11-1-2016

Psychiatric and physical comorbidity in adults with autism spectrum disorder

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A thesis submitted to the School of Postgraduate Studies,
Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland,
in fulfilment of the degree of Medical Doctorate

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Professor Declan Murphy

July 2016

Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of higher degree by MD, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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List of Abbreviations

5-HT, 5-Hydroxytryptophan Receptors
AED, Antiepileptic Drug
ASD, Autism Spectrum Disorder
ADHD, Attention Deficit Hyperactivity Disorder
ADOS, Autism Diagnostic Observation Schedule
ADOS-G, Autism Diagnostic Observation Schedule - Generic
ADI, Autism Diagnostic Interview
ADI-R, Autism Diagnostic Interview - Revised
AIDS, Acquired Immune Deficiency Syndrome
AQ, Autism Spectrum Quotient
BAARS-IV, Barkley Adult Attention Deficit Hyperactivity Disorder Rating Scale - IV
BFC, Bonferroni Correction
BGC, Behavioural Genetics Clinic, Outpatient Clinic of the Autism Assessment and Behavioural Genetics Service, Maudsley Hospital, London
BPAD, Bipolar Affective Disorder
CMHT, Community Mental Health Team
CNS, Central Nervous System
DISCO-11, Diagnostic Interview for Social and Communication Disorders - Version 11
DSM, Diagnostic and Statistical Manual of Mental Disorders
DSM-III, Diagnostic and Statistical Manual of Mental Disorders - 3rd Edition
DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders - 3rd Edition Revised
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders - 4th Edition
DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders - 4th Edition Text Revision
DSM-5, Diagnostic and Statistical Manual of Mental Disorders - 5th Edition
EEG, Electroencephalogram
ENT, Ear Nose and Throat
EUPD, Emotionally Unstable Personality Disorder
FANS, The Department of Forensic and Neurodevelopmental Sciences
GABA, Gamma-Aminobutyric Acid
GAD, Generalised Anxiety Disorder
GP, General Practitioner

HADS, Hospital Anxiety and Depression Scale

HIV, Human Immunodeficiency Virus

ICD, International Classification of Diseases

ICD-8, International Classification of Diseases, 8th Edition

ICD-9, International Classification of Diseases, 9th Edition

ICD-10, International Classification of Diseases, 10th Edition

ID, Intellectual Disability

IQ, Intelligence Quotient

MRI, Magnetic Resonance Imaging

MRN, Medical Record Number

NAPD, Nonaffective Psychotic Disorder

NCHD, Non-Consultant Hospital Doctor

NHS, National Health Service

NREM, Non Rapid Eye Movement

OCD, Obsessive Compulsive Disorder

OCI, Obsessive Compulsive Inventory

OCI-R, Obsessive Compulsive Inventory - Revised

PD, Personality Disorder

PLMS, Periodic Limb Movements of Sleep

PTSD, Post-Traumatic Stress Disorder

REM, Rapid Eye Movement

SCID, Structured Clinical Interview for DSM-IV Disorders

SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders

SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders

SPSS, Statistical Package for Social Science - Version 22

UK, United Kingdom

USA, United States of America

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Summary

Autism spectrum disorder (ASD) is a highly impairing neurodevelopmental condition, manifesting in childhood and continuing into adult life. Comorbid psychiatric and physical illness lends considerable increased mortality to the condition. An increased awareness of comorbid conditions in adults with normal IQ ASD could improve diagnostic formulation, facilitate targeted treatments and improve psychosocial outcomes.

This study examines the prevalence of comorbid psychiatric and physical illness in 413 adults with normal IQ ASD, attending a tertiary referral neurodevelopmental clinic in South London, to determine if rates of comorbid illness would be greater than rates reported in the general population.

This study noted autism spectrum disorder in 70% of participants, with a male-to-female ratio of 2.8:1. Milder forms of ASD were recorded for 88%. Participants with autism spectrum disorder were more likely to be single, unemployed and living in the company of others. Seventy-six percent suffered from a comorbid Axis I illness and 2% suffered from a comorbid Axis II condition. Anxiety spectrum disorders were the most common comorbid psychiatric illness, followed by attention deficit hyperactivity disorder, mood disorders and deliberate self-harm. Psychosis, substance-use disorder, eating disorder and tic disorder were rarely diagnosed. Participants with Asperger's syndrome were statistically more likely to be diagnosed with a comorbid psychiatric illness, most commonly obsessive compulsive disorder. Eighty-four percent of participants had a history of physical illness, most frequently asthma followed by head injury. Sleep difficulties and eating disturbance were notably high at 42% and 25% respectively.

Adults with normal IQ autism spectrum disorder suffer higher rates of physical and psychiatric morbidity, display a poorer ability to engage with treatment and have a lower chance of recovery compared to the general population. Increased awareness and a high degree of diagnostic skill to identify those with the disorder should be promoted among physicians and psychiatrists.

Acknowledgements

I am extremely grateful to Professor Kieran Murphy, my supervisor in this study, for the constant support and understanding he has provided through the many turns this project has taken.

Thank you to the patients attending the Behavioural Genetics Clinic, Maudsley Hospital who kindly consented to the use of their information. Their positivity regarding ongoing research into the disorder provided the incentive for this study.

I would like to highlight the hard work and high standard of assessment provided by both clinical and non-clinical staff at the Behavioural Genetics Clinic, Maudsley Hospital.

Thank you to Professor Declan Murphy, my co-supervisor, and Dr Susannah Whitwell who created The Clinical Research of Developmental Disorders Database and work tirelessly on a continued basis to sustain it.

Thank you to Nicola Gillan for her friendship and support during my time with the Department of Forensic and Neurodevelopmental Sciences.

Thank you to my colleague and good friend, Dr Jacqui Garland, who travelled with me to London gathering data in the early days of this project, for her support, enthusiasm and incredible energy.

Finally, thank you to Dominic, my husband, for his support and constant patience during this time, Tom our son, for his humour and good cheer and Sarah our little girl, for her wondrous ability to sleep as a newborn. Each of you sacrificed to allow this project reach completion, I am eternally grateful.

Dedication

To the exceptional, yet fragile, patients I consider myself fortunate to work with every day whose unique view of the world both fascinates and inspires me.

Chapter 1: Introduction Chapter

1.1 Overview

Autism spectrum disorder (ASD) is a pervasive disorder characterised by a triad of impaired social skills, rigid communication style and characteristic repetitive and ritualised behaviours, first evident in infancy and persisting into adulthood. This introductory chapter aims to introduce autism spectrum disorder, describe the history of the disorder, discuss epidemiology, aetiology, clinical presentation, methods of diagnosis and outline psychiatric and physical illnesses which can co-occur with the disorder.

