itself, but the (pre-lexical) process of recognising, categorising and sending the information to the appropriate brain networks. Therefore, more
basic sensory integration therapies may be a more appropriate avenue for the treatment of word and nonword processing difficulties in these groups.

The current study also contributes to a growing body of evidence that suggests when ASD and ADHD present together, the difficulties cannot simply be accounted for by the ASD diagnosis. Therefore, children who fall into this category may benefit from the same behavioural interventions to improve linguistic functioning as those with ADHD alone. To elaborate, lexical deficits in ADHD are driven by an overall slower processing speed for lexical information, while those with ASD alone do not have this processing speed deficit.

The current findings also suggest that when ASD and ADHD present together, they are indeed separate conditions, and early lexical processing is differentially affected in this group versus those with a pure version of each condition. Therefore, interventions targeted to those with comorbid ASD and ADHD need to keep in mind that a treatment plan that is appropriate for those with ASD or ADHD alone may not be appropriate or effective in this population. For example, therapies that improve overall processing speed may be beneficial for those with a comorbid diagnosis, even though slower processing is not a core deficit of those with ASD alone.

5.8.7 Summary and future directions

Overall, the current study found that, utilising the current lexical decision paradigm, a pattern of larger P100 amplitudes was found in the right versus the left hemisphere in neurotypical controls. This pattern was not shared by those with ADHD or ASD in particular. It is likely that this early ERP component reflects pre-linguistic processing, at a stage before the left hemisphere (which is specialised for language) takes over. Another possibility is that the P100 reflects the sorting of nouns into categories and this process is dominant in right-hemisphere networks. The atypical pattern of results demonstrated in the ADHD and ASD
groups fits with the behavioural difficulty with language seen in these conditions. The pattern
of ERPs, while different from neurotypical controls, were also different in the two pure
conditions. With regard to comorbidity, when ASD and ADHD was presented as a comorbid
condition a unique pattern of ERPs was produced. The current study contributes to a growing
body of evidence that suggests that, when ASD and ADHD are presented together, the
difficulties cannot simply be accounted for by the ASD diagnosis. That is, ADHD should not
be regarded as simply a more severe form of ASD when the two disorders are diagnosed in
the same individual.
6.1 Study Overview

The current study aimed to investigate inhibitory control in those with ADHD, ASD anxiety and neurotypical controls using EEG. This was investigated by using two ERP components, the N200 and P300, as the focus of analyses in response to a stop signal task. The results of the current study reveal that overall, larger N200 amplitudes are related to “stopping” a response, whereas larger P300 amplitudes are involved in making the correct response (i.e., the “go trials”). Group level analysis did not reveal any differences between the experimental groups. However, upon closer inspection, smaller N200 and P300 amplitudes were associated with more severe ADHD symptoms which suggests some disruption of the underlying neural response in those affected. While it is possible that there is no inhibitory control deficit in ASD and anxiety, a larger scale study is needed to confirm this. If this is the case, it is possible that those studies who have reported an inhibitory control deficit in ASD may have simply not properly screened their participants for co-existing ADHD, which may account for such an effect.

6.2 Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition for which there is no known cause or cure. Autism is a highly variable disorder, the most prominent difficulties of which include aberrant behaviour, poor social skills and disrupted communication skills (American Psychiatric Association, 2013). Additional conditions such as anxiety (particularly OCD) and ADHD (see Chapter 1 for full diagnostic criteria) commonly co-exist with ASD (Dawson et al., 2004a). Studying overlapping behaviours in the three conditions may give insight as to why they so commonly co-occur. Inhibitory control is defined as the ability to withhold action toward a dominant response, and lack of such an ability is a characteristic of those who are impulsive versus those who are not (Bari &
Robbins, 2013). Traits of impulsivity have been documented in ASD (Matson, Fodstad, Mahan, & Sevin, 2009), anxiety disorders (Summerfeldt, Hood, Antony, Richter, & Swinson, 2004) and is a core diagnostic criteria in ADHD (American Psychiatric Association, 2013). Thus, difficulties on an inhibitory control task may give important information about the shared basis of the three conditions.

6.2.1 Inhibitory control in ASD, ADHD and anxiety

Difficulties with inhibitory control are well documented in OCD (Bannon et al., 2002; Enright & Beech, 1993), and ADHD (Hart et al., 2013). However, the evidence for inhibitory control deficits in ASD is mixed, with some studies suggesting a deficit (Christ et al., 2007a) and others not (Kleinhans et al., 2005). Closer inspection into the nature of these difficulties in ASD shows that deficits in inhibitory control are negatively correlated with repetitive behaviours, where performance on inhibitory control tasks became poorer as the amount of repetitive behaviour increased (Mosconi et al., 2009). In addition, difficulties with inhibitory control in ASD become more pronounced with any comorbid diagnosis (Bühler et al., 2011).

From the research outlined above, it is unclear whether deficits in inhibitory control are a key feature of the ASD itself, or whether they can be entirely accounted for by the presence of comorbid conditions. Identifying differences or similarities in the brain activity in the three conditions may give further clues into the nature of this deficit.

6.2.2 Brain networks involved in inhibitory control

Deficits in inhibition in the three conditions can be mapped to brain regions necessary for motor inhibition. One study that investigated inhibitory control in ASD using a go, no-go paradigm during concurrent magnetoencephalography (MEG) recording found that those with ASD only recruited networks in the frontal lobe, whereas neurotypical adults also recruited networks in the parietal and temporal regions (Vara et al., 2014). In ADHD there is significantly less activation of the fronto-striatal networks compared to neurotypical controls.
during inhibitory control tasks (Booth et al., 2005). Significantly less activity in fronto-striatal-thalamic networks during inhibitory control tasks is also found in those with OCD (Woolley et al., 2008). Taken together, there is an established body of evidence to suggest that the frontal networks in the brain drive any potential inhibitory control deficits in the three conditions.

6.2.3 EEG measures of inhibitory control

A common approach to investigate how the brain processes stimuli is through the use of electroencephalography (EEG). The event related potentials (ERPs) that are recorded using EEG give information about the speed and cognitive effort in which certain stimuli are processed. A typical ERP consists of a waveform of positive and negative deflections which are labelled according to their presentation after stimulus onset. The peak of each positive or negative waveform is the amplitude, which measures the amount of neural resources devoted to a specific task at any one time (Dawson et al., 2005). Larger amplitudes reflect more neural activity and correlates to the amount of cognitive effort required (Spironelli & Angrilli, 2009). The peak of an ERP after stimulus onset is the latency, which measures processing speed (Handy, 2005).

There are two main ERP components associated with inhibitory control. The N200 is a large negative deflection which occurs around 270ms after stimulus onset and reflects the activity in the brain when required to withhold a response (Jodo & Kayama, 1992). The P300 is a later component of the ERP waveform that occurs around 350-500ms post-stimulus (Basar et al., 1984). This component is thought to reflect ‘cognitive function’ although the exact nature of this cognitive function is unclear (Arifuddin, Kota, Hazari, & Reddy, 2013).

In neurotypical controls, the latency of the P300 is shorter in successful versus unsuccessful stop trials (Wessel & Aron, 2015), and the amplitude of the N200 and P300 is larger in stop-trials versus go or no-go trials (Ramautar, Kok, & Ridderinkhof, 2004).
Determining whether the N200 or the P300 is affected during inhibitory control tasks in ASD, ADHD and anxiety will provide information about how the brain processes such information, and whether this is different when ASD is presented as a singular versus comorbid condition.

6.2.4 ERP research in ASD, ADHD and anxiety

In ADHD, ERP research has demonstrated significantly reduced N200 and P300 amplitudes on a “go, no-go” inhibitory control task compared to neurotypical controls. This reduction in amplitudes correlated with the severity of ADHD symptoms, where lower amplitudes were seen in those with more symptoms of ADHD (Woltering, Liu, Rokeach, & Tannock, 2013).

In anxiety, reduced inhibitory control may be limited to emotion-based stimuli. A recent study found that the N200 was significantly reduced in those with anxiety when performing a go, no-go task using emotionally negative stimuli (i.e., sad faces), but this reduction was not found when the same task was performed on categorising a neutral stimulus such as gender (Yu et al., 2015).

In ASD, a pattern of neurological abnormality may be present in the absence of any behavioural deficit. For example, Verbaten et al (1991) performed a visual selective-attention task with autistic individuals during concurrent EEG. Smaller P300a and P300b amplitudes to visual target stimuli were found despite normal visual fixation and behavioural performance. Frontally distributed attention related negativity (Nc), elicited by surprise stimuli under conditions of sustained attention, is also diminished in ASD despite normal task performance (Ciesielski et. al. 1990).

Imaging research discussed earlier does demonstrate links to the frontal networks in the brain when an inhibitory control deficit is present. However, it is unclear whether an inhibitory control deficit is a defining feature of ASD, ADHD or anxiety, and how this deficit...
would be reflected in the underlying ERP components. While the research presented above suggests that each of the three conditions should be associated with a reduced P300 amplitude on inhibitory control tasks, behavioural studies also discussed above show no deficits in inhibitory control, or show that these deficits are only associated with certain characteristics (e.g., emotion-based stimuli, instance of repetitive behaviour). Thus, more research is needed to establish whether an inhibitory control deficit is a defining characteristic of each condition, or whether it is a symptom of a specific behaviour that is more common in these groups.

6.3 Aims and Hypotheses

The main aims of the current study are, firstly, to determine whether inhibitory control difficulties are indeed a core feature of ASD, ADHD or anxiety. The second aim of this study is to investigate whether we can link any potential inhibitory control difficulties to specific behaviours seen in these conditions. This is part of a larger research effort to clarify the role of common co-existing conditions in ASD.

We expect to see a pattern of reduced N200 and/or P300 amplitudes in the anxiety and ADHD groups compared to neurotypical controls. If inhibitory control difficulties are a core feature of ASD we also expect to see significant differences in the accuracy or ERP amplitude or latency when compared to typically developing controls. However, if inhibitory control difficulties are not a core feature of ASD we expect to see no significant differences in the accuracy, amplitude or latency when compared to typically developing controls.

If inhibitory control difficulties are better conceived of as being associated with specific characteristics of each condition (i.e., hyperactivity, social deficits), rather than the broad conditions themselves, we expect to see an association between these characteristics and the accuracy or ERP waveforms in correlation or regression analyses.
CHAPTER SIX - STUDY FOUR: INHIBITORY CONTROL

6.4 Methods

6.4.1 Subjects

The initial sample consisted of 83 subjects. There were 26 subjects that were excluded from the final analyses: Electrical noise $n = 6$; withdrawal from experiment $n = 8$; technical difficulties $n = 12$. The final sample consisted on 57 subjects and were split into experimental groups (ADHD $n = 16$; anxiety $n = 9$; ASD $n = 15$; control $n = 17$). All subjects had normal or corrected-to-normal vision and no history of head injury. The overall sample consisted of 31 females and 26 males. However, within each group the gender ratio was not evenly split (see Table 6.1). This inevitable imbalance is in line with literature which suggests autism has a 4.3:1 ratio for males to females (Newschaffer et al., 2007), and anxiety is much more common in females than males (Lowe et al., 2008; Matza et al., 2011). The mean age of all participants was 25.98 years, with a range from 16.3 years to 54.2 years.

Table 6.1. Mean age, IQ and gender distribution for each experimental group in the inhibitory control study.

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th></th>
<th>anxiety</th>
<th></th>
<th>ASD</th>
<th></th>
<th>control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>26.33</td>
<td>(7.43)</td>
<td>25.22</td>
<td>(6.26)</td>
<td>27.29</td>
<td>(11.24)</td>
<td>24.89</td>
<td>(6.92)</td>
</tr>
<tr>
<td>IQ</td>
<td>119.80</td>
<td>(7.39)</td>
<td>117.63</td>
<td>(9.32)</td>
<td>110.53</td>
<td>(12.19)</td>
<td>111.65</td>
<td>(12.88)</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>2</td>
<td>11</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.4.2 Recruitment

Subjects were recruited using advertisements placed around the University of Auckland City Campus and on a participant recruitment website. Subjects were also recruited through organisations such as Altogether Autism, the Phobic Trust, the Parent and Family Centre and the ADHD Association. Once subjects contacted the researcher with their interest in the study, they were given an initial questionnaire to ensure they fit the study criteria.
Participants must have no history of head injury, no history of comorbid depression or schizophrenia, be right-handed and have English as their first language. Participants were given $20 in vouchers for their participation in this study.

6.4.3 Diagnoses

Control subjects consisted of mainly undergraduate students and had no history of any psychological illness (e.g., depression, anxiety). Subjects who fell into the experimental groups were diagnosed with their respective conditions by a registered medical professional (i.e., not self-diagnosed) prior to participation. From the 16 subjects in the ADHD group, four had an additional diagnosis of anxiety. In the ASD group, five subjects had a diagnosis of high functioning autism with no coexisting conditions; nine had a diagnosis of high functioning autism and coexisting anxiety or OCD; and the remaining one had a diagnosis of coexisting high functioning autism and ADHD. The anxiety group included those with a diagnosis of anxiety or OCD.

6.5 Measures

Stimuli consisted of black Times New Roman letters of the alphabet presented in the centre of a white screen, as shown in Figure 6.1. The stop signal was a red hexagon presented on a white background. Stimuli were presented using E-prime software (Schneider et al., 2002) and were displayed on a colour computer monitor with a screen resolution of 800 x 600 pixels.

6.6 Procedure

The experiment used in the current study was modelled closely after Nielson, Langenecker and Garavan (2002). The total experiment consisted of two trial blocks plus two practice blocks. The first block was a simple go/no-go paradigm while the second block added in the ‘stop’ element. The first block consisted of a total of 336 trials. The second block consisted of 480 trials. The stimuli were presented very rapidly (600 ms) with no ISI.
Participants were instructed to ignore all letters of the alphabet, except for R and S, where they were instructed to press the N key. These instructions were the same throughout the experiment with one exception. If the letter R or S was followed immediately by the stop stimulus, participants were instructed to withhold their response (i.e., not press the n key). The paradigm is visualised in Figure 6.1.

![Figure 6.1](image)

*Figure 6.1. Example of the procedure of the Stop Signal task. A rapid presentation of letters where participants should ignore all letters other than R or S. However, if that R or S is followed by a stop signal participants should withhold their desire to respond.*

### 6.6.1 EEG acquisition

EEG recordings were conducted in an electrically shielded room (Model L3000; Belling Lee, Enfield, England) using 128-channel Ag/AgCl electrode nets (Tucker, 1993). The Geodesic sensor net distributes electrodes from nasion to inion and from left to right mastoids at uniform intervals. EEG was recorded continuously (1000-Hz sample rate; 0.1–100 Hz analogue bandpass) with Electrical Geodesics Inc. amplifiers (300-MΩ input impedance). A Macintosh computer was used to acquire the data using NetStation software and this was then stored on the computer’s hard disk. Electrode impedances were kept below 40 kΩ, an acceptable level for this system (Tucker, 1993). Common vertex (Cz) was used as a reference, resulting in a total of 129 electrodes.
Triggers were programmed into E-Prime and synchronised with the EEG acquisition software via a parallel port. Triggers were sent as a function of stimulus type (three types: Go trials, No-Go trials and Stop trials) at stimulus onset, and again upon response (two types: correct, or incorrect), resulting in two triggers per trial.

6.6.2 EEG processing

Data was segmented using in house software (WinView) into ERP waveforms with any artefacts removed according to the guidelines set out in (Jervis et al., 1985). EEG data was segmented as a function of trigger type. Data included both correct and incorrect trials to increase power (results were not significantly different when incorrect trials were omitted). Each epoch was centred around the stimuli trigger (i.e., the trigger that was sent when the stimuli was displayed). Each epoch was 100ms pre stimulus and 500ms post-stimulus giving total epoch segments of 600ms. Artefact rejection was done on a trial-by-trial basis using the paramaters set out in Gratton and colleagues (2008). Epochs with bad channels, eye blinks, too much drift or electrical noise were discarded from analyses. From the 816 trials for each participant, 802.61 epochs on average were accepted. Epochs were averaged as a function of trial type (Go, No-go or Stop) giving a total of 3 ERPs. These ERPs were then grand-averaged and filtered using a 30-Hz low-pass (hi-pass 0.1) Butterworth Filter (Alarcon et al., 2000).