This literature review consisted of a database serach to identify articles examining the psychiatric and physical comorbidities of adults with normal intellectual ability suffering from autism spectrum disorder. Search topics included the history of autism spectrum disorder, epidemiology, clinical presentation, aetiology, assessment and diagnosis, comorbid psychiatric illness and comorbid physical illness based on the population under study. This population referred to adult males and females with an intelligence quotient greater than 70 suffering from autism spectrum disorder. The author selected suitable articles based on the title or occasionally by study author when an author was widely published in the area of autism spectrum disorder; examples include Kanner, Asperger, Wing and Lord. All abstracts were read and when referring to the population under study, the full article was retrieved. All full text articles were read in detail by the author.

1.2 The History of Autism Spectrum Disorder

Although the origins of autism spectrum disorder as a medical condition only date from 1943, the concept of individuals different to those around them, has existed since the Middle Ages. Medieval folklore speaks of ‘changeling children’; strange, beautiful, elf-like creatures left in the place of human babies by fairies and trolls who wished for their offspring to be reared by human parents. Folklore used this theory of changeling creatures to explain the existence of infants with unexplained illness such as intellectual or physical disability. Early accounts of changeling children list many

features consistent with autism spectrum disorder and may reflect early attempts to explain the unexplainable (Wing, 2002a).

Multiple terms continued to evolve over the following centuries and more recently over the past decades. Henry Maudsley expressed concern over odd patterns of childhood behaviour which he termed childhood insanity in 1867 (Wing, 2002a). Likewise other authors described and named a litany of childhood disorders which were most likely autism spectrum disorder or the rarer condition of childhood-onset schizophrenia. Such terms included ‘dementia precocissima’, ‘dementia precocissima catatonica’, ‘primitive catatonic psychosis of idiocy’, ‘symbiotic psychosis’ and ‘childhood psychosis’ (Wing, 1979).

‘Autism’ was introduced to medical nomenclature by Swiss psychiatrist Eugen Bleuler to describe a tendency towards social withdrawal and progressive loss of communication seen in patients with schizophrenia praecox (Bleuler 1911, Vannucchi 2014a). It was not until 1943 that Leo Kanner first introduced ‘autism’ in the way physicians and psychiatrists use the term today. Kanner used the term in a broader context than Bleuler and was the first to publish a series of case studies of individuals with social, communication and behavioural dysfunction. Erroneously, this duplication of a previously coined term led to autism being considered an early onset variant of schizophrenia for many decades until, after much research and debate, it was recognised as a condition in its own right (Kolvin 1971, Volkmar 1991, Konstantareas 2001, Stahlberg 2004).

Leo Kanner (1943) described a distinctive pattern of deficits he called ‘inborn autistic disturbances of affective contact’ in eleven children under the age of twelve years (Kanner 1943, Henninger 2012). Kanner painstakingly outlined the presenting complaint, family histories, clinical observations and treatment outcomes of eight boys and three girls, concluding their diagnosis to be ‘early infantile autism’. Kanner noted ten common criteria among the eleven children which he suggested could be used by other clinicians and psychiatrists to assess for early infantile autism in their patients. These included an inability to develop relationships with others, delay in speech acquisition, non-communicative use of speech after it developed, delayed echolalia, pronoun reversal, repetitive and stereotyped activities, obsessive insistence on the maintenance of sameness, lack of imagination, good rote memory and a normal physical appearance (Rutter, 1978). Kanner subsequently went on to publish further

on this condition (Kanner 1946, Kanner 1956, Kanner 1957, Kanner 1971, Kanner 1972). His instinct to continue publishing on the subject of early infantile autism allowed the condition to gain recognition throughout the academic and scientific communities.

Hans Asperger (1944) described ‘autistic psychopathy’ in four boys under his care in the University Children’s Hospital in Vienna in the 1940s. His criteria were very similar but slightly different to Kanner’s description. Asperger described normal timing of speech development but abnormally pedantic and often stereotyped content with difficulty using pronouns, impaired non-verbal communication including little use of facial expression, limited or clumsy gestures, perplexed affect, impaired two-way social interaction, lack of understanding, an inability to use the rules governing social behaviour, repetitive activities and resistance to change. A distinct difference was that Kanner’s initial descriptions focused mainly on children while Asperger’s account included some adults (Howlin, 2012). In addition, Kanner was unsure as to the IQ range associated with ‘early infantile autism’ while Asperger’s subjects all fell within the range of normal intelligence.

Historical literature is unclear as to the timing of Asperger’s first observations compared to those of Kanner and he was one year later in publishing. This however, is not the sole reason Asperger’s description remained relatively unknown. Other factors include a comparable lack of published articles, publication in the German language only (Asperger 1944, Asperger 1968), publication in non-medical literature (The National Autistic Society monthly magazine, 1979) and use of the term ‘psychopathy’ which limited his prospective readership. It was not until 1981, when his work was revisited and revised by Lorna Wing that his findings became accessible to the general scientific community. Asperger’s 1944 article, originally published only in German, was translated by Uta Firth in her book *Autism and Asperger Syndrome* in 1991, further increasing awareness of the condition among psychiatrists and physicians.

Steve Silberman, a science journalist with *Wired Magazine* has suggested the close timing of the Kanner (1943) and Asperger (1944) descriptions were not entirely coincidental. Silberman explains that Hans Asperger worked closely with a Jewish physician George Frankl in the Children’s Clinic at the University Children’s Hospital in Vienna in the 1930’s, until Austria was annexed by German troops. A physician of the same name is quoted as a staff member in the Child’s Study Home in Maryland in

Kanner's seminal 1943 article, when describing two weeks of observational study of Donal T (case 1). Silberman hypothesised that Frankl fled Nazi-occupied Austria to live in the United States of America bringing with him knowledge of the clinical presentation of Asperger's autistic psychopathy. Other authors suggest this as the reason for Kanner's use of the passive tense in the opening statement of his seminal article 'since 1938, there have come to our attention…' implying he does not take credit for the description and rather hints to the condition as alerted to him (Coplan, 2015).

Although, this literature review was unable to find reference by Kanner to Asperger's work, there is reference by Asperger to Kanner's findings. Personal communication between Hans Asperger and Lorna Wing (1981) states 'Asperger acknowledges that there were many similarities between his syndrome and Kanner's early infantile autism, nevertheless, he considered these were different because he regarded autism as a psychotic process and his own syndrome as a stable personality trait'. This is unusual, given the abundance of literature in the intervening years differentiating early infantile autism from childhood schizophrenia, especially Israel Kolvin's (1971) seminal work using age of onset to differentiate the two conditions. Since that time, including the year of Asperger's comment, the two diagnoses have been considered different and distinct entities.

Lorna Wing is credited for outlining the 'triad of impairments' in her work with Judith Gould, broadening the concept of Kanner's autism to include a range of deficits, each existing along a continuum of severity rather than as a discrete entity (Wing, 1979). These included lifelong deficits in reciprocal social interaction, communication skills and restricted interests and behaviours. Michael Rutter (1978) had published very similar findings the previous year, when he suggested autistic symptoms required grouping into the universal and specific to allow accurate diagnosis. He identified three broad symptom categories; a profound and general failure to develop social relationships, language retardation with impaired comprehension, echolalia and pronominal reversal and ritualistic or compulsive phenomena.

In 1981, Wing went on to strongly suggest Asperger's 'autistic psychopathy' be renamed 'Asperger's syndrome' due to the use of 'psychopathy' at the time to reflect sociopathic tendencies. Her proposed switch in diagnostic terminology was accepted by the medical profession and adopted into the medical nomenclature. Currently, the

term autism spectrum disorder is widely used to refer to this cohort of psychiatric patients (American Psychiatric Association, 2013)

1.3 Epidemiology of Autism Spectrum Disorder

Though difficult to measure (Hill, 2008), the importance of knowing the accurate prevalence and incidence rates of autism spectrum disorder cannot be understated. Epidemiological studies would provide data which could be used to direct future research, permit examination of clinical hypotheses, ensure funding to train diagnosticians, increase understanding of causal mechanisms (Lotter 1966, Hill 2008) and allow accurate service planning and provision.

Incidence is a measure of the number of new cases that develop in a population over a particular time period (Hill, 2008). Prevalence describes the number of people in a specific population who have an illness at a particular time point (Hill, 2008). Prevalence is considered important in understanding service needs and allowing service planning while incidence is required to allow for research into causality (Fombonne, 2005).

Timing onset in autism spectrum disorder is very difficult and this compromises the researcher's ability to accurately record its incidence rate. Many parents note their child to be 'different' to siblings or other children between six and eighteen months of age. However, this does not indicate onset of illness at age six months rather that symptoms were first noted or the illness diagnosed at this age.

As with much research into autism spectrum disorder, prevalence figures have shown a steady rise from the 1960s to the mid-1990s (Howlin 2012, Miles 2012). These studies have focused primarily on 'autism' to the exclusion of the autism spectrum (Newschaffer, 2003) and been largely based on child or mixed IQ cohorts. A selection of mixed age and mixed IQ studies is outlined in Table 1.1.

Table 1.1

Selection of Papers Showing Variable Prevalence Rates for Autism Spectrum Disorder across Six Decades

Author, Year of Publication	Means of Diagnosis	ASD Subtype	Rate per 10,000	Male: Female Ratio	Study Cohort
Lotter, 1966	Creak Criteria	Autistic Behaviour	4.1	2.6:1	Child cohort Mixed IQ
Wing, 1979	Triad of Impairments	Typical Autism	4.9	15:1	Child cohort Mixed IQ
Shah, 1982	Triad of Impairments	Kanner's syndrome	400	Unreported	Adult cohort All with ID
Ehlers, 1993	Gillberg & Gillberg Criteria	Asperger's syndrome	36	4.1:1	Child cohort Mixed IQ
CDC, 2000	National Environmental Public Health Tracking Network	Autism Spectrum Disorder	67	Unreported	Children born in 1992 Mixed IQ
Nylander, 2001	ASD - ASQ	Autism Spectrum Disorder	140	2.8:1	Adult cohort Mixed IQ
CDC, 2002	National Environmental Public Health Tracking Network	Autism Spectrum Disorder	66	Unreported	Children born in 1994 Mixed IQ
Wing, 2002a	Summary Paper of 39 studies from 1966 - 2002	Autism	0.7 - 60	Unreported	Mixed age Mixed IQ
Wing, 2002a	Summary Paper of 39 studies from 1966 – 2002	Asperger's syndrome	26 - 57	Unreported	Mixed age Mixed IQ

Author, Year of Publication	Means of Diagnosis	ASD Subtype	Rate per 10,000	Male: Female Ratio	Study Cohort
Wing, 2002a	Summary Paper of 39 studies from 1966 - 2002	Autism Spectrum Disorder	20 - 36	Unreported	Mixed age Mixed IQ
CDC, 2004	National Environmental Public Health Tracking Network	Autism Spectrum Disorder	80	Unreported	Child cohort Mixed IQ
Fombonne, 2005	Summary Paper of 37 studies from 1966 - 2005	Autism	0.7 - 72.6	1.4 - 16:1	Mixed age Mixed IQ
Baird, 2006	SCQ, ADI-R and ADOS-G	Autism Spectrum Disorder	116.1	3.3:1	Child cohort Mixed IQ
CDC, 2006	National Environmental Public Health Tracking Network	Autism Spectrum Disorder	90	Unreported	Child cohort Mixed IQ
Ellefsen, 2007	DISCO	Autism Spectrum Disorder	56	6:1	Child cohort Mixed IQ
CDC, 2008	National Environmental Public Health Tracking Network	Autism Spectrum Disorder	113	Unreported	Child cohort Mixed IQ
Williams K, 2008	State and National data on government record	Childhood Autism and Asperger's syndrome	3.6 - 40.8	4:1	Child cohort Mixed IQ
Williams E, 2008	NHS records	Autism Spectrum Disorder	51.1	6.8:1	Child cohort Mixed IQ

Author, Year of Publication	Means of Diagnosis	ASD Subtype	Rate per 10,000	Male: Female Ratio	Study Cohort
Williams E, 2008	NHS records	Childhood Autism	21.6	Unreported	Child cohort Mixed IQ
Williams E, 2008	NHS records	Atypical Autism	10.8	Unreported	Child cohort Mixed IQ
Williams E, 2008	NHS records	Asperger's syndrome	16.6	Unreported	Child cohort Mixed IQ
Williams E, 2008	NHS records	PDD-nos	13	Unreported	Child cohort Mixed IQ
CDC, 2010	National Environmental Public Health Tracking Network	Autism Spectrum Disorder	147	Unreported	Child cohort Mixed IQ
Brugha, 2011	AQ-20 and ADOS-G	Autism Spectrum Disorder	98	9:1	Adult cohort Mixed IQ
White, 2011	AQ-50	High-Functioning Autism Spectrum Disorder	190	1.5:1	Adult cohort Presumed normal IQ
Kim, 2011	ASSQ, ADOS and ADI-R	Autism Spectrum Disorder	264	2.5:1	Child cohort Mixed IQ
Kočovska, 2012	DISCO-11	Autism Spectrum Disorder	94	2.7:1	Mixed age Mixed IQ

Victor Lotter (1966) was the first author to look at the epidemiology of autism spectrum disorder. He identified a prevalence rate of 4.5 per 10,000 in a cohort of young children aged eight to ten years in the county of Middlesex, United Kingdom. As data were incomplete for three children, a conservative prevalence rate of 4.1 per 10,000 with a male-to-female ratio of 2.6:1 was reported. Over the years, this rate has steadily increased until Baird et al (2006) reported a significantly higher prevalence rate of

116.1 per 10,000 for autism spectrum disorder with a male-to-female ratio of 3.3:1, in the Special Needs and Autism Project (SNAP) in South London. This reflects an almost ten-fold increase in the prevalence of the disorder over 40 years.