6.6.3 ERP analysis

The four grand averaged waveforms for each participant were visually inspected for the N200 and P300 components. The coder was blind to experimental group. The N200 is a large negative deflection which occurs at around 270ms after stimulus onset and reflects the activity in the brain when required to withhold a response (Jodo & Kayama, 1992). The P300 is a later component of the ERP waveform that occurs around 350-500ms post-stimulus (Basar et al., 1984), and is thought to reflect ‘cognitive function’ (Intriligator & Polich,
The electrodes selected for analysis were 3, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16, 18, 19, 20, 22, 23, 24, 111, 112 and 124. These electrodes are located in the frontal area and are consistent with similar research in the area (Kaiser et al., 2006). From each ERP the amplitude and latency (i.e., the most negative or positive deflection) of the N200 and P300 were collected for each participant. This was done by visual inspection of the waveform.

6.6.4 Statistical analyses

All statistical analyses were conducted using SPSS version 20 software. The main statistical techniques used were ANOVA and regressions. Effects were deemed significant at the .05 level, unless stated otherwise. Initial analyses revealed that gender was not involved in any significant effects or interactions in any analysis. Thus, analyses were collapsed across this dimension to increase statistical power.

One behavioural measure was selected as a predictor of each ‘characteristic’. The CPT was selected to measure characteristics of ADHD. The ASQ was used to measure characteristics of ASD. The GAD was used to measure characteristics of anxiety. In addition the OCI was used to measure characteristics of OCD. We felt justified in using this approach because earlier studies in this thesis indicate that the tools are a valid means of identifying each disorder (see Chapters 2 and 3 for information on the validity and reliability of each measure).

6.7 Results

6.7.1 ANOVA analyses

A 2 (gender) x 4 (experimental group: ASD; ADHD; anxiety; controls) x 2 (condition: go or stop) ANOVA was conducted to determine whether there were differences in accuracy. There were no significant main effects or interactions (all $p > .05$).

A repeated measures 4 (experimental group: ASD; ADHD; anxiety; control) x 3 (condition: go; no-go; stop) ANOVA was conducted to determine whether there were
differences in the latency or amplitude of the N200. The latency and amplitudes can be visually inspected in Figures 6.3-6.5. There was a significant main effect of condition, \( F(2,98) = 12.54, p < .001 \), where amplitudes of the N200 toward the ‘go’ stimuli, \( (M = .40, SE = .27) \) were smaller than toward the stop \( (M = -1.30, SE = .48, p = .005) \) and the no-go stimuli \( (M = -0.28, SE = .22, p = .027) \), as seen in Figure 6.2. There were no other significant effects or interactions (all \( p > .05 \)).

![Figure 6.2.](image)

\( Figure \ 6.2. \) significant main effect of condition for the amplitudes of the N200.

A repeated measures 4 (experimental group: ASD; ADHD; anxiety; controls) x 3 (condition: go; no-go; stop) ANOVA was conducted to determine whether there were differences in the latency or amplitude of the P300. There were no significant main effects of Group or interactions. There was only a significant main effect of condition, \( F(2,106) = 3.66, p = .029 \), where amplitudes of the P300 in the no-go condition \( (M = .70, SE = .19) \) were smaller than in the go condition \( (M = 1.88, SE = .45, p = .015) \), as seen in Figures 6.3-6.6.

164
Figure 6.3. Significant main effect of condition for the amplitude of the P300.

Figure 6.4. Grand averaged ERP waveform for each experimental group in the no-go condition.

Figure 6.5. Grand averaged ERP waveform for each experimental group in the go condition.
6.7.2 Regressions

A series of multiple linear regressions were conducted to see whether the latencies or amplitudes of the N200 or P300 for each condition (three: go; no-go; stop), or accuracy, were related to the behavioural measures (three: ASQ; CPT; GAD). The latencies of either the N200 or P300 did not significantly predict scores on any of the behavioural measures (all $p > .05$).

The amplitudes of the N200 did not significantly explain the variance on the ASQ, OCI or the GAD. The amplitudes of the N200 did, however, significantly explain 24% of the variance on the CPT, ($R^2 = .24, F(3,53) = 5.50, p = .002$). The amplitude of the N200 in the go condition significantly predicted scores on the CPT, where larger amplitudes predicted an increase in CPT scores. The amplitude of the N200 in the stop condition also significantly predicted scores on the CPT, where an increase in amplitudes predicted an increase in CPT scores. Regression statistics are listed in Table 6.2. The amplitude in the no-go condition did not significantly predict CPT scores.
Table 6.2. Regression statistics for the amplitudes of the N200 and the variance on the CPT for each condition.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Std. Error</th>
<th>t</th>
<th>Sig. (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N200 no-go amplitude</td>
<td>0.68</td>
<td>2.51</td>
<td>0.27</td>
<td>0.79</td>
</tr>
<tr>
<td>N200 go amplitude</td>
<td>4.75</td>
<td>2.04</td>
<td>2.33</td>
<td>0.02</td>
</tr>
<tr>
<td>N200 stop amplitude</td>
<td>2.47</td>
<td>1.01</td>
<td>2.44</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The amplitudes of the P300 did not significantly explain the variance on the ASQ, OCI or the GAD. The amplitudes of the P300 did, however, approach a significant amount of variance on the CPT, ($R^2 = .12, F(3,53) = 2.44, p = .075$). The amplitude of the P300 in the no-go condition significantly predicted scores on the CPT, where larger amplitudes were associated with an increase in CPT scores. Regression statistics can be seen in Table 6.3. The amplitudes in the go or stop conditions did not predict CPT scores.

Table 6.3. Regression statistics for the amplitudes of the P300 and the variance on the CPT for each condition.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Std. Error</th>
<th>t</th>
<th>Sig. (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P300 no-go amplitude</td>
<td>6.58</td>
<td>2.70</td>
<td>2.43</td>
<td>0.02</td>
</tr>
<tr>
<td>P300 go amplitude</td>
<td>-0.55</td>
<td>1.18</td>
<td>-0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>P300 stop amplitude</td>
<td>0.43</td>
<td>1.04</td>
<td>0.42</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Accuracy in the no-go or stop condition did not significantly explain the variance on the ASQ, OCI or GAD. Accuracy did approach significance to explain the variance on the CPT, ($R^2 = .10, F(2,50) = 2.75, p = .074$). Accuracy in the no-go condition significantly predicted scores on the CPT, where higher accuracy predicted an increase in CPT scores. Accuracy in the stop condition did not significantly predict CPT scores (see Table 6.4).
### 6.8 Discussion

The main aim of the current study was to clarify the nature of inhibitory control deficits in ASD, ADHD and anxiety disorders. In general, we expected to see a pattern of larger N200 and/or P300 amplitudes in the stop versus no-go or go conditions for neurotypical controls. Overall, the results indicated larger N200 amplitudes toward the stop trials versus the no-go or go trials, and larger P300 amplitudes to toward the go rather than the no-go stimuli. If the profile of ERPs evoked on an inhibitory control task were different in ASD, ADHD or anxiety compared to neurotypical controls, we expected to see smaller ERPs in these groups. Unexpectedly, the main ANOVA analysis did not show any significant differences between groups in the accuracy, latency or amplitude of the ERP components. This finding is in line with previous research, which has not consistently demonstrated the presence of an inhibitory control deficit in ASD, ADHD and anxiety. This will be discussed in detail later in the discussion.

Analyses which investigated whether there was a link between specific behaviour and ERPs did reveal that the amplitudes of the N200 and P300 are associated with characteristics of ADHD, but not ASD, anxiety or OCD. Specifically, larger amplitudes on the N200 ERP component predicted higher scores on the CPT in the go and stop conditions. Larger amplitudes on the P300 also predicted higher scores on the CPT in the stop condition. As higher scores on the CPT indicate better performance in visual and auditory attention, we can
CHAPTER SIX - STUDY FOUR: INHIBITORY CONTROL

conclude that smaller amplitude in response to the stimuli is associated with higher visual and auditory attention deficits.

6.8.1 Main effects of the N200 and P300

The results of the current study found overall larger N200 amplitudes toward the stop trials versus the no-go or go trials. In addition, an overall larger P300 amplitude was found in the go versus the no-go or stop trials. This finding is in line with previous literature which demonstrates the involvement of the N200 and P300 in inhibitory control tasks (e.g., Ramautar et al., 2004). A larger amplitude toward a stimuli is argued to reflect more neural activity dedicated to the process at that particular time (Dawson et al., 2005). The results of the current analyses suggest that the N200 component was involved in withholding a dominant response (i.e., inhibition), while the later P300 component was then involved in the production of the correct response (i.e., “go”). Support for these findings will now be discussed in turn.

One study has demonstrated that the N200 is specifically involved in conflict monitoring. There were three conditions, a simple go-no go paradigm, but with the addition of a go-go condition and participants were asked to respond to these trials with either maximum force or maximum speed (Donkers & van Boxtel, 2004). Amplitudes of the N200 were greater in the go-go condition versus the go, or no-go conditions. This tells us that the N200 is specifically associated with deciding between two conflicting responses (i.e., inhibition of irrelevant information) in an inhibition task. A similar pattern of results was found in the current study, where amplitudes were larger on the trials which required participants to change their desired response from “go” to “no-go”, rather than the simple “no-go” trials. This suggests that the N200 is likely involved in higher order inhibition.
CHAPTER SIX - STUDY FOUR: INHIBITORY CONTROL

There is an established body of research which has demonstrated that the P300 is at maximum amplitude for ‘‘go’’ versus ‘‘no-go’’ responses (Pfefferbaum, Ford, Weller, & Kopell, 1985; Pfefferbaum & Ford, 1988). This finding is supported by recent research that shows a higher level of neural synchrony in the first 300ms for go over no-go responses (Müller & Anokhin, 2012). Thus, the results of our study support the finding that the P300 is involved in response production.

6.8.2 The N200 and P300 in ASD, anxiety and neurotypical controls

The main ANOVA analyses did not show any group differences on the latency or amplitude of the N200 or the P300. In line with our hypotheses, the absence of group differences suggests that inhibitory control deficits are not a core feature of ASD, ADHD or anxiety. Research on the presence of inhibitory control deficits in ASD and anxiety has been mixed, with some research showing a deficit (Christ, Holt, White, & Green, 2007b), and others not (Kleinmans et al., 2005). Our findings agree with a behavioural study using a very similar stop-signal paradigm to the current study found that those with ASD performed comparably on no-go and stop responses to neurotypical controls (Ozonoff & Strayer, 1997), suggesting that inhibition was left intact. As mentioned earlier, in anxiety inhibitory control deficits may be limited to negative social stimuli rather than being a global deficit (Yu et al., 2015). As the current study used emotion-neutral stimuli (i.e., letters) any inhibitory control deficit may not have been evident in the anxiety group. While the current study did not specifically manipulate the appropriate variables to conclude this, the findings support this theory. The current study suggests that there is no global inhibitory control deficit present in ASD or anxiety.

It is, however, possible that in ASD an inhibitory control deficit is not reflected by the ERP components selected in the current study. A study using a visual oddball paradigm demonstrated that while there were increased amplitudes in very early ERP components (the
P100) in the autism group versus neurotypical controls, this effect was not present in the later N200 or P300 components (Sokhadze et al., 2009). As the P100 is argued to be involved in early stimulus processing (Handy, 2005), and later components are argued to reflect inhibitory control, it is possible that any inhibitory control deficits reported in ASD are due to the misrecognition of the stimuli, rather than true dysfunctional inhibition networks.

While the results of the ANOVA analyses did not reach significance, visual inspection of the ERPs suggest that there may be a difference between the experimental groups. Visually, there are group differences in the grand averaged waveforms for each experimental group, where those with ASD and anxiety appear to have larger N200 and smaller P300 amplitudes in the go and no-go conditions. In the current study there was a high rate of exclusion due to the difficulty of the task. Unfortunately, this resulted in a sample size of between 9 and 17 participants in each group. An increased sample size would have helped to reduce bias and increase statistical power, especially when examining conditions with large phenotypic diversity (Wolf, Harrington, Clark, & Miller, 2013). It is possible that small sample sizes contributed to a lack of statistical significance in the current study and therefore masked any true effects between the experimental groups.

6.8.3 The N200 and P300 in ADHD

The presence of inhibitory control deficits in ADHD are well established (e.g., Barkley, 1997; Woltering et al., 2013) and therefore it is unexpected that there were no group differences between those with ADHD and neurotypical controls. Upon closer inspection, regression analyses uncovered an association between ADHD and amplitudes of the N200. In all three conditions, higher CPT scores (which indicates fewer symptoms of ADHD), predicted higher amplitudes of the N200, P300 and accuracy of no-go. Those with more severe ADHD had smaller amplitudes and were less accurate than those with less severe ADHD. This is in line with previous research that has demonstrated that those with ADHD
have significantly reduced N200 amplitudes on stop trials in a stop-signal task (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005). It is possible that impulsivity, a core behaviour of those with ADHD (American Psychiatric Association, 2013), drive these inhibitory control deficits.

In addition, the finding that inhibitory control differences are only associated with characteristics of ADHD, but not ASD, may give us important clues about the nature of coexisting conditions. This finding is consistent with recent research that was able to differentiate those with ASD and ADHD on tasks of inhibitory control. In this study, those with ADHD had impaired inhibitory control and those with ASD did not. Further, this study also included a group of individuals with comorbid ASD and ADHD. They found that this group also had significantly poorer performance on inhibitory control than the pure ASD group (Tye, Asherson et al., 2014). It is possible that researchers who report inhibitory control deficits in ASD may not have properly screened their participants for co-existing ADHD. Patterns of inhibitory control deficits may in fact be a characteristic of the co-existing ADHD rather than the ASD itself. This finding highlights the need to properly screen participants for the presence of additional comorbid conditions.

6.8.4 Limitations

Sample size did not allow full statistical analyses of experimental groups when split by comorbid condition (i.e., ASD alone, ASD and OCD, ASD and ADHD). Therefore, we could not conclude the exact role of inhibitory control deficits when the conditions present as a comorbid condition. This was addressed in the current study by using behavioural profiling measures to determine whether certain behaviour associated with each condition predicted a specific ERP response. A larger-scale study to determine the exact nature of inhibitory control deficits in comorbid conditions is needed in the future.
In addition, the calculation of a stop-signal reaction time (SSRT) may have provided more information about the behavioural performance of participants during inhibition. Unfortunately this was not possible due to modification of the experimental design to make it appropriate for EEG recording.

6.8.5 Summary and future directions

The results of the current study demonstrate the N200 component is involved with “stopping” (i.e., higher-order inhibitory control functions), and the P300 is involved with producing a correct response (i.e., “go”) during a stop-signal task. While the current study does not provide support for the presence of an inhibitory control deficit in ASD and anxiety, this may be due to small sample sizes (which results in less statistical power). There was, however, an association between smaller amplitudes of the N200 and the P300 and symptoms of ADHD. This suggests that aberrant inhibitory control may be a product of those with visual and auditory deficits. If there is no true inhibitory control deficit in anxiety or ASD, then the research that reports such a deficit may be accounted for by comorbid ADHD. Therefore, proper screening for coexisting difficulties is greatly important to researchers when establishing core difficulties in a neurodevelopmental condition. Further research is needed to establish the exact nature of these deficits.
7.1 Study Overview

The study in the Chapter 7 will investigate neural connectivity in ASD, ADHD and anxiety using EEG coherence measures. Connectivity is a concept that describes the degree to which regions of our brain communicate with one another. Such communication is essential for functions that require integration of different brain networks. There is a growing body of evidence that suggests altered brain connectivity may be a defining feature of disorders such as ASD, OCD, anxiety and ADHD. The current study aims to investigate whether characteristics of these conditions are associated with altered resting state connectivity using EEG coherence. Overall, the analyses revealed increased coherence across central electrodes over the primary motor cortex, and decreased coherence in the frontal lobe networks in those with ASD compared to neurotypical controls. In addition, there was increased coherence in occipital lobe networks in the ADHD group. For those with anxiety, there was an association between higher symptoms of generalised anxiety and higher frontal-occipital intra-hemispheric (alpha only) coherence and higher occipital inter-hemispheric coherence (alpha, approaching theta band). The patterns of coherence in the ASD pure group were different when additional conditions are included in the analyses, suggesting that aberrant coherence in the frontal and central areas of the brain are specifically associated with ASD. Taken together, this information supports the idea that comorbid conditions are additive, rather than being symptoms of the same disorder.

7.2 Introduction

Brain connectivity describes the degree to which the regions of our brain communicate with each other. Connectivity is broadly split into functional connectivity (which describes the similarity of temporal characteristics of brain activity in different brain
regions) or structural connectivity (the physical connections of regions) (Vissers, Cohen & Geurts, 2012). Communication and integration of segregated areas or networks of the brain are vital in order for the successful execution of cognitive and motor functions (Rubinov & Sporns, 2010). Measuring synchronization or coherence of EEG while the brain is at rest is a common method with which to gauge cortical connectivity. Given that EEG provides whole-head measurements of brain activity in the millisecond range, it is an appropriate tool for measures of connectivity (Schoffelen & Gross, 2009). Resting state connectivity allows investigators to study the flow of mental events in the absence of task performance (which requires the employment of task specific regions). Brain activation during resting state connectivity investigations can thus be used as a measure of baseline brain activity (Friston, 2011).

7.2.1 Connectivity in ASD

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition that involves a spectrum of impairments in social, communication and behavioural domains (American Psychiatric Association, 2013) that prevents the development of normal social interactions and relationships between the individual and others around them. Differential patterns of connectivity may be responsible for a mismatch of behaviour to environment in ASD. An under-connected system would be particularly disruptive to those higher-order psychological functions that require the coordination of many different types of information processing (Minshew & Williams, 2007). The difficulties that occur with an under connected system would produce a multitude of problems with psychological functions (i.e., language, social skills or executive functions) (Belmonte et al., 2004). Together these problems may give rise to the difficulties evident in ASD.
7.2.2 Neuroimaging research on connectivity in ASD

There is a growing body of research showing aberrant connectivity in ASD. Altered patterns of connectivity are implicated in many brain regions (Belmonte et al., 2004). Earlier resting-state studies using functional magnetic resonance imaging (fMRI) have revealed that those with ASD show functional under-connectivity between anterior and posterior regions (Cherkassky, Kana, Keller & Just, 2006). Diffusor Tensor Imaging studies, which trace white matter tracts in the brain, have demonstrated altered structural connectivity in ASD at rest. Compared to typically developing adults, those with ASD show increased mean and radial diffusion in white matter tracts forming cortico-cortical and inter-hemispheric connections (Ameis et al., 2011). This putatively indicates reduced fibre density of these tracts in those with ASD. However, other studies have failed to replicate these findings (e.g., Delmonte, Gallagher, O'Hanlon, McGrath, & Balsters, 2013; Tyszka, Kennedy, Paul, & Adolphs, 2014). This discrepancy, in part, may be resolved by closely examining the characteristics of ASD within the spectrum. Recently, a study using fMRI demonstrated that connectivity may be related to the symptoms of ASD (which vary from individual to individual) rather than being a blanket feature of ASD itself. Specifically, those with more severe ASD symptoms show greater deviations in connectivity patterns from typically developing controls, than those with less severe ASD symptoms (Hahamy, Behrmann, & Malach, 2015). Studies such as these highlight the importance of examining individual variation in disorders that are highly variable from individual to individual.

7.2.3 Connectivity in common co-existing conditions with ASD

Altered connectivity is also thought to be present in obsessive compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD). In OCD, resting-state fMRI studies have demonstrated patterns of increased connectivity in the cortico-striatal regions
and fronto-subcortial circuitry (Harrison et al., 2009; Jang et al., 2010). In ADHD, there is a distinct pattern of under-connectivity between anterior and posterior regions (Konrad & Eickhoff, 2010; Yu-Feng, et al. 2007) and reduced connectivity in the fronto-striatal connections (Casey et al., 2007; Cubillo et al., 2010). In OCD and ADHD the patterns of altered connectivity seem to be associated with fronto-striatal circuitry.

Taken together, resting state imaging studies have shown connectivity abnormalities in each disorder (ASD, ADHD and OCD). Despite high comorbidity rates between the three disorders it is unclear how patterns of coherence present when two or more of these conditions present as a comorbid condition. The differential pattern of connectivity seen in these disorders suggests that specific brain regions may not be properly linked to each other.

7.2.4 Connectivity and EEG

Electroencephalography (EEG) is a useful tool in investigating connectivity using coherence measures. Coherence measures the amount of neural synchronisation between two electrodes (or groups of electrodes) on the scalp. High coherence between two EEG signals reflects co-occurrence of neuronal oscillations at the same frequency (suggesting functional integration between neural populations), whereas low coherence suggests independently active populations (suggesting functional segregation) (Murias, Webb, Greenson, & Dawson, 2007). Coherence can be determined from the power of oscillations in each frequency band (e.g., delta (1.5-3Hz) theta (3.5-7.5Hz), alpha (8-12Hz)). Power reflects to the number of neurons that discharge in synchrony in each band (Klimesch, 1999). The encoding of new information has been proposed to be reflected in theta oscillations, whereas alpha oscillations are associated with retrieval of long-term memories (Klimesch, 1999). Power is also associated with task demands. As opposed to task-related research, the power of alpha increases and theta decreases in resting state studies (Klimesch, 1999).
Differences in coherence may measure default mode network activity, a system associated with rest. The default mode network is a specific group of brain areas that are active in the absence of task performance. A study by Greicius, Krasnow, Reiss and Menon (2003) demonstrated that the posterior cingulate cortex and ventral anterior cingulate cortex show greater activity during resting states than during cognitive tasks. The authors theorised that this so-called default mode network is responsible for ongoing mental processes (such as working memory) during rest (Greicius et al., 2003).

7.2.5 Coherence in ADHD, anxiety and ASD

Patterns of over- and under-connectivity are also evident in ASD using coherence measures, as measured in each power band. One resting-state study by Murias, Webb, Greenson and Dawson (2007) found elevated coherence (frontal and temporal regions) in the theta band and reduced coherence (frontal regions) in the lower alpha range (8-10Hz). Another study found decreased inter-hemispheric delta and theta, and decreased intra-hemispheric delta and theta in the frontal regions (Coben, Clarke, Hudspeth, & Barry, 2008).

Altered patterns of coherence are also a feature of ADHD. Increased power in the theta band at rest is one of the most consistent findings in those with ADHD (Tye, Rijsdijk & McLoughlin, 2014). A resting state study investigating coherence in ADHD found that at shorter inter-electrode distances, children with ADHD had elevated intra-hemispheric coherences in the theta band and reduced lateral differences in the theta and alpha bands. At longer inter-electrode distances, ADHD children had lower intra-hemispheric alpha coherences than controls. Frontally, ADHD children had inter-hemispheric coherences elevated in the delta and theta bands, and reduced in the alpha band (Barry, Clarke, McCarthy, & Selikowitz, 2002).
Coherence measures of OCD are in line with imaging studies demonstrating altered subcortical circuitry. To elaborate, there is a significant increase in the theta band in fronto-occipital coherence in those with OCD versus typically developing controls (Desarkar, Sinha, Jagadheesan, & Nizamie, 2007). In addition, there is decreased inter-hemispheric coherence in OCD (Velikova et al., 2010). However, the evidence for coherence anomalies in the broader anxiety category is unclear. Another resting-state EEG study discovered that self-reported traits of anxiety are associated with decreased delta-beta coherence (Putman, 2011), suggesting this parameter may underlie emotion-driven behaviour. Further research needs to be done into this area to clarify patterns of connectivity in anxiety.

7.3 Aims and Hypotheses

Together, the literature demonstrates different connectivity profiles in each disorder relative to their typically developing counterparts. However, there has been little research conducted comparing the connectivity profiles of each disorder. The current study aims to investigate whether differences in resting state connectivity are shared by each condition. In addition, the current study seeks to answer if altered connectivity patterns are associated with specific behavioural characteristics.

Overall, given the research outlined above, we expect to see patterns of increased coherence in those with anxiety and ADHD compared to neurotypical controls. We also expect to see patterns of increased and decreased coherence in those with ASD compared to neurotypical controls, given that this pattern has been previously found in those with ASD. Additionally, given that altered coherence is associated with many neurobehavioural conditions, we expect to see a significant correlation between coherence values and scores on behavioural profiling measures.
We also want to investigate whether the experimental groups share patterns of altered connectivity or have different connectivity profiles from one another. We expect that if patterns of resting state connectivity are not different between the four experimental groups, then there would be no significant differences in resting state coherence values for any condition between the groups. However, if patterns of resting state connectivity are different between the experimental groups, we expect to see significant difference in coherence values for one or more of the experimental groups.

7.4 Methods

7.4.1 Subjects

The initial sample consisted of 47 subjects. One subject was excluded from the final analyses due to technical difficulties. All subjects had normal or corrected-to-normal vision and no history of head injury. The final sample (Total $n = 46$; ADHD = 11, anxiety = 10, ASD = 13 and control = 12) consisted of 20 females and 26 males. Within each group the gender ratio was not evenly split (see Table 7.1). This is in line with literature which demonstrates autism is more common in males (Newschaffer et al., 2007), and anxiety is much more common in females (Lowe et al., 2008; Matza et al., 2011). The mean age of all participants was 25.48 years, with a range from 16.3 years to 46.5 years.
Table 7.1. Mean age and IQ with standard deviations in parentheses and gender distribution for each experimental group in the resting state task.

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Anxiety</th>
<th>ASD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>23.36</td>
<td>(3.93)</td>
<td>25.82</td>
<td>(8.50)</td>
</tr>
<tr>
<td>IQ</td>
<td>116.60</td>
<td>(8.46)</td>
<td>116.56</td>
<td>(8.62)</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

7.4.2 Recruitment

Subjects were recruited using advertisements placed around the University of Auckland City Campus and on a participant recruitment website. Subjects were also recruited through organisations such as Altogether Autism, the Phobic Trust, the Parent and Family Centre and the ADHD Association. Once subjects contacted the researcher with their interest in the study, they were given an initial questionnaire to ensure they fit the study criteria. Participants were required to have no history of head injury, no history of comorbid depression or schizophrenia, be right-handed and have English as their first language. Participants were given $20 in vouchers for their participation in this study.

7.4.3 Diagnoses

Control subjects consisted of mainly undergraduate students who had no history of psychological illness (e.g., depression, anxiety). Subjects who fell into the ASD, anxiety or ADHD groups were diagnosed with their respective conditions by a registered medical professional prior to participation. Subjects were also asked to disclose any coexisting conditions. From the 11 subjects in the ADHD group, three had an additional diagnosis of anxiety. In the ASD group, five subjects had a diagnosis of high functioning autism with no
coexisting conditions; seven had a diagnosis of high functioning autism and coexisting anxiety or OCD; and the remaining two had a diagnosis of coexisting high functioning autism and ADHD. The anxiety group included those with a diagnosis of anxiety or OCD.

7.4.4 Behavioural profiling measures

Participants were asked to answer six questionnaires that measured specific behaviours. The questionnaires were: 1. The Integrated Visual and Auditory Continuous Performance Task (CPT) which tests sustained attention to visual and auditory stimuli (Rosvold et al., 1956); 2. The Behavioural Inhibition/Activation Scale (BIS/BAS) which identifies patterns of behaviour in an individual’s personality (Carver & White, 1994). The questionnaire consists of four subscales. The subscales are: i. Behavioural Inhibition (BIS) or punishment sensitivity scale. This measures an individual’s experience of anxiety in a situation where there are punishment cues (e.g., “I worry about making mistakes”); ii. Reward Responsiveness measures positive responses in anticipation of a reward (e.g., “When good things happen to me, it affects me strongly”); iii. Drive measures an individual’s pursuit of desired objects (e.g., “I go out of the way to get things I want”) and; iv. Fun Seeking, which measures the willingness to approach new events which may give a reward (e.g., “I am always willing to try something new if I think it might be fun”); 3. The Generalised Anxiety Disorder Scale (Spitzer et al., 2006), a brief clinical measure for generalised anxiety; 4. The Obsessive Compulsive Inventory – Revised (OCI), an 18-item questionnaire that measures OCD symptoms (Foa et al., 2002); 5. The Adult ADHD Self Report Symptom Checklist (ASRS; (Kessler et al., 2005)), an 18-item self-report questionnaire which asks about clinical symptoms of ADHD as reported in the DSM-IV (e.g., “How often do you fidget or squirm when you have to sit down for long periods of time?”); and 6. The autism spectrum quotient (Baron-Cohen et al., 2001), a 50-item self-report questionnaire that measures autistic-like
traits in the typically developing population. See Chapter two for a complete description including the validity and reliability of each measure.

7.5 Procedure

Resting state EEG was collected at the end of the experimental session. The experiment consisted of two trial blocks, eyes closed and eyes open. Each block lasted for two minutes. The order of blocks (i.e., eyes closed or eyes open first) was counterbalanced across participants. In the eyes open condition, participants were instructed to fixate on a black cross presented in the centre of a white screen. In the eyes closed condition participants were simply asked to close their eyes. Participants were instructed to remain still, try to relax and not tense their muscles during the course of the experiment.

7.5.1 EEG acquisition

EEG recordings were conducted in an electrically shielded room (Model L3000; Belling Lee, Enfield, England) using 128-channel Ag/AgCl electrode nets (Tucker, 1993). The Geodesic sensor net distributes electrodes from nasion to inion and from left to right mastoids at uniform intervals. EEG was recorded continuously (1000-Hz sample rate; 0.1–100 Hz analogue bandpass) with Electrical Geodesics Inc. amplifiers (300-MΩ input impedance). A Macintosh computer was used to acquire the data using NetStation software and this was then stored on the computer’s hard disk. Electrode impedances were kept below 40 kΩ, an acceptable level for this system (Tucker, 1993). Common vertex (Cz) was used as a reference, resulting in a total of 129 electrodes.

7.5.2 EEG processing

Coherence is a measure of the degree to which there is a co-occurrence of a particular frequency oscillation in the EEG recorded at different electrodes on the scalp. Coherence
measures can give researchers an idea of the synchronisation of activation between locations (Vissers, Cohen, & Geurts, 2012b).

The processing of the resting state data was conducted in a two steps. The first step was to segment the data and separate into frequency bands. Data were segmented using in house software (WinView) to remove any artefacts according to the guidelines set out in (Jervis et al., 1985). Thereafter, the data was split into alpha (5-7Hz) and theta (8-12Hz) bands. The second step was to transform the data for each condition using a Fast Fourier Transform (ArcTanH(sqrt(y))) to calculate the variation of the correlation as a function of time in each power band. 512ms windows, shifting across each block, was subject to a Fast Fourier Transformation to change the data from the time to the frequency domain. This resulted in four conditions for each participant. 1. Alpha Band: Eyes closed, 2. Alpha Band: Eyes open, 3. Theta Band: Eyes closed, 4. Theta Band: Eyes open.

7.5.3 Coherence analysis

Pairs of electrodes were selected for coherence analysis (see Table 7.2 for a list of electrode pairs). The pairs selected were the same as those used in similar research. Electrode pairs were selected using the international 10-20 system (Homan, Herman, & Purdy, 1987).
Table 7.2. Table shows all electrode pairs selected for analysis in the experiment, the area of the brain they are located over, and whether they are inter-hemispheric or intra-hemispheric connections.