From 1966 through to 2012, rates as low as 0.7 per 10,000 (Wing 2002a, Fombonne 2005) and as high as 400 per 10,000 (Shah, 1982) have been reported. Unfortunately, the highly diverse populations under study make these rates almost impossible to interpret. Study populations range from those with severe-profound intellectual disability (Shah, 1982) to high functioning autism spectrum disorder (White, 2011) and from birth (Fombonne, 2005) to 75+ years (Brugha, 2011).

Relatively little is known about the prevalence rate of autism spectrum disorder in adults (Spencer, 2011). Brugha et al (2011) were the first to report data on prevalence rates in an adult only cohort. This survey was conducted in 2007 and originally published by the National Health Service Information Centre for Health and Social Care as '*Autism Spectrum Disorders in adults living in households throughout England: Report from the Adult Psychiatric Morbidity Survey, 2007'*. Four years later, on May 2nd 2011, Brugha et al published the '*Third National Adult Psychiatric Morbidity Survey in England'* quoting findings from their 2007 report. This paper described the prevalence rate of autism spectrum disorder as 98 per 10,000 adults within the United Kingdom. This cohort, though adult only and the first publication of its kind, did include individuals with intellectual disability.

The only publication identified by this literature review looking at the prevalence rate of autism spectrum disorder among adults with normal range IQ was a study by White et al (2011). White et al (2011) recruited 667 college students, with presumed normal range IQ, in a public university in the south-eastern United States of America. A prevalence rate of 1.9% (190 per 10,000) for high-functioning autism spectrum disorder was reported. White et al (2011) do not refer to their study as the first to examine prevalence of autism spectrum disorder in normal IQ adults, yet it was the earliest and only paper identified in current scientific literature by this review.

Figure 1.1 - 1.3, demonstrate the variability of prevalence rates across the past six decades.