<table>
<thead>
<tr>
<th>Electrode Pair</th>
<th>Area</th>
<th>Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3 – O1</td>
<td>Frontal – Occipital</td>
<td>Intra-hemispheric</td>
</tr>
<tr>
<td>F4 – O2</td>
<td>Frontal – Occipital</td>
<td>Intra-hemispheric</td>
</tr>
<tr>
<td>Fp1 – F3</td>
<td>Frontal polar – Frontal</td>
<td>Intra-hemispheric</td>
</tr>
<tr>
<td>Fp2 – F4</td>
<td>Frontal polar – Frontal</td>
<td>Intra-hemispheric</td>
</tr>
<tr>
<td>C3 – P3</td>
<td>Central* – Parietal</td>
<td>Intra-hemispheric</td>
</tr>
<tr>
<td>C4 – P4</td>
<td>Central* – Parietal</td>
<td>Intra-hemispheric</td>
</tr>
<tr>
<td>Fp1 – Fp2</td>
<td>Frontal Polar – Frontal Polar</td>
<td>Inter-hemispheric</td>
</tr>
<tr>
<td>F7 – F8</td>
<td>Frontal – Frontal</td>
<td>Inter-hemispheric</td>
</tr>
<tr>
<td>F3 – F4</td>
<td>Frontal – Frontal</td>
<td>Inter-hemispheric</td>
</tr>
<tr>
<td>C3 – C4</td>
<td>Central* – Central*</td>
<td>Inter-hemispheric</td>
</tr>
<tr>
<td>P3 – P4</td>
<td>Parietal – Parietal</td>
<td>Inter-hemispheric</td>
</tr>
<tr>
<td>O1 - O2</td>
<td>Occipital – Occipital</td>
<td>Inter-hemispheric</td>
</tr>
</tbody>
</table>

* Please note that there exists no central lobe and this is simply a reference to the placement of the electrodes

7.5.4 Statistical analyses

All statistical analyses were conducted using SPSS version 20 software. The main analyses used were ANOVA and Pearson’s correlations to investigate if there were any differences within or between subjects on coherence measures for each power band. Due to unequal sample sizes, Kruskall Wallis non-parametric statistics were conducted on comorbid populations. All p-values were deemed significant at the .05 level unless otherwise indicated. All significant effects were followed up by Bonferroni post-hoc tests.

In order to increase statistical power, values for each pair of electrodes were averaged across area. For example, the frontal-frontal electrode pairs (F7-F8 and F3-F4) were averaged to produce one value for frontal-frontal coherence. Preliminary analyses revealed that there
were no significant differences in coherence values between electrode pairs before they were averaged \((p > .05)\).

### 7.6 Results

#### 7.6.1 Alpha eyes closed

A 2 (gender: male, female) X 4 (experimental group: ADHD, anxiety, ASD and control) multivariate ANOVA was conducted on the eyes closed alpha band coherence values. There were no significant effects for any coherence values for either gender or experimental group. There was an interaction between gender and experimental group for the frontal-frontal inter-hemispheric coherence scores that was approaching significance, \(F(3,39) = 2.80, p = .053\). For the ADHD group only, males \((M = 1.08, SE = .10)\) had significantly higher coherence values than females \((M = .72, SE = .13, p = .035)\), as shown in Figure 7.1.

![Figure 7.1](image)

*Figure 7.1. Interaction between gender and experimental group for the frontal-frontal inter-hemispheric coherence values in the alpha eyes closed condition.*

#### 7.6.2 Alpha eyes open

A 2 (gender) X 4 (experimental group: ADHD, anxiety, ASD and control) multivariate ANOVA was conducted on the eyes open alpha band coherence values. There was a significant main effect of gender for the frontal-frontal intra-hemispheric coherence
values, $F(1, 38) = 7.81, p = .008$, where females ($M = 1.20, SD = .37$) had lower coherence than males ($M = 1.44, SD = .43$), as shown in Figure 7.2.

There was also an interaction between experimental group and gender that was approaching significance for central-central inter-hemispheric coherence scores, $F(3, 38) = 2.52, p = .072$, as shown in Figure 7.3. For males only, those with ADHD ($M = .77, SD = .13$) had higher coherence values than controls ($M = .24, SD = .13, p = .044$). In addition, for those with ADHD only, females ($M = .25, SE = .17$) had lower coherence values than males ($p = .015$).
7.6.3 Theta eyes closed

A 2 (gender) X 4 (experimental group: ADHD, anxiety, ASD and control) multivariate ANOVA was conducted on the eyes closed theta band coherence values. There was a significant main effect of gender for central-central inter-hemispheric coherence scores, $F(1, 39) = 5.44, p = .025$, where females ($M = .51, SE = .06$) had higher coherence than males ($M = .32, SE = .06$), as shown in Figure 7.4.
There was also a significant main effect of experimental group for central-central inter-hemispheric coherence values, $F(3, 39) = 3.32, p = .030$. Post hoc test however, reveal no differences between the groups.

### 7.6.4 Theta eyes open

A 2 (gender) X 4 (experimental group: ADHD, anxiety, ASD and control) multivariate ANOVA was conducted on the eyes open theta band coherence values. There was a significant main effect of gender for central-central inter-hemispheric coherence values, $F(1, 39) = 5.28, p = .027$. Females ($M = .56, SE = .07$) had higher coherence values than males ($M = .33, SE = .07$), as shown in Figure 7.5.
There was a main effect of experimental group for the frontal-frontal intra-hemispheric coherence values that was approaching significance, $F(3, 39) = 2.39, p = .083$. Post hoc tests however, show no differences between the groups. There was also a main effect of experimental group for occipital-occipital inter-hemispheric coherence that was approaching significance $F(3, 39) = 2.73, p = .057$ (see Figure 7.6). Those with ASD ($M = 1.41, SE = .47$) had lower coherence than those with ADHD ($M = 1.89, SE = .40, p = .076$).
Figure 7.6. Significant main effect of occipital-occipital inter-hemispheric coherence in the theta eyes open condition.

There was an interaction between gender and experimental group for central-central inter-hemispheric coherence values that was approaching significance, $F(3, 39) = 2.49, p = .074$. For those with ASD only, males ($M = .33$, $SE = .09$) had lower coherence scores than females ($M = .87$, $SE = .17$, $p = .010$), as shown in Figure 7.7.

Figure 7.7. Significant interaction between experimental group and gender of central-central inter-hemispheric coherence values in the theta eyes open condition.
CHAPTER 7 - STUDY FIVE: RESTING STATE

7.6.5 Non-parametric analyses

A Kruskall-Wallis test was conducted to investigate whether coherence values were different between pure experimental groups, and were followed up with Mann Whitney-U tests. The results show a significant difference between groups for the alpha central-central inter-hemispheric eyes closed condition, $\chi^2(3) = 7.83, p = .050$. The ASD group ($M = .58, SE = .32$) had higher coherence than the control group ($M = .27, SE = .03$) for the alpha central-central inter-hemispheric eyes closed condition, $U = 8.00, p = .020$, and the anxiety ($M = .37, SE = .11$) group $U = 7.00, p = .027$, as shown in Figure 7.8.

![Figure 7.8](image)

*Figure 7.8. Significant main effect of pure experimental groups in the alpha central-central inter-hemispheric eyes closed condition.*

The theta frontal-frontal intra-hemispheric coherence eyes closed values were approaching significance, $\chi^2(3) = 6.93, p = .074$. The ASD group ($M = .82, SE = .12$) had lower coherence scores than the control group ($M = 1.19, SE = .07, U = 8.00 p = .020$), and the anxiety group ($M = 1.21, SE = .08, U = 6.00, p = .020$), as shown in Figure 7.9.
7.6.6 Correlations

A Pearson’s correlation was conducted between the following variables and coherence for the Alpha and Theta bands: Continuous Performance Task (CPT), Behavioural Inhibition Scale, Response Reward, Drive, Fun Seeking, GAD, Obsessive Compulsive Inventory (OCI), Adult Self-Report ADHD scale (ASRS) and the Autism Spectrum Quotient (ASQ). Given that Chapter 3 reveals that these tools accurately capture participants diagnoses, we feel justified in using them for this correlational analyses. There was a significant moderate positive correlation between Frontal-Occipital Intra-hemispheric eyes closed and the GAD, $r = .30, p = .041$, a moderate positive relationship between the Frontal-Occipital Intra-hemispheric Eyes open and Fun Seeking scores, $r = .30, p = .038$, a moderate negative correlation between the Central-Parietal Intra-hemispheric Eyes Open and the CPT, $r = -.39, p = .006$, a moderate positive correlation between the Frontal-Frontal Inter-hemispheric Eyes Open and fun seeking scores, $r = .34, p = .023$, and the ASRS, $r = .37, p = .023$, a moderate negative correlation between the Central-Central Inter-hemispheric Eyes Open and the CPT, $r = -.42, p = .004$, and fun seeking scores $r = .29, p = .045$, a moderate
positive correlation between the Parietal-Parietal Inter-hemispheric Eyes Open and the ASRS, \( r = .32, p = .027 \), and finally a moderate positive correlation between the Occipital-Occipital Inter-hemispheric Eyes Open and the GAD, \( r = .39, p = .006 \), and the ASRS, \( r = .38, p = .009 \). In addition, many correlations approached significance. These can be seen in Table 7.3.

There was a significant moderate negative correlation between the Frontal-Occipital Intra-hemispheric Eyes Open and CPT scores, \( r = -.37, p = .021 \), and the Central-Parietal Intra-hemispheric Eyes Open condition and CPT scores, \( r = -.44, p = .002 \), a moderate positive correlation between the Parietal-Parietal Inter-hemispheric Eyes Closed and BIS scores, \( r = .32, p = .032 \), and the GAD scores, \( r = .44, p = .026 \), and a weak negative correlation between the Occipital-Occipital Inter-hemispheric Eyes Open and ASQ scores, \( r = -.29, p = .048 \). In addition, many correlations approached significance. These can be seen in Table 7.4.
### Table 7.3. Correlations between coherence measures for each area, with eyes open or closed for the Alpha band.

<table>
<thead>
<tr>
<th>Alpha Area</th>
<th>Continuous Performance Task</th>
<th>Behavioural Inhibition Scale</th>
<th>Response Reward</th>
<th>Drive</th>
<th>Fun Seeking</th>
<th>GAD</th>
<th>Obsessive Compulsive Inventory</th>
<th>Adult Self-Report ADHD scale</th>
<th>Autism Spectrum Quotient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eyes Closed</td>
<td>0.008</td>
<td>0.157</td>
<td>0.041</td>
<td>-0.02</td>
<td>-0.226</td>
<td>0.299*</td>
<td>0.162</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>Eyes Open</td>
<td>-0.214</td>
<td>-0.062</td>
<td>-0.063</td>
<td>-0.215</td>
<td>0.303*</td>
<td>-0.054</td>
<td>-0.055</td>
<td>0.137</td>
</tr>
<tr>
<td>Frontal Occipital Intra-hemispheric</td>
<td>Eyes Closed</td>
<td>0.049</td>
<td>-0.059</td>
<td>-0.001</td>
<td>-0.052</td>
<td>0.037</td>
<td>-0.008</td>
<td>-0.04</td>
<td>0.118</td>
</tr>
<tr>
<td></td>
<td>Eyes Open</td>
<td>-0.086</td>
<td>-0.031</td>
<td>0.116</td>
<td>-0.091</td>
<td>0.157</td>
<td>0.002</td>
<td>-0.032</td>
<td><strong>0.265</strong>*</td>
</tr>
<tr>
<td>Central Parietal Intra-hemispheric</td>
<td>Eyes Closed</td>
<td>-0.172</td>
<td>0.056</td>
<td>0.039</td>
<td>-0.062</td>
<td>-0.015</td>
<td>0.035</td>
<td>-0.014</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>Eyes Open</td>
<td><strong>-0.393</strong>*</td>
<td>-0.026</td>
<td>0.151</td>
<td>0.051</td>
<td>0.225</td>
<td>-0.187</td>
<td>-0.139</td>
<td>0.083</td>
</tr>
<tr>
<td>Frontal Frontal Inter-hemispheric</td>
<td>Eyes Closed</td>
<td>-0.143</td>
<td>-0.04</td>
<td>-0.119</td>
<td>-0.23</td>
<td>0.062</td>
<td>0.082</td>
<td>-0.05</td>
<td>0.232</td>
</tr>
<tr>
<td></td>
<td>Eyes Open</td>
<td><strong>-0.246</strong>*</td>
<td>-0.057</td>
<td>0.062</td>
<td>-0.079</td>
<td><strong>0.335</strong>*</td>
<td>-0.036</td>
<td>0.016</td>
<td><strong>0.336</strong>*</td>
</tr>
<tr>
<td>Central Central Inter-hemispheric</td>
<td>Eyes Closed</td>
<td>-0.089</td>
<td>0.193</td>
<td>0.054</td>
<td>0.151</td>
<td>0.085</td>
<td>0.016</td>
<td>-0.183</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>Eyes Open</td>
<td><strong>-0.417</strong></td>
<td>-0.021</td>
<td>0.143</td>
<td>-0.215</td>
<td><strong>0.294</strong>*</td>
<td>-0.167</td>
<td>-0.225</td>
<td><strong>0.251</strong>*</td>
</tr>
<tr>
<td>Parietal Parietal Inter-hemispheric</td>
<td>Eyes Closed</td>
<td>-0.127</td>
<td>0.043</td>
<td>0.077</td>
<td>0.079</td>
<td>0.092</td>
<td>0.201</td>
<td>0.086</td>
<td>0.206</td>
</tr>
<tr>
<td></td>
<td>Eyes Open</td>
<td>-0.103</td>
<td>0.232</td>
<td>0.073</td>
<td>-0.058</td>
<td>0.187</td>
<td>0.277</td>
<td><strong>0.263</strong>*</td>
<td><strong>0.322</strong>*</td>
</tr>
</tbody>
</table>
## CHAPTER 7 - STUDY FIVE: RESTING STATE

| Occipital Occipital Inter-hemispheric | Eyes Closed | | | | | | | | Eyes Open | | | | | | | | | | |
|---------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
|                                       | -0.134      | -0.08       | 0.118       | -0.04       | 0.054       | 0.113       | 0.009       | 0.197       | -0.07       |
|                                       | 0.001       | 0.048       | 0.158       | 0.036       | 0.129       | 0.392**     | 0.202       | 0.378**     | -0.101      |

* Significant at the .05 level. ** Significant at the .001 level *** Approaching significance at the < .1 level
## Table 7.4. Correlations between coherence measures for each area, with eyes open or closed for the theta band.

<table>
<thead>
<tr>
<th>Theta area</th>
<th>Continuous Performance Task</th>
<th>Behavioural Inhibition Scale</th>
<th>Response Reward</th>
<th>Drive</th>
<th>Fun Seeking</th>
<th>GAD</th>
<th>Obsessive Compulsive Inventory</th>
<th>Adult Self-Report ADHD scale</th>
<th>Autism Spectrum Quotient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Occipital Intra-hemispheric Eyes Closed</td>
<td>0.051</td>
<td>0.104</td>
<td>-0.047</td>
<td>0.058</td>
<td>-0.136</td>
<td>0.065</td>
<td>-0.034</td>
<td>-0.253***</td>
<td>-0.056</td>
</tr>
<tr>
<td>Eyes Open</td>
<td>-0.336*</td>
<td>-0.122</td>
<td>-0.013</td>
<td>-0.043</td>
<td>0.257***</td>
<td>0.145</td>
<td>-0.075</td>
<td>0.167</td>
<td>0.059</td>
</tr>
<tr>
<td>Frontal Frontal Intra-hemispheric Eyes Closed</td>
<td>0.153</td>
<td>-0.014</td>
<td>0.013</td>
<td>-0.019</td>
<td>-0.103</td>
<td>0.126</td>
<td>0.109</td>
<td>0.005</td>
<td>-0.236</td>
</tr>
<tr>
<td>Eyes Open</td>
<td>0.019</td>
<td>-0.022</td>
<td>0.136</td>
<td>-0.119</td>
<td>0.017</td>
<td>0.13</td>
<td>0.054</td>
<td>0.187</td>
<td>-0.254***</td>
</tr>
<tr>
<td>Central Parietal Intra-hemispheric Eyes Closed</td>
<td>-0.122</td>
<td>0.107</td>
<td>0.23</td>
<td>0.18</td>
<td>-0.087</td>
<td>0.11</td>
<td>-0.024</td>
<td>-0.057</td>
<td>0.121</td>
</tr>
<tr>
<td>Eyes Open</td>
<td>-0.439**</td>
<td>0.076</td>
<td>0.278***</td>
<td>0.265***</td>
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<td>0.06</td>
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<td>0.2</td>
<td>0.056</td>
</tr>
<tr>
<td>Frontal Frontal Inter-hemispheric Eyes Closed</td>
<td>-0.004</td>
<td>0.093</td>
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<td>-0.11</td>
<td>-0.208</td>
<td>0.14</td>
<td>0.044</td>
<td>0.045</td>
<td>0.036</td>
</tr>
<tr>
<td>Eyes Open</td>
<td>-0.105</td>
<td>0.032</td>
<td>-0.013</td>
<td>-0.147</td>
<td>0.121</td>
<td>0.038</td>
<td>0.016</td>
<td>0.053</td>
<td>-0.083</td>
</tr>
<tr>
<td>Central Central Inter-hemispheric Eyes Closed</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes Open</td>
<td>0.014</td>
<td>-0.01</td>
<td>0.098</td>
<td>-0.209</td>
<td>0.174</td>
<td>0.174</td>
<td>-0.075</td>
<td>-0.032</td>
<td>0.186</td>
</tr>
<tr>
<td>Eyes Open</td>
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<td>0.037</td>
<td>-0.1</td>
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<td>0.096</td>
<td>-0.065</td>
<td>-0.265***</td>
<td>0.006</td>
<td>0.029</td>
</tr>
<tr>
<td>Parietal Parietal Inter-hemispheric Eyes Closed</td>
<td>-0.027</td>
<td>0.324*</td>
<td>0.094</td>
<td>0.141</td>
<td>-0.113</td>
<td>0.440</td>
<td>0.227</td>
<td>0.162</td>
<td>0.192</td>
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<tr>
<td></td>
<td>Eyes Open</td>
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<td>-0.002</td>
<td>-0.103</td>
<td>0.208</td>
<td>0.153</td>
<td>0.048</td>
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</tr>
<tr>
<td><strong>Occipital Occipital Inter-hemispheric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes Closed</td>
<td>-0.048</td>
<td>0.022</td>
<td>0.14</td>
<td>-0.022</td>
<td>-0.091</td>
<td><strong>0.266</strong>*</td>
<td>0.024</td>
<td>0.156</td>
<td>-0.163</td>
</tr>
<tr>
<td>Eyes Open</td>
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<td>0.066</td>
<td>0.08</td>
<td>0.161</td>
<td>0.138</td>
<td>-0.139</td>
<td>0.231</td>
<td><strong>-0.290</strong>*</td>
</tr>
</tbody>
</table>

* Significant at the .05 level. ** Significant at the .001 level. *** Approaching significance at the < .1 level.
7.7 Discussion

The main aim of this study was to investigate whether resting state connectivity, measured by 128 channel EEG oscillation coherence, differs between developmental disorders. This is part of a larger research effort to identify the role that comorbid conditions play in ASD. Analyses were conducted separately on groups with and without comorbid conditions. Overall, the analyses revealed differential patterns of coherence in the ASD group (in particular, higher coherence in the primary motor cortex, and lower coherence in the frontal lobe networks compared to neurotypical controls). In addition, there was increased coherence in the occipital lobe in the ADHD group. These patterns of altered connectivity were expected given the research outlined above. Each will now be discussed in turn.

7.7.1 Pure ASD, ADHD, anxiety and neurotypical controls

Differences in resting state coherence were apparent when the groups included only the pure form of each disorder (i.e., removing those with comorbid conditions from the analyses). Those with ASD have higher coherence in alpha across central inter-hemispheric sites when the eyes were closed, relative to those with only anxiety or controls. That the difference is apparent in the eyes closed condition is consistent with previous research that demonstrates that alpha power increases when subjects close their eyes (Goldman, Stern, Engel, & Cohen, 2002). The central inter-hemispheric electrodes (C3 and C4 using the international 10-12 system) are located over the primary somatosensory cortex, in the parietal lobe, which is responsible for processing touch and sensation in addition to keeping track of the location of your body parts (Geyer, Schleicher, & Zilles, 1999). As mentioned previously, higher coherence reflects a higher synchrony of neural oscillations in a particular band (the amount of neural activity dedicated to that process) (Klimesch, 1999). Higher alpha coherence in this region is interesting given that those with ASD have well-documented
sensory hypersensitivity, especially to touch (Baron-Cohen, Ashwin, Ashwin, Tavassoli, & Chakrabarti, 2009), and have aberrant body movements (American Psychiatric Association, 2013). Therefore, the results of the current study suggest that the behavioural profile of sensory hypersensitivity to stimuli may be reflected in increased alpha power across the primary somatosensory cortex.

The theta frontal intra-hemispheric coherence values when the eyes were closed were lower in the ASD group versus those with anxiety or controls. This finding is consistent with research demonstrating high theta power in neurotypical controls during rest or relaxation (Klimesch, 1999). To illustrate, one study found significantly higher theta power in the frontal and temporal-central areas of the brain during meditation versus rest (Lagopoulos et al., 2009), suggesting that theta increases as higher relaxation occurs. This pattern of activity was not evident in the ASD group. The electrodes used in the current study for the theta frontal intra-hemispheric coherence analysis were all located over the frontal lobe. The frontal lobe is associated with executive function, complex tasks that require working memory, motor planning and logical and emotional attention (Stuss, Alexander, & Benson, 1997). A pattern of hypocoherence in the Fp1-F3 and Fp2-F4 electrodes has been specifically associated with less efficient integration of motor actions and logical attention (Walker, Kozlowski, & Lawson, 2007). Those with ASD have well-documented difficulties with motor actions and logical attention, especially joint attention (Dawson et al., 2004b; Théoret et al., 2005). Thus, these behavioural difficulties could be reflected in lower overall theta power in the frontal lobe.

7.7.2 Group level analyses including comorbid conditions

There were few differences in resting state connectivity between groups when comorbid conditions were included. One effect that was trending toward significance was
that the ADHD group had higher inter-hemispheric theta (eyes open) coherence across the occipital lobe relative to the ASD group. While a pattern of increased connectivity suggests more dedicated neural processing, a pattern of coherence higher to that seen in neurotypical controls suggests that the processes are less flexible in these individuals (White et al., 2009). This finding is consistent with previous literature demonstrating increased theta coherence in the inter-hemispheric occipital regions in ADHD (Clarke et al., 2007). The occipital lobe is primarily involved in visual processing. As such, a pattern of hypercoherence in this area has been shown to result in a lack of flexibility in visual sensations (Walker et al., 2007). This finding fits with the behavioural profile of those with ADHD who experience difficulties with visual attention (Lopez et al., 2006). The results of the current study suggest that visual attention difficulties in ADHD may be driven by hypocoherence in the occipital lobe.

This inter-hemispheric increase in coherence may also be associated with the established patterns of atypical laterality in ADHD. While typically developing controls show hemispheric specialisation (i.e., higher involvement of one hemisphere over the other) for tasks such as language, this hemispheric specialisation is not as pronounced in ADHD (e.g., Maxwell et al., 2013; Waldie & Hausmann, 2010). It is possible that the pattern of hypocoherence seen in the occipital lobe in those with ADHD may be, in part, caused by atypical laterality in the ADHD brain.

In the alpha band with eyes open, females had lower intra-hemispheric coherence than males in the frontal regions. In the theta band with eyes closed and eyes open, females had higher inter-hemispheric coherence scores than males in the central region. Gender differences in EEG coherence have been reported in the past, and may be due to anatomical differences in brain structure and development between the sexes (Hanlon, Thatcher, & Cline, 1999). As these differences are limited to the central and frontal regions, both regions
where aberrant connectivity was found in those with ASD, it is also possible that the gender imbalance in the ASD group contributed to this effect.

An overall aim of the current study is to determine whether comorbid conditions in ASD are separate (i.e., additive) or simply symptoms of the ASD itself (i.e., a misdiagnosis). Some theorists and practitioners believe that hyperactivity or anxiety when presented together with ASD is simply a characteristic of the ASD (Taurines et al., 2012). If this were the case, then we would expect the patterns of coherence differences that are evident in the ASD only group to be either very similar, albeit more pronounced when additional conditions are added to the analyses. Evidence from the current data suggest that this is not the case. The patterns of coherence in the ASD pure group are no longer present when additional conditions are included in the analyses. Data from the pure group analyses show coherence differences are limited to the sensory motor cortex and frontal cortex in ASD, and the occipital lobe in ADHD. Therefore, the patterns of aberrant coherence in the frontal and central areas of the brain are specifically associated with ASD and a different pattern of coherence is produced when ASD presents as a comorbid condition. This suggests that the two conditions are additive.

### 7.7.3 Correlational analyses

The final question of interest was whether coherence values were associated with the phenotype of the various disorders (i.e., hyperactivity, anxiety, social skill difficulties). Differences in coherence scores are indeed associated with characteristics of ADHD and generalised anxiety. Overall, there was a pattern of increased coherence associated with increased characteristics of ADHD and anxiety. In ASD however, while there was less of an association, patterns of decreased coherence were somewhat associated with an increase in symptoms. Below the CPT, ASRS, fun-seeking and GAD coherence results will be discussed
The regions associated with increased coherence on the CPT and fun-seeking scales were similar. As scores on the continuous performance task (which measures visual and auditory attention) decreased (demonstrating more severe symptoms of ADHD), coherence scores increased in the following areas: the central-parietal intra-hemispheric (in both alpha and theta); the central inter-hemispheric (alpha, with theta trending toward significance) regions; and the frontal inter-hemispheric (trending toward significance in alpha, theta), and the frontal-occipital intra-hemispheric (theta only) regions. As determined in Chapter three, fun-seeking scores were a significant predictor of ADHD. Using this measure we were able to distinguish those with ADHD from neurotypical controls, where those with ADHD had higher fun-seeking scores. As scores on the fun seeking scale increased, so did coherence for the frontal-occipital intra-hemispheric (alpha, theta trending toward significance), frontal inter-hemispheric (alpha) and the central inter-hemispheric regions (alpha).

As scores on the ASRS increased, coherence in the frontal inter-hemispheric (alpha, theta trending), parietal inter-hemispheric (alpha only) and the occipital inter-hemispheric (alpha only) increased. There was a trend towards an effect in the frontal intra-hemispheric and the central intra-hemispheric areas (with both increasing simultaneously in alpha only). This finding is in line with the group level analyses discussed earlier that demonstrated increased coherence in the occipital area for those with ADHD.

Increased inter-hemispheric coherence in the frontal and central areas have been shown to be associated with lack of flexibility in logical attention. Increased coherence in the central parietal region has been associated with less flexible sensorimotor integration, and finally, increased coherence in frontal-occipital coherence has been associated with less flexible integration of visual sensations (Walker et al., 2007). As mentioned previously, a pattern of coherence higher to that seen in neurotypical controls suggests that the processes are less flexible in these individuals (White et al., 2009). Accordingly, behavioural studies
CHAPTER 7 - STUDY FIVE: RESTING STATE

have established a pattern of difficulties with logical attention (Mirsky, Pascualvacca, Duncan, & French, 1999), sensorimotor integration (in particular, motor preparation, timing and adjustment, and delayed motor action processes) and visual sensations (Banaschewski, Besmens, Zieger, & Rothenberger, 2001; Lopez et al., 2006) in ADHD.

Increases in coherence scores are also associated with characteristics of anxiety. As scores on the GAD increase, so did coherence scores in the frontal-occipital intra-hemispheric (alpha only) region and the occipital inter-hemispheric region (alpha, approaching theta band). In the theta band as scores on the GAD increased, so did coherence values in the parietal inter-hemispheric region. As scores on the OCI increased, there was a trend toward an increase in parietal inter-hemispheric coherence scores in the alpha band, and central inter-hemispheric scores in the theta band. Increased coherence in these regions has been linked to a lack of flexibility in visual sensations (Walker et al., 2007).

While there is little literature to suggest a link between less flexible visual sensations and anxiety, it is well known that those with anxiety have an automatic and instinctive reaction to objects or situations that may or may not represent true danger (Mowrer, 1939). To illustrate, one study presented participants with anxiety with either positive or negative motivational (i.e., a ‘win’ or a ‘loss’ in a game) stimuli. Those with anxiety were significantly faster to respond to the negative versus positive stimuli, which suggests earlier processing for negative emotional states (Derryberry & Reed, 1998). In addition, those with anxiety show a high vigilance toward threatening stimuli (where threatening stimuli are processed much more quickly that non-threatening stimuli) (Calvo & Eysenck, 2000). This pattern of early processing for negative over positive stimuli could be driven by less flexible response to visual stimuli, where there is automaticity for processing negative or threat-based stimuli that is driven by a pattern of hypercoherence in underlying brain networks. To the best of our knowledge, there are no studies investigating resting-state EEG coherence in anxiety. Thus,
CHAPTER 7 - STUDY FIVE: RESTING STATE

this is the first study to demonstrate that increased coherence in the frontal occipital, occipital and parietal regions is associated with increased behaviour of anxiety.

There is less of an association between scores on the ASQ and coherence values. As scores on the ASQ increased, coherence values decreased in the occipital inter-hemispheric region, and there was a trend toward significance in the theta band for the frontal intra-hemispheric region (where coherence scores decreased as ASQ scores increased). Decreased theta coherence in the frontal region fits with the analyses conducted on ASD pure groups demonstrating the same effect. However, the decreased coherence in the occipital lobe was not found in the initial analyses. This may be due to small sample sizes contributing to lower statistical power. Interestingly, this pattern of decreased coherence in the occipital lobe is the exact opposite to the profile seen in those with ADHD (where coherence was increased). Therefore, while a lack of flexibility to visual sensations is seen in ADHD, decreased coherence in ASD suggest dysfunctional integration of information related to visual sensations.

Coherence measures underlying connectivity of brain networks, that is, the amount of neural activity communicated between regions (Murias et al., 2007). The current study found overall patterns of decreased coherence, therefore suggesting decreased connectivity in those with ASD. While an initial overgrowth in brain volume is evident in ASD in early childhood, this overgrowth slows and brain volumes are comparable to healthy controls in adulthood (Courchesne, Campbell, & Solso, 2011). This suggests that the neural pruning mechanisms in the ASD brain do not function as they do in neurotypical adults, which may result in patterns of decreased connectivity in specific pathways. This finding is in line with an established body of literature demonstrating decreased connectivity in ASD (Anderson et al., 2011; Kana, Keller, Cherkassky, Minshew, & Just, 2006). Interestingly, connectivity is decreased in the areas of the brain which reflect emotional and sensorimotor processing, processes which
those with ASD display deficits. Decreased neural integration for these functions may underlie these difficulties.

### 7.7.4 Practical implications

It is possible to alter the strength of neural coupling (i.e., connectivity) in the brain with training. The brain is plastic and therefore responds to change with physical alterations of function or anatomy (Draganski & May, 2008). For example, research has demonstrated that training on a working memory task increased white matter tracts in the parietal region and the corpus callosum in the brain (Takeuchi et al., 2010). Another study found that relational reasoning training increased fronto-parietal and parietal-striatal connectivity at rest (Mackey, Miller Singley, & Bunge, 2013). It is possible, that intensive targeted training may help to increase connectivity in those with ASD, resulting in an improvement in behaviour. However, those with ADHD and anxiety show overall patterns of increased connectivity. It is unclear whether training would help to decrease the connectivity in this instance. Further research is needed to establish whether training would improve patterns of hyperconnectivity in those affected.