Figure 1.1

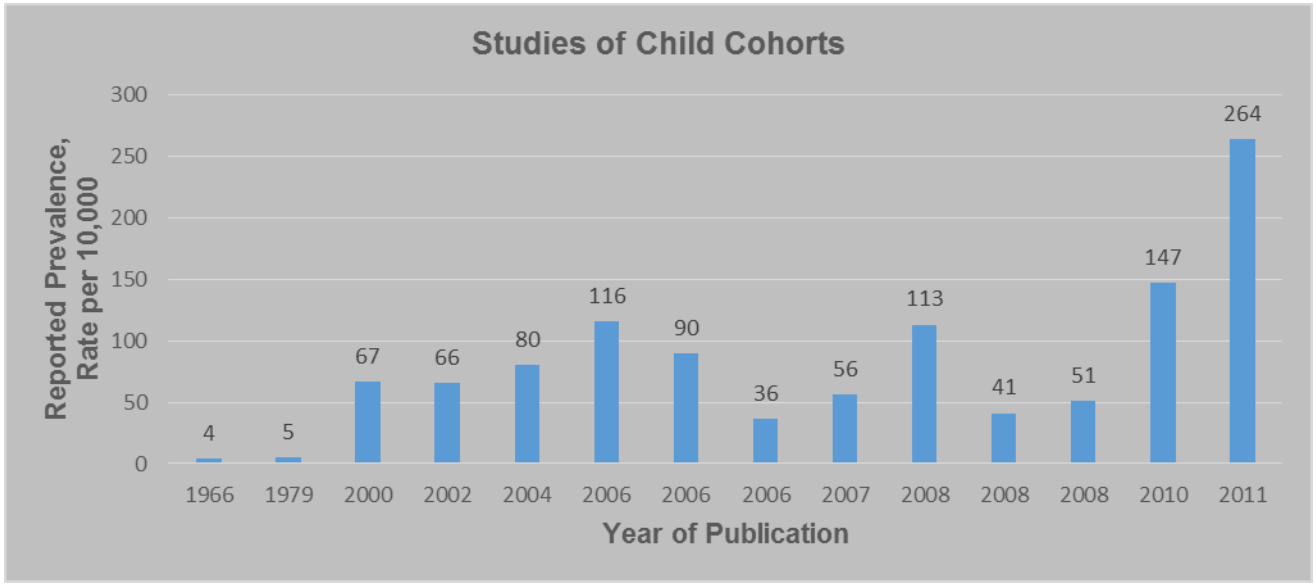


Figure 1.2

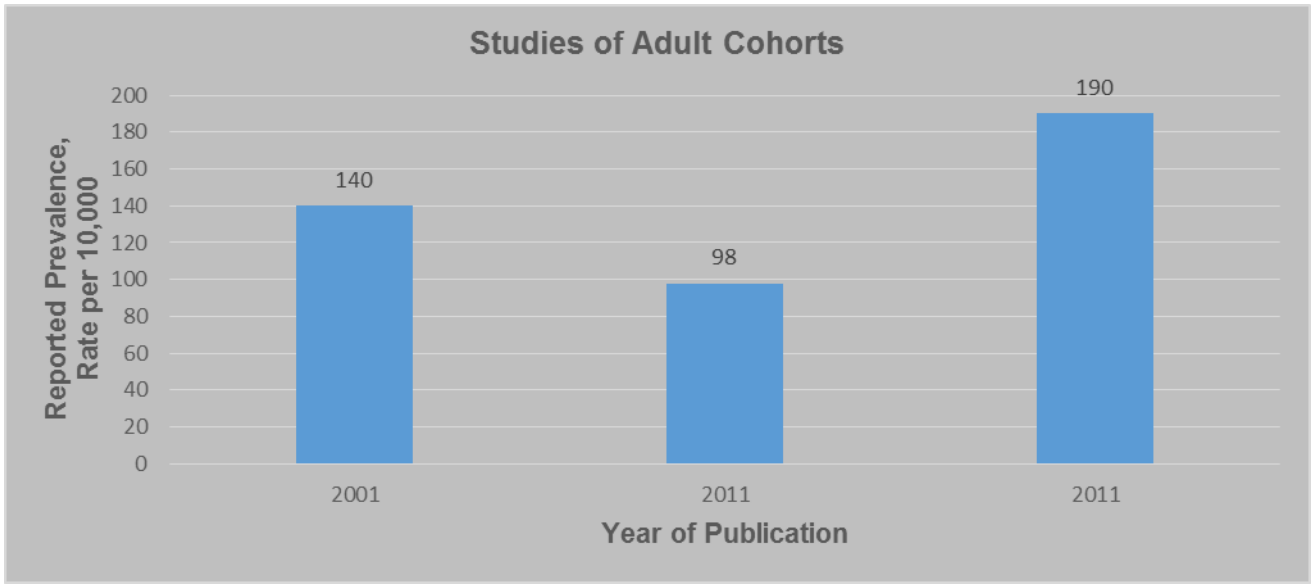
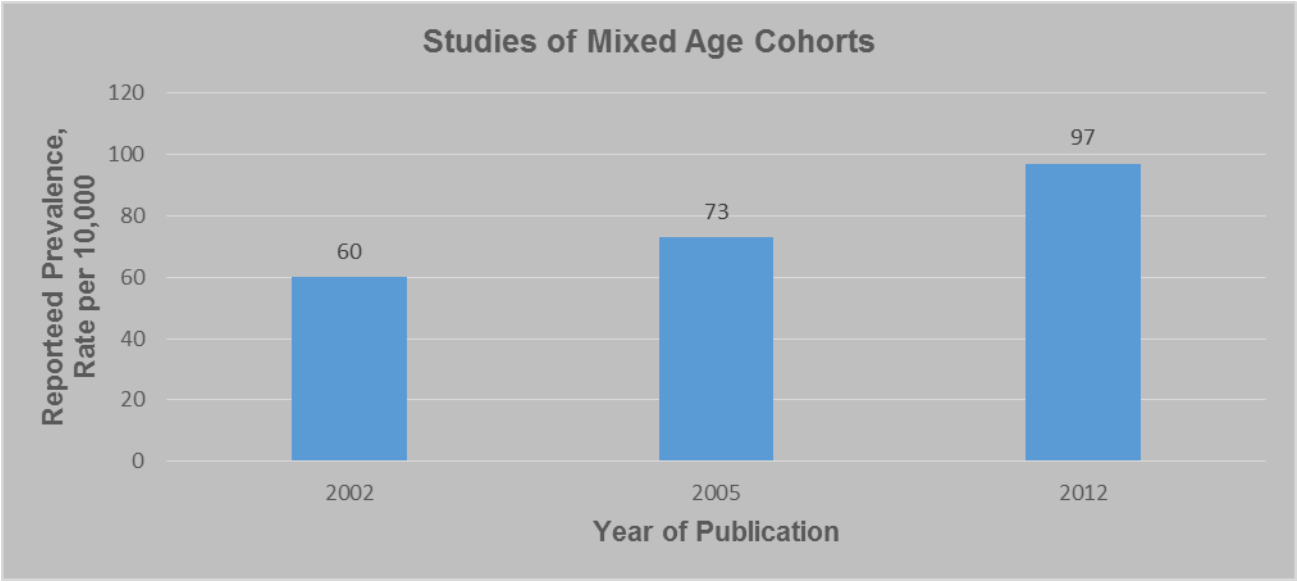


Figure 1.3



It is now agreed that autism spectrum disorder constitutes 0.6% - 1% of the child population (Baird 2006, Hill 2008). In relation to estimates for adult rates, the dearth of published literature makes this figure impossible to report as part of this literature review. However, reported prevalence rates over the past six decades suggest autism spectrum disorder is a pervasive disorder which persists throughout life and is impervious to the effects of environment or education (Asperger 1943, Wing 1981, World Health Organisation 1992, Newschaffer 2003, Wentz 2005, Baird 2006, Sizoo 2010, Oldershaw 2011, White 2011, Vannucchi 2014b).

1.4 What Causes Autism Spectrum Disorder?

The aetiology of autism spectrum disorder is not yet completely clear and although several explanatory models exist, no all-embracing concept provides a full explanation for the multiplicity of the clinical presentation or all the disorder's core features (Roy, 2013). Likewise, there is no evidence for a clear-cut genetic disorder or syndromal cause to autism spectrum disorder (Van Elst, 2013). It is proposed that a combination of the current existing models is likely to provide the most accurate explanation for this combination of impairments (Tyson, 2012). Each theory could possibly, in turn, be linked to genetic, environmental, neurobiological or biochemical aetiologies. 'On the

other hand, autism could turn out to be a behavioural syndrome without a single cause' (Rutter, 1978).

1.4.1 Neurocognitive Models in Autism Spectrum Disorder

A number of cognitive theories for autism spectrum disorder have been proposed throughout child, adolescent and adult literature. Theories have included high arousal, lack of motivation, language impairment, perceptual problems and poor emotional perception (Ozonoff 1991, Frith 1994). Although agreement remains that autism spectrum disorder affects cognitive function, each of these theories have been sequentially disproven.

While investigating anomalous 'spiky' IQ profiles, researchers noted recurring themes for individuals with autism spectrum disorder. Both child and adult samples demonstrated consistent strength in block design but poor performance on picture arrangement (Frith, 1994). This led to research into cognitive processing abilities in those with autism spectrum disorder and the currently accepted neurocognitive models for autism spectrum disorder were devised. These include theory of mind deficits, executive dysfunction and weak central coherence (Baron-Cohen 1989, Ozonoff 1991, Happé 1993, Frith 1994, Baron-Cohen 2001b, Frith 2001, Happé 2001a, Hill 2004a, Happé 2006, Rydén 2008b, Oldershaw 2011, Tyson 2012).

Theory of Mind

Theory of mind is the ability to recognise thoughts and feelings in others. It allows an individual to attribute mental states to themselves and others helping to explain and predict behaviour (Happé, 2001a). The terms theory of mind, mentalising, mind-blindness, mind-reading and understanding other's minds are used interchangeably throughout the literature. Theory of mind or mentalising requires the ability to understand others as independent from the self, to take an allocentric (he/she/they) stance, compared to the egocentric (me/I) stance where others are only understood in terms relating to oneself (Rydén 2008b, Raja 2009).

The theory of mind model can account for many deficits in social functioning although it is not entirely applicable to non-social deficits in autism spectrum disorder (Happé,

2001a). Theory of mind can explain how an individual with autism spectrum disorder is capable of social approach; being present in the room with others or watching others engage in social interactions, but lacks the ability to mentalise another's viewpoint preventing them partaking or sharing. Simon Baron-Cohen (1989) attempted to clarify this discrepancy by dividing theory of mind into first- and second-order functions. First-order theory of mind refers to the ability to infer what another may be thinking while second-order requires the ability to predict what another person thinks someone else is thinking (Ozonoff, 1991). He rationalised that some individuals with autism spectrum disorder may pass a test relating to first-order theory of mind but all would fail testing of second-order theory of mind. Not only did Francesca Happé (1993) disprove Baron-Cohen's theory relating to first- and second-order theory of mind, Ozonoff et al (1991) also showed theory of mind could be attributed to illnesses other than autism spectrum disorder.