### 7.7.5 Limitations

There are limitations in the current study that warrant mention. The first and most obvious limitation is sample size. A larger-scale study where parametric statistics could be run investigating the pure-groups to their comorbid counterparts would have provided valuable information. Secondly, the individuals in the current study were high functioning. All individuals had a normal IQ with no language deficits. It could be argued individuals who are lower functioning show a completely different connectivity profile to their lower functioning counterparts. Thus, the results of the current study may not be applicable to the
entire ASD population, but rather a specific sub-set who were once referred to as having “Asperger’s”.

7.7.6 Conclusion

Overall, the results of the current study demonstrate patterns of decreased coherence in those with ASD, and patterns of increased coherence in ADHD and anxiety. Therefore, in their pure form, ASD, ADHD and anxiety have different resting state connectivity profiles from one another and neurotypical controls. These patterns are no longer evident when comorbid conditions are included in the analyses which suggests that additional conditions cannot be accounted for through the ASD diagnosis. In ASD, this decrease likely reflects a lack of neural integration for tasks relating to sensorimotor and emotional processing. In ADHD and anxiety, patterns of increased coherence likely reflect a lack of flexibility in the processing of visual stimuli, attention and sensorimotor integration. For those with anxiety, the increase in connectivity is limited to visual sensations which is likely related to their increased sensitivity to threat stimuli.
8.1 Summary of Findings

The overall aim of the current thesis was to investigate the shared behavioural and neuropsychological basis of coexisting ADHD and anxiety in ASD. Determining the nature of comorbidity in ASD is important as, while there is currently no cure for ASD, there are medical interventions that are effective in ADHD and anxiety (e.g., medication or cognitive behavioural therapies; Hofmann & Smits, 2008). The treatment of additional conditions, if they are in fact true comorbid conditions, could greatly improve everyday functioning for the ASD individual. In addition, there is often debate surrounding the presence of absence of specific difficulties in ASD. One particular example is inhibitory control, with some research suggesting a deficit (Christ, Holt, White, & Green, 2007) and others not (Kleinhans, Akshoomoff, & Delis, 2005). It is possible that inadequate screening for comorbid conditions produces a variable result in research findings. Therefore, clarifying the role of comorbidity in ASD will be valuable in maintaining consistency in the literature.

As discussed in Chapter 1, there is currently a debate in the literature over whether comorbid conditions are in fact true separate conditions, or whether they can simply be accounted for through the ASD diagnosis. To review, Wood and Gadow (2010) propose that a true comorbid condition is one in which either: (1) the presentation of each disorder together with ASD is identical to its monomorbid form in the unaffected individual (i.e., anxiety, OCD or ADHD); or (2) a condition phenotypically altered by ASD symptoms. Alternatively, symptoms are not truly comorbid, but are instead an aspect of the phenology of ASD (i.e., a behaviour or subtype of ASD) or an inaccurate diagnosis. Given the research outlined above, we argue, in this thesis, that if comorbid conditions are better conceived of as an aspect of ASD phenomenology, then the patterns of brain activation in comorbid ASD should be either a similar or an exaggerated version of that seen in pure ASD.
Until recently, most research compared the conditions separately in their pure forms, rather than comparing the pure forms to their comorbid counterparts. While this is interesting in determining how the conditions differ from one another, it does not tell us how the conditions present when they occur together. The current thesis addressed these limitations by analysing data in three ways. Firstly, using the broader diagnostic groups (i.e., ASD, ADHD and anxiety groups). Secondly, more in-depth comorbidity analyses was conducted on those with ASD only (i.e., pure ASD group) versus those with comorbid ASD and ADHD or ASD and anxiety. Third, the current thesis had the methodological advantage of a behavioural profile for each participant. That is, characteristics of ASD, ADHD, OCD and anxiety were measured using profiling tools (see Chapter 2 for a full description) to assess symptom severity. Using these continuous variables enabled us to measure the strength of the relationship between a specific behaviour and performance on the tasks in the current study.

To determine how the brain and behaviour was affected in singular versus comorbid ASD we focussed on tasks that reflected the DSM diagnostic criteria. This was achieved by examining participants’ behavioural characteristics using profiling techniques in addition to four experimental tasks during EEG recording: emotion processing; lexical decision; inhibitory control; and resting state. Together, these tasks covered a spectrum of core difficulties evident in ASD: difficulties with social interactions; language; repetitive behaviour (inhibitory control) and aberrant brain growth. By examining these neuropsychological difficulties when they occur alone in ASD versus together with ADHD or anxiety, we were able to build a profile of singular and co-occurring ASD, which may help to establish whether the difficulties are independent or simply part of the ASD diagnosis (from a neuropsychological viewpoint).
CHAPTER 8 – GENERAL DISCUSSION

The specific hypotheses and results of each study will now be summarised. Thereafter, a more detailed link to the existing body of literature will be made, with respect to the overall findings.

8.1.1 Study one – behavioural profiling

In Study 1, a number of behavioural profiling techniques (ASQ, CPT, OCI-R, ASRS, GAD, BIS/BAS) were used in order to build a behavioural phenotype of ASD, ADHD and anxiety when they occur alone versus together as a comorbid condition with ASD. This was to investigate the shared and separate nature of any symptoms in the conditions when they occur alone, and to see how this pattern of behaviour is altered when ASD presents as a comorbid condition.

Given that these profiling tools have been demonstrated to have sound validity and reliability (see Chapter 2 for a full description), we expected that each condition in its pure form would be easily differentiated from one another, and from neurotypical controls, using these measures. This is exactly what was found. Using the wider diagnostic categories (e.g., ASD, ADHD and anxiety) each group was able to be distinguished from one another and from neurotypical controls using the profiling measures.

If ADHD or anxiety were indeed separate when they presented as a comorbid condition, we expected that the scores measuring ASD symptoms would not increase but scores on the scale measuring the comorbid symptoms would increase. This is exactly what was found when ASD occurs together with anxiety. In individuals who present with both ASD and anxiety together, the symptoms of ASD do not increase, but symptoms of anxiety do increase compared to those with ASD alone. This suggests that anxiety is a separate condition when it occurs together with ASD.

On the contrary, when ASD and ADHD occur together there were significantly higher ASD symptoms than in the ASD only group. Secondly, the ASD and ADHD group show
significantly lower ADHD symptoms than the ADHD alone group, but not the ASD only group. Given the hypotheses described above, the results of the current study suggest that there might be some degree of overlap when ASD and ADHD present as a comorbid condition.

8.1.2 Study two – emotion processing

In Study 2, an emotion recognition task (responding to sad versus neutral eye or mouth stimuli) was used with EEG recording to investigate social information processing in ASD alone and in ASD when it presents as a comorbid condition with ADHD and anxiety. There are well documented differences in the N170 in those with ASD compared to neurotypical controls (e.g., O’Connor et al., 2005) where those with ASD often show a pattern of earlier and smaller N170 latencies and amplitudes. In addition those with anxiety show larger N170 with an earlier latency (Mühlberger et al., 2009), and those with ADHD may have intact N170 but altered N400 in response to emotion-based stimuli (Tye et al., 2014). The P250 has been related to the processing of facial identity and familiarity (Marzi & Viggiano, 2007) and was therefore also used in the current study.

We expected to see a pattern of earlier and smaller N170 amplitudes in the ASD group, and a pattern of larger N170 in those with anxiety compared to neurotypical controls. We also expected that the later, P250 component may be affected in those with ADHD compared to neurotypical controls. Contrary to our expectation, there were no group differences in the latency or amplitude of the N170 found in the current study.

There were however, differences in the amplitude of the P250. Those with ASD and ADHD showed a differential profile in response to sad and neutral stimuli on the P250 from one another. Those with ASD had larger amplitudes toward mouth stimuli than eye stimuli and those with ADHD had larger amplitudes toward eye stimuli toward mouth stimuli. This suggests that initial recognition of emotions is intact in ASD and ADHD but further
processing of emotion-based stimuli (as reflected in later ERP components) is differentially affected in the two groups. Additionally, there was a trend for those with anxiety to be slower to decipher the emotion portrayed (which was also reflected in the latency of the P250). This may reflect the automaticity for those with anxiety to view stimuli as threatening.

A comorbidity analyses was then conducted which specifically compared those with ASD only to those with comorbid ASD and anxiety or ADHD. This analysis demonstrated a pattern of larger N170 amplitudes in the ASD pure group versus those with ASD and anxiety or ADHD. Given that we hypothesise the pattern of ERPs should be the same or similar in those with ASD alone and comorbid ASD if the conditions were simply an aspect of ASD itself, the results of the current study suggests that the additional conditions are indeed separate and warrant their own diagnoses.

8.1.3 Study three – lexical decision

Study 3 aimed to clarify the nature of lexical information processing, using a lexical decision paradigm (deciding between real English words and nonwords or psuedowords) during EEG recording in the experimental groups (ADHD, anxiety and ASD alone versus ASD comorbid with ADHD or anxiety) versus neurotypical controls.

Given that it is well documented that the left hemisphere is responsible for language (Knecht et al., 2000), in neurotypical controls we expected to see larger and earlier left hemisphere amplitudes in this group. There is also evidence to suggest that language is not typically organised in ASD or ADHD; therefore, we did not expect to see the same degree of left hemisphere lateralisation in these groups. It was unknown whether there would be a typical or atypical lateralisation in those with anxiety, given the lack of studies in this area.

Surprisingly, the results demonstrated larger P100 amplitudes in the right versus the left hemisphere. We theorise that this early ERP component likely reflects pre-linguistic processing (e.g., the sorting of nouns into categories) at a stage before the left hemisphere,
which is specialised for language, takes over. This pattern of right hemisphere dominance of
the P100 was not shared to the same extent by those with ADHD or ASD. This suggests that
there may be some pre-lexical dysfunction in these groups. While the anxiety group also did
not share the same extent of right-hemisphere dominance for the P100, visual inspection of
the data suggest that this may be due to smaller sample size, rather than a true effect.

Next the ASD pure group was compared to its comorbid counterpart. If symptoms of
ADHD or anxiety were simply part of the ASD diagnosis, we expected to see a pattern of
ERPs similar to what was found in the ASD pure group. This was not what was found. When
the ASD and ADHD presented as a comorbid condition the latency of the P100 adopted
characteristics of each condition in its pure form (i.e., the mean latency for the comorbid
group lay between the two means for the ASD and ADHD pure groups). This suggests that
there was an additive presentation of difficulties.

8.1.4 Study four – inhibitory control

In this study, inhibitory control was investigated in those with ADHD, ASD, anxiety,
and neurotypical controls using EEG. This was done by examining two ERP components
which reflect the neural processes involved with inhibition, the N200 and P300, in response
to a stop signal task. The stop signal task is a basic go/no-go paradigm with an additional
“stop” element. This is where participants are presented with a “go” stimuli which is closely
followed by a signal to stop responding. Participants must therefore inhibit their desire to
continue with their “go” response.

While there is some uncertainty in the literature if a true inhibitory control deficit
exists in ASD, there are well documented difficulties with this function in those with ADHD
and anxiety (e.g., Bannon et al., 2002; Barkley, 1997). Therefore, we expected to see a
difference in the amplitude or latency of the N200 and P300 in those with ADHD and
anxiety, and possibly those with ASD compared to neurotypical controls. Contrary to our expectation, this was not what was found.

Group level analysis did not show any differences between the experimental groups on the latency or amplitude of the N200 or P300 components. This suggests that those with ADHD, ASD and anxiety may not be strongly associated with an inhibitory control deficit. However, when the ERP waveforms were collapsed across experimental groups, results do reveal that larger N200 amplitudes are related to “stopping” a response, whereas larger P300 amplitudes are involved in making the correct response (i.e., the “go trials”). This is in line with previous literature on the N200 and P300 components and demonstrates that the task is an appropriate measure of inhibition.

Upon closer inspection using regression analyses, smaller N200 and P300 amplitudes were associated with more severe symptoms of ADHD. This suggests some disruption of the underlying neural networks in those affected. Therefore, while no distinct profiles between the main experimental groups emerged, an inhibitory control deficit may be associated with characteristics of ADHD only.

8.1.5 Study five – resting state

The final study in this thesis aimed to investigate whether characteristics of ASD, ADHD, or anxiety are associated with altered resting state connectivity as assessed with EEG coherence. There is evidence to suggest altered resting state cortical activity in each of the three conditions (e.g., Belmonte et al., 2004; Jang et al., 2010; Konrad & Eickhoff, 2010). Therefore, we expected to see group differences in coherence values for the ASD, anxiety and ADHD groups compared to neurotypical controls. This is indeed what was found. The results demonstrate patterns of decreased coherence in those with ASD, and patterns of increased coherence in ADHD and anxiety compared to neurotypical controls.
CHAPTER 8 – GENERAL DISCUSSION

Given the research discussed in-depth in Chapter 7, we theorise that in ASD this decrease likely reflects a lack of neural integration for tasks relating to sensorimotor and emotional processing. In ADHD and anxiety, patterns of increased coherence likely reflects a lack of flexibility in the processing of visual stimuli, attention and sensorimotor integration. For those with anxiety, the increase in connectivity is limited to integration of visual sensations which is likely related to their increased sensitivity to threat stimuli. Therefore, in their pure form, ASD, ADHD and anxiety have different resting state connectivity profiles from one another and from neurotypical controls.

In accordance with the overall hypothesis of this thesis, if symptoms of ADHD or anxiety were simply part of the ASD diagnosis, we expected to see a pattern of coherence alterations similar to what was found in the ASD pure group. However, this was not what was found. The patterns of coherence established in the ASD pure group are no longer evident when comorbid conditions are included in the analyses. This suggests that the conditions are additive as a different pattern of coherence is evident in those with comorbid ASD.

8.2 Comorbidity in ASD

Few theories on the basis of comorbidity in ASD exist. However, researchers and practitioners are divided on determining true comorbidity from symptoms of ASD. Bradshaw’s frontostriatal model (2001) proposes that ASD, ADHD and anxiety all stem from a dysfunction in the frontostriatal system of the brain. The conditions seem separate as they each adopt different difficulties that stem from frontal lobe dysfunction (i.e., executive function deficits), but are essentially all caused by the same core deficit. This suggests that the comorbid conditions are not separate, but rather those with symptoms of more than one conditions simply adopt more of these ‘frontal lobe deficits’ than others.
Since the research for the current thesis began, there has been an emerging body of work that also investigates the neuropsychological profile of ASD in its pure versus comorbid form. For example, a recent study which investigated temporal discounting using fMRI demonstrated that while those with ASD and ADHD have different patterns of brain activity, those with comorbid ASD and ADHD do not show a pattern of activity that more strongly resembles that of either ASD or ADHD in its pure form (Chantiluke et al., 2014). The authors argue that this is evidence for neither separate nor additive effects, but rather something else altogether (which the authors do not speculate). In another study, Tye and colleagues (2014), who investigated responses to emotional stimuli (i.e., images of faces with disgust, fear, anger, joy or neutral expressions) in children with ASD, ADHD and coexisting ASD and ADHD, found that while the ASD and ADHD children had different neurophysiological profiles in response to the stimuli, those with coexisting ASD and ADHD showed unique deficits of each disorder. This suggests that when presented as a coexisting disorder, the individual adopts characteristics of each disorder, suggesting an additive effect.

Taken together, the results in the current thesis are in line with the existing body of research which demonstrates the additive nature of comorbid ASD and ADHD or anxiety. While the literature outlined in Chapter 1 certainly demonstrates that there are behavioural similarities between the three conditions, the results of the current thesis suggest that these difficulties may be more widespread than the frontal lobe, as suggested in Bradshaw’s (2001) model. Specific evidence for this argument will now be provided below.

8.3 ASD and Anxiety

The results in the current thesis support the theory that the ASD and anxiety are indeed additive (i.e., separate) conditions. In particular, the results of Studies 1, 3 and five provide the strongest support for this theory. Each will now be discussed.
In Study 3, the comorbidity analyses show significantly lower amplitudes in those with comorbid ASD versus those with ASD alone (who had significantly larger amplitudes than those in the comorbid ASD group). Interestingly, correlational analyses in the same study demonstrated that symptoms of anxiety and OCD are associated with lower amplitudes. Thus, the addition of anxiety produced a pattern of ERPs that was lower than that in ASD alone. This suggests that when the two conditions present together the underlying neural networks adopt unique characteristics of each condition.

In Study 1, ASD symptom severity scores did not increase in those with ASD and anxiety as we would expect if the anxiety was a misinterpreted symptom of ASD. In contrast, anxiety scores in those with ASD and anxiety did increase compared to those with pure ASD.

Finally, the results of Study 5 also support the theory that ASD and anxiety are separate conditions. In their pure forms, anxiety was associated with increases in connectivity, whereas ASD was associated with decreases in connectivity. When comorbid conditions were included in the analyses the two groups no longer had significantly different patterns of coherence from one another. This suggests that the phenotype of connectivity in ASD is altered when anxiety is included in the analyses.

Results from Study 5 also show that aberrant connectivity (compared to neurotypical controls) is limited to connections in the occipital lobe, whereas those with ASD demonstrate alterations in connectivity in the frontal area. This finding does not support Bradshaw’s frontostriatal model (2001) that both anxiety and ASD stem from difficulties in the frontal lobe. If this were the case we would expected the anxiety group to share alterations in connectivity in the frontal lobe. This provides further support for the theory that the conditions are indeed separate.

However, the results of Study 1 also demonstrate that there is a higher rate of anxiety in those with ASD only versus neurotypical controls. This suggest that there may be some
degree of overlap in the diagnostic criteria of anxiety and ASD. As discussed in Chapter 1, those with ASD may show behaviour of anxiety due to their difficulty with everyday social situations (i.e., a lack of functional skills to be able to cope in a social situation), whereas those with true anxiety disorder may view a benign social situation as threatening and therefore display anxiety (Wood & Gadow, 2010). The distinction here is that anxiety due to a known inability to perform could be considered relatively normal (liken this to a student being anxious about a test for which they have not studied) whereas anxiety for no particular reason may warrant a diagnosis. Therefore, determining the amount of anxiety that is considered ‘typical’ may help to clarify anxiety in ASD and could even reduce comorbidity rates (by determining disordered versus typical anxiety).

Alternately, this distinction in the diagnostic criteria of ASD and anxiety is reflected in the results of Studies 2 and 5. ASD is classified as pervasive developmental disorder while GAD and OCD are a subset of anxiety disorders (American Psychiatric Association, 2013). The most notable difference is that ASD is a lifelong neurodevelopmental disorder for which there is no cure, whilst anxiety disorder may be a temporary state (e.g., may come and go throughout an individual’s life) and is curable through techniques such as cognitive behavioural therapy (Hofmann & Smits, 2008). This distinction between ASD and anxiety in their pure forms is reflected in the results of the emotion processing tasks and overall brain connectivity studies in this thesis.

8.4 ASD and ADHD

The results for the ASD and ADHD comorbid group are somewhat mixed. While studies 2, 3, and 5 give support that ASD and ADHD are separate conditions when they occur together, the results of Study 1 suggest that the ADHD may be part of the ASD diagnosis.

In Study 3 the results of the comorbidity analysis revealed that the latency of the P100 in the ASD and ADHD comorbid group took on specific characteristics seen in the pure
ADHD and pure ASD groups. Given that ASD and ADHD in their pure form had significantly different P100 latencies, we would have expected the latencies to mimic either one or the other of the groups if they were entirely separate conditions.

In Study 2, while the amplitude of the N170 was not significantly different between the wider diagnostic groups (e.g., ASD, ADHD or anxiety), closer inspection of those within the ASD group only demonstrated significantly different ERPs in those with pure ASD versus those with comorbid ASD. Again, this suggests that the conditions are separate as those with comorbid ASD adopt a different pattern of N170 ERPs compared to those with pure ASD which we would not expect if the conditions stem from the same origin.

The results of Study 5 also support the theory that ASD and ADHD are separate conditions. In their pure forms, ADHD was associated with increases in connectivity, whereas ASD was associated with decreases in connectivity. When comorbid conditions were included in the analyses the two groups no longer had significantly different patterns of coherence from one another. This suggests that the phenotype of connectivity in ASD is altered when ADHD is included in the analyses.

However, in Study 1 the results are in line with what we would expect to see if ADHD behaviour, when presented together with ASD, is a characteristic of the ASD itself. Firstly, the ASD and ADHD group show significantly higher ASQ scores than the ASD only group, indicating more severe ASD symptoms. Secondly, the ASD and ADHD group show significantly lower scores on the ASRS than the ADHD alone group, but not the ASD only group. If these conditions were indeed separate, we would expect higher ASRS scores in the comorbid group than the ASD only group, but the ASD scores between those with ASD only and ASD and ADHD should remain similar. These results suggest there is some degree of misinterpretation of ADHD symptoms within the ASD spectrum.
As mentioned above, the results of Studies 2, 3 and 5 in particular show opposite patterns of ERPs or coherence between the those with ADHD and ASD. This is important given that the results of Study 1 do suggest some overlapping symptoms. Firstly, this establishes that ADHD is indeed a developmental condition with brain-based differences to those seen in neurotypical controls. In the past there has been debate about the validity of ADHD as a real disorder (Moncrieff & Timimi, 2010). While this finding has been largely out-ruled, the results of the current research support the established body of literature which demonstrates brain-based differences in those with ADHD versus neurotypical controls (e.g., Bruce et al., 2006; Cubillo et al., 2012; Rubia et al., 2014). Secondly, this finding suggests that ADHD and ASD cannot be thought of as a condition stemming from the same origins. The idea that ADHD and ASD are differential symptoms of one overarching condition, as suggested by van der Meer and colleagues (2012), is not supported by the results in the current thesis. This is in line with a recent body of research which clearly show a distinct profile between the two conditions (Joshi et al., 2014; Sinzig, Walter, & Doepfner, 2009).

The current thesis supports the theory that ASD and ADHD are conditions with separate brain signatures, which reflects the differential diagnostic criteria between the two conditions. Together with the results of Study 1, it is probable that while ASD and ADHD are distinct conditions, there may be some misinterpretation of ADHD symptoms in those with ASD.

Misinterpretation of symptoms highlights the importance of proper and thorough screening for true comorbid conditions versus symptoms of an existing condition. It is not uncommon for the same deficit or behaviour to be driven by different brain anomalies (Whelan et al., 2012). While there is some similarities in behaviour, opposite patterns of ERPs were found in the ASD and ADHD in this thesis. This suggests that even though the underlying brain function is different in the two groups when performing emotion or lexical processing tasks, they both present with the same behaviour of lexical difficulties or troubles.
CHAPTER 8 – GENERAL DISCUSSION

with emotion processing. However, this behavioural similarity may lead to misdiagnosis by health professionals. While the presenting behaviour may be identical, it is important to recognise the difficulties in each condition as distinct, and treat them as such. Future research that identifies a screening tool to distinguish between conditions with the same behaviour but different underlying brain signatures will be of value.

8.5 Why Might These Conditions Commonly Co-occur?

The majority of the studies in the current thesis suggest that when comorbid conditions occur together with ASD, they are likely separate conditions that warrant their own diagnoses. Comorbidity rates are significantly higher in ASD than in the general population (Joshi et al., 2013). While the current thesis does not directly address the reason for this high comorbidity rate, the findings may give clues to this basis, which serves as an avenue for future research.

The findings from Study 5 show that there are distinct patterns of atypical connectivity present in both ADHD and ASD. ADHD and ASD are both classified and diagnosed as ‘pervasive developmental disorders’ (American Psychiatric Association, 2013), this categorisation could reflect similar neuronal underpinnings. There is a link between aberrant connectivity and faulty neuronal pruning. To illustrate, a study by Paulocelli (2011) and colleagues found that microglia (cells that have a search and scavenge function to eliminate excess synaptic material, a process necessary for neuronal pruning) do not function properly in those with neurodevelopmental conditions. It is therefore possible that ADHD and ASD are both caused by a mechanism which promotes aberrant brain growth from birth. If a person had such a mechanism in their genetic makeup, it is entirely plausible that they are at a higher risk for one or more conditions that is caused by faulty neuronal pruning. While findings from the current study help us toward some understanding of atypical brain
development in ASD, future research that includes a full scale genetic analysis is needed to find the cause of faulty neuronal pruning.

As discussed earlier, it is possible that some anxiety in ASD may be an aspect of the ASD diagnosis and can be distinguished from a true anxiety disorder. This suggests that a degree of anxiety in ASD may be typical and a proportion of comorbidity rates may be due to uncertainty about this distinction. While this may account for some overlap in diagnosis, the results of Studies 1 and 5, in particular, show that there is a true distinction between the two conditions. The high rates of comorbid ASD and anxiety could be caused by either a genetic contribution for anxiety (i.e., inheriting genes associated with anxiety), an environmental contribution (i.e., the learned behaviour of anxiety from caregivers), or an epigenetic contribution (i.e., the triggering of the ASD genes in-utero due to maternal stress). For example, exposure to anxiety in utero may alter an individual’s genetic presentation by acting as a trigger for the genes that underlie ASD, which suggests that ASD is caused by a combination of epigenetic and environmental factors (Persico & Bourgeron, 2006). Research has demonstrated that in-utero exposure to stress increases the risk of developing ASD (Kinney, Munir, Crowley, & Miller, 2008). This theory is further supported by genetic research which concludes that it is likely autism has a complex, epigenetic basis (Carter & Scherer, 2013). If in-utero exposure to stress triggers the ‘ASD gene’ in affected individuals, comorbid anxiety could be caused by either inheritance of an ‘anxiety gene’, or environmental exposure to anxiety behaviour from caregivers.

There is a higher rate of anxiety (especially social anxiety) in unaffected siblings and parents of those with ASD (Kuusikko-Gauffin et al., 2013). Additionally, research that investigated identical twins raised together versus raised apart has demonstrated anxiety is a highly heritable condition that can be independent of environment (Chen, Yu, Li, & Zhang, 2015). Very recent research has also identified a specific gene associated with stress and
anxiety disorders (Spadaro et al., 2015). Therefore, it is possible that in-utero exposure to stress triggers the genetic sequence necessary for ASD, while also putting the individual at increased risk for the inheritance of the anxiety genes.

Finally, the high rates of comorbidity between ASD and anxiety may be a learned behaviour from parents. There is an established body of research that demonstrates having a child with autism causes extreme stress and anxiety on the caregiver (Stuart & McGrew, 2009). The same twin studies described above also demonstrate that a proportion of anxiety can be accounted for through shared environment (Chen et al., 2015). Therefore, it is possible that anxiety in ASD is driven by learned behaviour from exposure to stressed caregivers. If this is the case, then the mental health of caregivers to those with ASD should not be overlooked, and may contribute to a decreased rate of anxiety in the ASD individual if properly managed. Further investigation into why the conditions appear to be separate (at least from a neuropsychological perspective), but have an extremely high rate of comorbidity is the next step in untangling the uncertainty surrounding comorbidity in ASD.

8.6 Summary

Together, the results of the current thesis suggest that those with ASD, ADHD and anxiety have different behavioural and brain profiles from neurotypical controls and from one another. When ASD presents as a comorbid condition, the majority of results in this thesis demonstrate that ERPs adopt unique characteristics of each condition in its pure form. We argue that this is evidence for an additive effect which suggests that the conditions are indeed separate, rather than a misinterpretation of ASD symptoms.

8.7 Limitations of the Current Thesis

While each study has its own set of limitations that are discussed within each chapter, the biggest overall limitation of the current thesis is sample size. The sample size of the experimental groups, when broken down by their comorbid condition, did not allow for a
full-scale statistical comparison of these groups. While all efforts were made to recruit as many participants as possible, it is a common problem for researchers in atypical development to encounter a low sample size. Firstly, this is due to difficulty finding participants that fit the criteria (e.g., no additional symptoms of depression, schizophrenia, epilepsy) and secondly due to the high amount of data excluded from the final analyses on account of participants difficulties (e.g., becoming distressed or claustrophobic, lack of attention to the task). The low sample size was addressed in the current thesis by utilising non-parametric correlational and regression techniques which allow for fewer a-priori assumptions of the data.

In addition, there are general limitations with the methodology used in the current thesis. For example, the profiling measures used in the current study were self-report rather than diagnostic interviews. While diagnostic interviews are superior at independently identifying problem behaviours, these methods were unfortunately beyond the resources available to the researchers. To address this issue, each profiling method was carefully selected with respect to the validity and reliability. The studies selected to determine these measures were conducted by independent researchers, rather than by the authors of the tools which can lead to a conflict of interest.

Finally, while EEG has excellent temporal resolution, spatial resolution is sacrificed. While dense-array nets help to address these issues and provide good spatial resolution, the exact region from which a signal is being produced cannot be concluded with certainty.

8.8 Future directions

The results of the current thesis help to establish that comorbid conditions are indeed separate conditions that warrant their own diagnoses. While a proportion of this amount can be attributed to misdiagnoses of ADHD symptoms, or a lack of clarity in the diagnostic criteria as to how much anxiety should be considered normal, the overall rate of comorbidity
in ASD is still much larger than in the general population. It remains unclear why the comorbidity rate is between 50-70% in ASD (Ghaziuddin & Zafar, 2008). The next step in the current research is to increase the sample size in Study 6 to determine whether there are any true effects of inhibition in the condition studied. Future investigation into the underlying cause of comorbidity in ASD, especially to genetic causes, may give us useful and valuable information about the origins of the condition.

8.9 Conclusion

Autism Spectrum Disorder (ASD) is a lifelong neurodevelopmental condition that involves impairments in social, communication and behavioural domains (American Psychiatric Association, 2013). Additional neuropsychological conditions like Attention Deficit Hyperactivity Disorder (ADHD) and anxiety (particularly Obsessive Compulsive Disorder (OCD)) are known to affect between 50-70% of individuals with ASD (Ghaziuddin & Zayfar, 2008). Until recently, it was unclear why such a high rate of comorbidity in those with ASD exists, as research tended to compare the groups separately. The current thesis established a distinct profile of behaviour and EEG activity in those with ASD, anxiety and ADHD. We argue that the five studies in the current thesis suggest that the profiles seen in those with comorbid ASD and singular ASD are indeed separate, and warrant their own diagnoses. This information is important to researchers when screening for comorbid conditions in ASD research, as underlying brain activity is altered which may affect research findings. In addition, the results of the current study will also help to inform medical practitioners when administering a diagnosis and deciding on a plan to treat specific difficulties associated with comorbid ASD.
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APPENDICES
Appendix A: Ethics Approval

UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE

16-Nov-2012

MEMORANDUM TO:

Assoc Prof Karen Waelde
Psychology

Re: Application for Ethics Approval (Our Ref. 8697)

The Committee considered your application for ethics approval for your project entitled The neurological basis Asperger’s syndrome and common coexisting conditions.

Ethics approval was given for a period of three years.

The expiry date for this approval is 16-Nov-2015.

If the project changes significantly, you are required to submit a new application to UAHPEC for further consider in order that an up-to-date record can be maintained, you are requested to notify UAHPEC once your project is completed.

The Chair and the members of UAHPEC would be happy to discuss general matters relating to ethics approvals if you wish to do so. Contact should be made through the UAHPEC Ethics Administrators at humanethics@auckland.ac.nz the first instance.

All communication with the UAHPEC regarding this application should include this reference number: 8697.

(This is a computer generated letter. No signature required.)

UAHPEC Administrators
UNIVERSITY of AUCKLAND Human Participants Ethics Committee
c.c. Head of Department / School, Psychology
Prof Jan Kirk
Miss Ashleigh Saunders
Assoc Prof Douglas Ellis

Additional information:
1. Do not forget to fill in the ‘approval wording’ on the Participant Information Sheets and Consent Forms, giving the dates of approval and the reference number, before you send them out to your participants.