On the whole, although successful in explaining most symptoms of autism spectrum disorder, theory of mind cannot successfully account for all symptoms or all individuals along the spectrum. Further research led to developments in this area by describing executive dysfunction and central coherence.

Executive Dysfunction

Executive function is an umbrella term for higher order problem-solving cognitive abilities required to achieve flexible and adaptive behaviour in the pursuit of goals (Hill 2004a, Happé 2006). Interest in executive function deficits or executive dysfunction in autism spectrum disorder were born from the inconsistencies in the theory of mind model. Psychologists utilising the Tower of Hanoi and Wisconsin Card Sorting Test noted reproducible impairments in individuals with autism spectrum disorder (Frith, 1994). Parallels were drawn with those suffering from acquired brain injury noting common deficits in planning, inhibition, monitoring and flexibility (Oldershaw, 2011).

Tests of planning, the complex dynamic operation of sequencing an action, using the Tower of London test, is impaired in individuals with autism spectrum disorder (Hill, 2004a). Likewise, poor mental flexibility is noted by their inability to shift from a particular thought or action, rigidity and perseveration is seen in set rituals and routines, poor generativity is noted in lack of imagination and poor self-monitoring is reflected in

social skill deficits such as difficulty with chit-chat and turn taking (Hill 2004a, Hill 2004b). The higher-order ability of inhibition, though grouped within executive dysfunction for individuals with acquired brain injury, does not appear impaired in those with autism spectrum disorder. James Russell (2002) reasoned this inconsistency by deducing that a rule valid to the ASD brain is easily adhered to. Namely, if the request makes reasonable sense to the ASD individual, they agree and perform, falling back on their savant skills of consistency and preference for logic.

However, similar to the concept of theory of mind deficits, researchers noted executive dysfunction to again fall short on explaining all ASD symptoms and difficulties (Ozonoff, 1991).

Weak Central Coherence

The third and final neurocognitive theory of autism spectrum disorder, central coherence, was introduced by Uta Frith (1989) to bridge the gap in attempts by theory of mind and executive dysfunction to explain the continuum of impairments in autism spectrum disorder (Happé, 2001a).

Central coherence is the ability to draw together diverse information to allow understanding of events as they arise (Frith, 1994). Strong central coherence confers ability to extract meaning but surface information, such as typos, are missed while weak central coherence allows excellent attention to detail with preference for parts over the whole, forgoing the meaning and overall context (Happé, 2001a). Frith (1989 and 1994) felt those with autism spectrum disorder fell into the weak category, which would provide strength in ability to absorb local, fine detail information but sacrifice the ‘bigger picture’ thereby losing the global meaning (Råstam, 2008). Both skill-sets have advantages and disadvantages which allow the central coherence model to address both weaknesses and strengths in autism spectrum disorder. By comparison, theory of mind and executive dysfunction only focus on impairments, without successfully accounting for savant skills (Happé, 2006).

Happé (1993) tested the ability to distinguish homographs within written text to demonstrate weak central coherence in children with autism spectrum disorder. To successfully pronounce homographs, words spelled the same but of different meaning, one is required to assimilate the context from the sentence as it is read. She noted that

all participants with autism spectrum disorder failed to provide the correct, in context, pronunciation to words such as ‘tear’ and ‘bow’, typically providing the most frequently used pronunciation regardless of context. This deficit was consistent across groups irrespective of ability in first- and second-order theory of mind.

To date, a neuroanatomical basis to each of the three cognitive models remains elusive. While attempts have been made to reconcile psychology’s findings with those of neuroscience and neuroimaging specialists, including tenuous links to the right hemisphere, medial prefrontal regions and posterior superior temporal regions, findings have been inconsistent (Frith 2001, Hill 2004a, Happé 2006, Oldershaw 2011). This is primarily attributed to the difficulties encountered in designing suitable mentalising tasks to distinguish between participants with autism spectrum disorder and neurotypical controls (Frith, 2001).

Generally, although Baron-Cohen and colleagues continue to argue the all-inclusive nature of theory of mind, most researchers agree that a single cognitive deficit cannot account for a disorder as wide ranging and complex as autism spectrum disorder. Table 1.2 has been designed as part of this literature review to link the clinical syndrome of autism spectrum disorder, to each of the above neurocognitive models.

Table 1.2

Autism Spectrum Disorder as explained by the Neurocognitive Models

Neurocognitive Model	**ICD-10 symptoms**
Theory of Mind	• Failure to develop peer relationship that involve a mutual sharing of interests, activities and emotions • Lack of socio-emotional reciprocity as shown by an impairment or deviant response to other people's emotions • Lack of spontaneous seeking to share enjoyment, interests or achievements with other people • Lack of varied spontaneous make-believe play or social imitative play

Neurocognitive Model	ICD-10 symptoms
Executive Dysfunction	• Relative failure to initiate or sustain conversational interchange in which there is reciprocal responsiveness to the communications of the other person • Stereotyped and repetitive use of language or idiosyncratic use of words or phrases • An encompassing preoccupation with one or more stereotyped and restricted patterns of interest • Apparently compulsive adherence to specific non-functional routines and rituals • Stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting or complex whole body movements
Weak Central Coherence	• Failure to use eye-to-eye gaze, facial expression, body posture and gestures to regulate social interaction • Preoccupations with part-objects of non-functional elements of play materials

1.4.2 Neuroanatomical Aetiology in Autism Spectrum Disorder

Multiple brain structures have been implicated in the aetiology of autism spectrum disorder (Abrahams 2010, Miles 2012). To date, such findings have been inconsistent (Toal, 2010) and studies identified as part of this literature review mirror this trend. It is hypothesised that inconsistent findings in the area of neuroanatomical research in autism spectrum disorder is most likely due to different methodologies and heterogeneity of study samples varying in age, gender, ASD subtype, intellectual capacity and presence or absence of a comorbid disorder.

Neuroanatomical studies have looked at a number of potentially causative structural brain abnormalities in autism spectrum disorder. Probably the most researched is total brain volume. Total brain volume was initially implicated by Kanner when he described increased head size in five of his cases (Toal, 2005). Researchers have gone on to replicate findings of increased brain volume in children (Toal 2005, Miles 2012) though

findings in adult subjects are more inconsistent varying from increased volume (Toal, 2010) to no difference (Murphy 2012, Rieldel 2014).

In addition to variation in total brain volume, individuals with autism spectrum disorder show variation in brain structure. Gross changes in white and gray matter are noted in almost all lobes of the brain. Findings include increased gray matter in the frontal lobe, increased and reduced gray matter in the temporal lobes, reduced white matter in the temporal lobes, increased white matter in the parietal lobes and reduced gray matter in the occipital lobe (McAlonan 2002, Craig 2007, Toal 2009, Toal 2010). Subcortical structural abnormalities include reduced gray matter and increased white matter in the limbic system and normal sized, smaller and larger amygdala have been reported (Craig 2007, Maier 2015). Findings also vary in relation to the cerebellum which has been reported as of normal volume, smaller and larger in individuals with autism spectrum disorder compared to neurotypical controls (Toal, 2010). It is estimated that between 10% and 40% of children with autism spectrum disorder have abnormal brain structure (Miles, 2012). This literature review could not identify a percentage of affected adults with autism spectrum disorder.