2. Should you need to make any changes to the project, write to the UAHPEC Administrators by email (humanethics@auckland.ac.nz) giving full details of the proposed changes including revised documentation.

3. At the end of three years, or if the project is completed before the expiry, please advise UAHPEC of its
completion.

4. Should you require an extension, write to UAHPEC by email before the expiry date, giving full details along with revised documentation. An extension can be granted for up to three years, after which a new application must be submitted.

5. If you have obtained funding other than from UniServices, send a copy of this approval letter to the Manager - Funding Processes, UoA Research Office. For UniServices contracts, send a copy of the approval letter to the Contract Manager, UniServices.

6. Please note that UAHPEC may from time to time conduct audits of approved projects to ensure that the research has been carried out according to the approval that was given.
PARTICIPANT INFORMATION SHEET

Project title
Towards a better understanding of high functioning autism and common co-existing conditions.

About the researcher
My name is Ashleigh Saunders and I am currently working towards a PhD in the School of Psychology at the University of Auckland under the supervision of Associate Professor Karen Waldie. I would like to invite you to participate in my research. Please read the following document carefully so you can make an informed decision about whether you would like to participate in the research. I have invited you to participate in this research as you have contacted me showing your potential interest in the study and may have also signalled to me that you have high functioning autism.

About the research
The overall aim of this research is to investigate why some conditions (such as ADHD, anxiety, OCD) commonly co-occur in individuals with high functioning autism. I am interested in investigating whether the same cognitive, electrophysiological (EEG), and family factors underlie high functioning autism when it occurs alone versus when people have more than one condition. With regard to family members, I am interested in investigating if immediate family members share similar behavioural characteristics to you or not.

If you would like to participate in the research you will be invited to answer a number of questionnaires. You will also be asked to perform a number of tasks on a computer which includes pressing a button in response to a certain event. These various tasks are designed to find out more about executive functioning, which is an umbrella term for thinking about all the things you would like to do (like making a decision, solving a problem, memory, attention, and planning an action). The data collected from the research will be used to write my PhD thesis and in various presentations and publications.

What is involved?
Once you have shown an interest in the research, I will contact you to determine if you are eligible to participate. If eligible, you may be invited to attend two separate sessions over the period of one year. The first session will involve answering a number of questionnaires and will also determine your eligibility for the next session. The second session will involve a neuroimaging technique, electroencephalogram (EEG), which will help me to measure what is happening in your brain as you perform various tasks.

For the first session, you will be asked to fill out a number of questionnaires that will ask for information about you and/or your diagnosis. Questionnaires you may be invited to answer include:

1. Demographic Questionnaire. This will ask for general background information including information on any diagnosis you or any immediate family members may have.

2. Wechsler Abbreviated Scale of Intelligence (WASI), performance IQ. This will measure your performance IQ.
APPENDIX C: Participant consent form

RESEARCHER: Ashleigh Saunders

Research title: The brain basis of high functioning autism and common co-existing conditions.

I have read and understood the accompanying Participant Information Sheet, which explains this research project and my role as a participant. I understand why I have been selected to participate in this research. I have had an opportunity to ask questions and have had them answered satisfactorily.

In particular I understand that:

- I will be asked to take part in a functional magnetic resonance imaging (fMRI)
- I have the right to stop participation at any time without having to give a reason, and will retain my participation incentive.
- I will receive $20 in petrol or supermarket vouchers as a participation incentive for each session I attend.
- Whether or not I participate will not affect my relationship with the researchers.
- For three months after my participation I will still have the right to request that my data be withdrawn from the study.
- My name will appear only on this form. The data from this research will be stored anonymously, and securely, coded by number. Research publications and presentations from this study will not contain any information that could identify me and will then be securely destroyed after ten years.
- I understand that any personal information given to the researcher will be kept confidentially.
- I understand and the researcher has explained the times during the experiment that I could become distressed, and that if this occurs I have the right to stop the experiment.
- The researcher will be present to answer any questions or concerns I have and will be able to refer me to further help should I need it.
- I understand that I can receive a summary of the results from the questionnaires and a summary of the findings from the research if I wish.
- I understand that the responses to my questionnaires do not constitute a medical diagnosis.
- If I am a student of the researchers, I understand that I have been assured that my participation or non-participation in this study will have no affect on my grades or relationship with the university, and that I may contact your HOD should I feel this assurance is not met.

I voluntarily agree to take part in this research

Name: ___________________________ Date:____________________

Signature ___________________________ Participant ID ________
APPENDIX D: DEMOGRAPHIC QUESTIONNAIRE

Participant I.D. _________

Providing this information is entirely voluntary. Any information provided will be treated with strict confidentiality.

1. Date of Birth

__________________

2. Gender (circle one)  Male / Female


___________________________________________________________________________

4. Do you speak more than one language? (Circle one)  Yes / No

5. If yes, what is your first language?

___________________________________________________________________________

6. Do you currently hold a job? (Circle one)  Yes / No

7. What is your highest education attainment (i.e., NCEA L2 or L3, Bachelor’s degree etc.)? Please elaborate.

___________________________________________________________________________

8. Have you ever received a diagnosis of Autism Spectrum Disorder / Asperger’s? (Circle one)  Yes / No

9. If yes, how old were you when you were diagnosed?

___________________________________________________________________________

10. If yes, have you ever received any remediation (i.e., ABA therapy)? Please elaborate.

___________________________________________________________________________

11. Have you ever received one of the following diagnoses? (Circle when yes)
ADHD / OCD / Anxiety

12. If yes, please provide details (when, any treatment)?
___________________________________________________________________________

13. Are you currently taking any psychoactive medications (i.e., antidepressants, antipsychotics etc.)?
(circle one) Yes / No

14. If yes, what are they?
___________________________________________________________________________

15. Do you have any other physical or mental health difficulties? (Circle one) Yes / No

16. If yes, please provide details (when, any treatment)?
___________________________________________________________________________

17. Do you have any learning disabilities? (Circle one) Yes / No

18. If yes, please provide details (when, any treatment)?
___________________________________________________________________________

19. Do you have a history of head injury (i.e., concussion)? (Circle one) Yes / No

20. If yes, please elaborate
___________________________________________________________________________

Thank you.
APPENDIX E: AUTISM SPECTRUM QUOTIENT

The Autism-Spectrum Quotient
Please answer the following questions by circling your response to each question. Please do this as quickly as possible (without thinking about your response for too long) and on your own.

The Autism-Spectrum Quotient

<table>
<thead>
<tr>
<th>Number</th>
<th>Statement</th>
<th>Definitely Agree</th>
<th>Slightly Agree</th>
<th>Slightly Disagree</th>
<th>Definitely Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I prefer to do things with others rather than on my own.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I prefer to do things the same way over and over again.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>If I try to imagine something, I find it very easy to create a picture in my mind.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I frequently get so strongly absorbed in one thing that I lose sight of other things.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I often notice small sounds when others do not.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I usually notice car number plates or similar strings of information.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Other people frequently tell me that what I’ve said is impolite, even though I think it is polite.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>When I’m reading a story, I can easily imagine what the characters might look like.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I am fascinated by dates.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>In a social group, I can easily keep track of several different people’s conversations.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>I find social situations easy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>I tend to notice details that others do not.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>I would rather go to a library than a party.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>I find making up stories easy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>15. I find myself drawn more strongly to people than to things.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>16. I tend to have very strong interests, which I get upset about if I can’t pursue.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>17. I enjoy social chit-chat.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>18. When I talk, it isn’t always easy for others to get a word in edgeways.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>19. I am fascinated by numbers.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>20. When I’m reading a story, I find it difficult to work out the characters’ intentions.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>21. I don’t particularly enjoy reading fiction.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>22. I find it hard to make new friends.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>23. I notice patterns in things all the time.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>24. I would rather go to the theatre than a museum.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>25. It does not upset me if my daily routine is disturbed</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>26. I frequently find that I don’t know how to keep a conversation going.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>27. I find it easy to “read between the lines” when someone is talking to me.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>28. I usually concentrate more on the whole picture, rather than the small details.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>29. I am not very good at remembering phone numbers.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>30. I don’t usually notice small changes in a situation, or a person’s appearance.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>---</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31. I know how to tell if someone listening to me is getting bored.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. I find it easy to do more than one thing at once.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33. When I talk on the phone, I’m not sure when it’s my turn to speak.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34. I enjoy doing things spontaneously.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. I am often the last to understand the point of a joke.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36. I find it easy to work out what someone is thinking or feeling just by looking at their face.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. If there is an interruption, I can switch back to what I was doing very quickly.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38. I am good at social chit-chat.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39. People often tell me that I keep going on and on about the same thing.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40. When I was young, I used to enjoy playing games involving pretending with other children.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41. I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42. I find it difficult to imagine what it would be like to be someone else.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43. I like to plan any activities I participate in carefully.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44. I enjoy social occasions</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45. I find it difficult to work out people’s intentions.</td>
<td>definitely agree  slightly agree  slightly disagree  definitely disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>46. New situations make me anxious.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>47. I enjoy meeting new people.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>48. I am a good diplomat.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>49. I am not very good at remembering people's date of birth.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
<tr>
<td>50. I find it easy to play games with children that involve pretending.</td>
<td>definitely agree</td>
<td>slightly agree</td>
<td>slightly disagree</td>
<td>definitely disagree</td>
<td></td>
</tr>
</tbody>
</table>
# APPENDIX F: ADULT ADHD SELF-REPORT SCALE

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Today's Date</th>
</tr>
</thead>
</table>

1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

2. How often do you have difficulty getting things in order when you have to do a task that requires organization? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

3. How often do you have problems remembering appointments or obligations? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

6. How often do you feel overly active and compelled to do things, like you were driven by a motor? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

7. How often do you make careless mistakes when you have to work on a boring or difficult project? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

10. How often do you misplace or have difficulty finding things at home or at work? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

11. How often are you distracted by activity or noise around you? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

13. How often do you feel restless or fidgety? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

14. How often do you have difficulty unwinding and relaxing when you have time to yourself? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

15. How often do you find yourself talking too much when you are in social situations? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

17. How often do you have difficulty waiting your turn in situations when turn taking is required? [Never] [Rarely] [Sometimes] [Often] [Very Often] 

18. How often do you interrupt others when they are busy? [Never] [Rarely] [Sometimes] [Often] [Very Often]
APPENDIX G: OBSESSIVE COMPULSIVE INVENTORY

OCI-R

The following statements refer to experiences that many people have in their everyday lives. Circle the number that best describes HOW MUCH that experience has DISTRESSED or BOTHERED you during the PAST MONTH. The numbers refer to the following verbal labels:

<table>
<thead>
<tr>
<th></th>
<th>0 Not at all</th>
<th>1 A little</th>
<th>2 Moderately</th>
<th>3 A lot</th>
<th>4 Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I have saved up so many things that they get in the way.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>I check things more often than necessary.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>I get upset if objects are not arranged properly.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>I feel compelled to count while I am doing things.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>I find it difficult to touch an object when I know it has been touched by strangers or certain people.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>I find it difficult to control my own thoughts.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>I collect things I don’t need.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>I repeatedly check doors, windows, drawers, etc.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>I get upset if others change the way I have arranged things.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>I feel I have to repeat certain numbers.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>I sometimes have to wash or clean myself simply because I feel contaminated.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>I am upset by unpleasant thoughts that come into my mind against my will.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>I avoid throwing things away because I am afraid I might need them later.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>I repeatedly check gas and water taps and light switches after turning them off.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>I need things to be arranged in a particular way.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>I feel that there are good and bad numbers.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
17. I wash my hands more often and longer than necessary.

18. I frequently get nasty thoughts and have difficulty in getting rid of them.
APPENDIX H: GENERALISED ANXIETY DISORDER SCALE

The Generalised Anxiety Disorder Scale

ID____________

Over the past two weeks, how often have you been bothered by the following problems?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious or on</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>edge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Not being able to stop or control</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>worrying</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Worrying too much about different</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>things</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it is hard</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>to sit still</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Becoming easily annoyed or</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>irritable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Feeling afraid as if something</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>awful might happen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX I: BEHAVIOURAL INHIBITION/ACTIVATION SCALE

Behavioural Inhibition Scale / Behavioural Activation Scale
ID: __________
Date: __________

For each statement below, please indicate your level of agreement or disagreement by circling one of the scale categories in the columns next to the statement

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If I think something unpleasant is going to happen I usually get pretty “worked up”</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I worry about making mistakes</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Criticism or scolding hurts me quite a bit</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I feel pretty worried or upset when I think or know someone is angry at me</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Even if something bad is about to happen to me, I rarely experience fear or nervousness</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. I feel worried when I think I have done poorly at something</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I have very few fears compared to my friends</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. When I get something I want, I feel excited and energized</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. When I’m doing well at something, I love to keep at it</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. When good things happen to me, it affects me strongly</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. It would excite me to win a contest</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. When I see and opportunity for something I like, I get excited right away</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
13. When I want something, I usually go all out to get it

14. I go out of the way to get things I want

15. If I see a chance to get something I want, I move on it right away

16. When I go after something, I use a “no holds barred” approach

17. I will often do things for no other reason than that they might be fun

18. I crave excitement and new sensations

19. I’m always willing to try something new if I think it will be fun

20. I often act on the spur of the moment
APPENDIX J: DATA SCREENING

All data screening was conducted prior to Missing Values Analysis. Notable violations of normality are indicated in bold.

<table>
<thead>
<tr>
<th>Scale</th>
<th>N</th>
<th>Mean</th>
<th>Std. Error</th>
<th>Std. Deviation</th>
<th>Skewness</th>
<th>Std. Error</th>
<th>Kurtosis</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous performance task full score</td>
<td>75</td>
<td>81.4</td>
<td>3.33</td>
<td>28.80</td>
<td>-1.41</td>
<td>0.28</td>
<td>1.26</td>
<td>0.55</td>
</tr>
<tr>
<td>Behavioural Inhibition Scale</td>
<td>82</td>
<td>21.23</td>
<td>0.42</td>
<td>3.83</td>
<td>-0.44</td>
<td>0.27</td>
<td>-0.43</td>
<td>0.53</td>
</tr>
<tr>
<td>Response Reward</td>
<td>82</td>
<td>16.12</td>
<td>0.27</td>
<td>2.44</td>
<td>-0.56</td>
<td>0.27</td>
<td>-0.05</td>
<td>0.53</td>
</tr>
<tr>
<td>Drive</td>
<td>80</td>
<td>10.15</td>
<td>0.29</td>
<td>2.57</td>
<td>0.24</td>
<td>0.27</td>
<td>-0.29</td>
<td>0.53</td>
</tr>
<tr>
<td>Fun Seeking</td>
<td>79</td>
<td>10.75</td>
<td>0.31</td>
<td>2.77</td>
<td>0.14</td>
<td>0.27</td>
<td>-0.51</td>
<td>0.54</td>
</tr>
<tr>
<td>Generalised Anxiety Disorder Scale</td>
<td>82</td>
<td>7.20</td>
<td>0.56</td>
<td>5.04</td>
<td>0.51</td>
<td>0.27</td>
<td>-0.54</td>
<td>0.53</td>
</tr>
<tr>
<td>Obsessive Compulsive Inventory</td>
<td>83</td>
<td>20.41</td>
<td>1.49</td>
<td>13.61</td>
<td>1.03</td>
<td>0.26</td>
<td>0.63</td>
<td>0.52</td>
</tr>
<tr>
<td>Adult Self-Report ADHD scale</td>
<td>83</td>
<td>36.04</td>
<td>1.37</td>
<td>12.50</td>
<td>0.22</td>
<td>0.26</td>
<td>-0.60</td>
<td>0.52</td>
</tr>
<tr>
<td>Autism Spectrum Quotient</td>
<td>83</td>
<td>23.45</td>
<td>1.03</td>
<td>9.41</td>
<td>0.21</td>
<td>0.26</td>
<td>-0.74</td>
<td>0.52</td>
</tr>
</tbody>
</table>