The absence of a single absolute diagnostic symptom makes it difficult to localise pathology to a specific brain region in adults with normal IQ autism spectrum disorder. Although abnormalities have been noted in the frontal, temporal, parietal and occipital lobes, limbic system and cerebellum no consistent structural abnormality has been identified in all individuals with autism spectrum disorder (Gargaro, 2011).

1.4.3 Genetic Aetiology in Autism Spectrum Disorder

Hans Asperger and Leo Kanner both noted similarities in disposition between the children under their care and their fathers, namely ‘eccentricity’ and ‘single-mindedness’ (Wing 1981, Happé 2001b). They felt these common traits implied familial tendency and by extension, genetic inheritance. Over the following six decades, researchers have been in agreement that autism spectrum disorder is the ‘most strongly genetic’ of the multifactorial psychiatric illnesses (Bailey 1995, Howlin 1999, Happé 2001b, Murphy DG 2002, Newschaffer 2003, Stahlberg 2004, Ellefsen 2007). Autism spectrum disorder is now considered a genetic condition with a notably high heritability index (>0.90) (O’ Roak 2008, Miles 2012). Increased concordance among

monozygotic twins (36% - 95%) compared to dizygotic twins (0% - 10%) and a sibling recurrence rate of 8% indicate a significantly higher risk among first-degree relatives compared to the general population (Miles 2011, Miles 2012, CDC 2013). This is not unique to cohorts of mixed age and mixed IQ but also applicable to individuals with normal IQ autism spectrum disorder (Zafeiriou, 2013). The subsequent search for a genetic basis to autism spectrum disorder is an area of particular research interest due to its potential to provide a greater understanding of the underlying aetiology of this disorder, allow for genetic counselling, predict those patients at greatest risk for the disorder and possibly lead to new treatment modalities (Maestrini, 2000). Reliable and repeatable genetic markers however have been difficult to isolate.

Approximately 10% of autism spectrum disorder is associated with a known medical disorder (Geschwind, 2008). The remainder of cases are considered to be of unknown aetiology. The mode of inheritance in such 'idiopathic' or 'non-syndromal' autism spectrum disorder is complex and believed to be polygenic or oligogenic rather than simple monogenic or Mendelian inheritance (Maestrini 2000, Wassink 2004, Ma 2005, Willsey 2015). Such a mode of inheritance has led to the identification of several susceptibility genes, each of only weak or moderate effect and individually unable to cause the disorder, but acting together could possibly give rise to the clinical phenotype of autism spectrum disorder (Maestrini, 2000). Some researchers suggest 17 of the 22 autosomal chromosomes along with the X chromosome could be involved while the number of genes involved in the inheritance of autism spectrum disorder could range from three to more than one hundred (Wassink 2004, O' Roak 2008, Willsey 2015). Original studies and review papers date from 1977 and outline hundreds of associations. Though unquestionably incomplete, those chromosome and gene associations identified as part of this literature review are outlined in Tables 1.3 and 1.4. Despite genome-wide and candidate gene association studies replicating a number of chromosome and gene associations, results in this area are disappointing for the most part (Miles, 2011). Most mutations are considered to be de novo, rare and of small effect size. In essence, the true genetic aetiology of this profoundly heterogeneous disorder remains elusive and research in the area continues.

Table 1.3 Genome Wide Screens in Autism Spectrum Disorder	
Author, Year of Publication	**Chromosomes**
The International Molecular Genetic Study, 1998	Chromosomes 2q, 7q, 16p, 17q
Philippe, 1999	Chromosomes 4q, 5p, 6q, 10q, 18q and Xq
Risch, 1999	Chromosome 1p
Collaborative Linkage Study of Autism, 1999	Chromosomes 7q, 13q
Ashley-Koch, 1999	Chromosome 7q
Buxbaum, 2001	Chromosomes 1q, 6q, 19p
Liu, 2001	Chromosomes 5q, 8q, 16p, 19p and Xq
Alarcón, 2002	Chromosome 7q
Auranen, 2002	Chromosomes 1q, 3q, 7q
Shao, 2002	Chromosomes 2q, 3, 7q, 15q, 19 and X
Yonan, 2003	Chromosomes 4q, 5p, 8q, 11p, 17q
McCauley, 2005	Chromosomes 3p, 6q, 7q, 12p, 16p, 17q, 19p
Liu, 2008	Chromosomes 11p, 15q

Table 1.4 Chromosome and Gene Findings in Autism Spectrum Disorder	
Chromosome	**Genes**
Ma, 2009	Chromosome 5p
Weiss, 2009	Chromosomes 5p, 6q, 20p
2p	Neurexin 1 (NRXN*1*)
2q	Mitochondrial transporter (SLC*25*A*12*)
3p	CTN*4* Oxytocin Receptor gene (OXTR)
4p	GABA*alpha4*
4q	PCDH*10*
5p	NIPBL
5q	GABA*alpha1*
6p	CNTN*3* CNTN*4* RNF8
7q	AUTS*2* CNTNAP*2* EN*2* FOXP*2* IMMP*2*L LAMB*1* NRCAM NPTX*2* RAY*1*/ST*7* RELN TCAG_*413353* WNT*2*
11p	C-Harvey-ras-*1* (HRAS*1*)

Chromosome	Genes
12p	CACNAIC
15q	$GABA_A$ Receptor Subunit → α*5*, β*3*, γ*3* Ubiquitin Protein Ligase (UBE*3*A)
16p	Ataxin *2*-binding protein *1* (A*2*BP*1*) CACNA*1*H
17p	Homeobox A*1* (HOXA*1*)
17q	Homeobox B*1* (HOXB*1*) Serotonin Transporter gene (5-HTT, SERT)
22q	SHANK*3*
Xq	Neuroligin *3* (NLGN*3*) MECP*2*
Xp	Neuroligin *4* (NLGN*4*)

1.4.4 Medical Factors in Autism Spectrum Disorder

A link between autism spectrum disorder and prenatal, perinatal or post-natal complications was first suggested over 30 years ago (Wing, 1981). Findings however remain largely contradictory. While some epidemiological studies, case reports and short series implicate prenatal rubella, cytomegalovirus, teratogens, anoxia, cerebral damage and post-natal toxin exposure, others show no significant causal relationship with obstetric factors, intrauterine exposure to medications, receipt of vaccinations, immigrant status, socioeconomic status or ethnicity (Muhle, 2004). Human and animal testing have suggested Thalidomide, Valproate, Ethanol and Misoprostol exposure in pregnancy as possible causes of autism spectrum disorder in offspring (Strömland 1994, Narita 2002, Dufour-Rainfray 2011). Judith Miles (2011) suggests in utero exposure to Valproate could increase an offspring's risk of autism spectrum disorder seven fold. Methylmercury exposure had also been postulated as a cause of autism spectrum disorder but long-term epidemiological data do not support this theory (Ellefsen, 2007).

Authors have considered maternal illness / infection during pregnancy, unfavourable prenatal conditions such as chemical exposure, birth complications, postnatal vaccination and parenting style as possible causes of the condition. Generally, all have been either discarded or discredited in favour of biological and genetic aetiology. An argument could possibly remain for intrauterine haemophilus influenza and cytomegalovirus infection in the early stages of pregnancy (Muhle, 2004) a theory which remains under review.

It is believed that up to 10% of autism spectrum disorder is directly attributable to a chromosomal or genetically determined disorder however no single condition causes more than 1% of cases (Geschwind 2008, Riedel 2014). An average figure of 5.9% has been suggested by researchers and the terms 'syndromal autism' or 'secondary autism' are sometimes used to refer to such cases (Fombonne 2005, Mouridsen 2011). This ASD phenotype is present to varying degrees across multiple medical conditions however no medical condition shows 100% penetrance for ASD symptomatology (Muhle, 2004). Medical conditions as identified by this literature review are outlined in Table 1.5.

Table 1.5

Medical Conditions with Associated Autism Spectrum Disorder

Medical Condition	**Chromosomal / Genetic Mutation**
Angleman syndrome	UBE*3*A on 15q11
Chromosome 2q37 deletion syndrome	Deletion on 2q37
Cohen syndrome	VPS*13*B on 8q22
Cornelia de Lange syndrome	NIPBL on 5p13 *or* SMC*1*A on Xp11 *or* SMC*3* on 10q25
Cowden syndrome	PTEN on 10q23
Down syndrome	Trisomy 21q22
Duchenne Muscular Dystrophy	DMD on Xp21
Fragile X syndrome	FMR*1* on Xq27

Medical Condition	Chromosomal / Genetic Mutation
Joubert syndrome	AH*11* on 9q34
Landau-Kleffner syndrome	GRIN*2*A on 16p13
Lujan-Fryns syndrome	MED*12* on Xp13
Mitochondrial chain disorders	Maternal mitochondria
Moebius syndrome	13q12
Myotonic Dystrophy	DMPK on 19q13
Neurofibromatosis 1	NF*1* on 17q11
Prader-Willi syndrome	NDN or SNRPN on 15q11
Rett syndrome	MECP2 on Xq28
San Filippo syndrome	SGSH on 17q25
Smith-Lemi-Opitz syndrome	DHCR*7* on 11q12
Smith-Magenis syndrome	RA*1* on 17p11
Sotos syndrome	NSD*1* on 5q35
Timothy syndrome	CACNA*1*C on 12p13
Tuberous Sclerosis	TS*1* on 9q34 *or* TS*2* on 16p13
Turner's syndrome	Deletion of Xq
Velocardiofacial syndrome	TBX*1* on 22q11
Williams-Beuren syndrome	Microdeletion on 7q11

1.4.5 Biochemical Factors in Autism Spectrum Disorder

Although a tentative link has been made between oxytocin, vasopressin, secretin and symptoms of autism spectrum disorder (Hollander 2003, Walsh 2008) a clear evidence-based link is yet to be established (Tyson, 2012). It was hypothesised that these peptides played a role in social attachments, social communication and repetitive behaviour (Hollander, 2003) however fifteen further case-control studies failed to replicate a link (King, 2005).

Anomalies in the serotonergic system, serotonin transporter gene and dopaminergic systems have been implicated in a more robust manner in the aetiology of autism spectrum disorder (King 2005, Råstam 2008). The serotonergic system influences social behaviour, cognitive function, amygdala response to facial expression and repetitive behaviours (Wassink 2004, Murphy 2006). It is recognised that individuals with autism spectrum disorder both with and without associated intellectual disability show 25% - 50% higher serum concentrations of serotonin (Anderson, 2016). Despite strong evidence for a link between serotonin and autism spectrum disorder, researchers have found contradictory evidence when attempting to determine the mechanism of serotonin dysfunction in the disorder (Muhle, 2004) and the precise role of the serotonin transporter gene in ASD symptomatology remains under study.

1.4.6 Environmental Theories in Autism Spectrum Disorder

Suggested environmental aetiologies in autism spectrum disorder are many and varied. Early research, from the 1940s to 1960s, considered the possibility of emotional causes or abnormal child-rearing methods in the aetiology of autism spectrum disorder, especially where parents or siblings displayed similar features (Happé 2001b, Wing 2002a, Newschaffer 2003). It was once believed that ‘detached and sterile care of the infant’ led to autism spectrum disorder (Schain, 1960). It has since been clarified that there is no evidence to support such theories (Wing 1981, Happé 2001a, Wing 2002a).

Though retracted, another distressing aetiological association was that between the MMR vaccine and autism spectrum disorder. A 1998 publication by Wakefield et al detailing case reports of 12 children is probably the highest impact environmental link for autism spectrum disorder to date. Wakefield et al described 12 children, aged 6 - 10 years who reportedly lost acquired skills in communication and developed gastrointestinal symptoms including abdominal pain, diarrhoea, bloating and food intolerance following receipt of the MMR vaccine. The group described the onset of behavioural problems on average 6.3 days following MMR vaccination. Wakefield and colleagues described the connection between intestinal and behavioural pathologies as ‘real and reflects a unique disease process’, relating to ‘an inflamed or dysfunctional intestine’ following ‘the measles, mumps and rubella immunisation’. Though the paper

was careful in advising a causal link had not been proven, they did warn that a rise in autism spectrum disorder could be anticipated following the introduction of the MMR vaccine.

Although many researchers have attempted to replicate Wakefield et al's (1998) findings, all found a significant lack of evidence to support a link between autism spectrum disorder and the MMR vaccine (Wing, 2002a). The General Medical Council also conducted a 217 day investigation of the authors' purported findings and found that the paper lacked appropriate ethical approval and patients were not consecutively referred (Godlee, 2011). On these grounds, the Lancet retracted Wakefield et al's paper. However, other authors investigating the publication outline further fraudulent reporting including skilful case selection, misrepresentation of the case histories, lack of symptoms to constitute a new disorder, falsified timing regarding the onset of bowel symptoms, documentation of behavioural problems prior to receipt of the MMR vaccine in some cases and Wakefield's personal role in litigation against the vaccine's manufacturer (Deer, 2011). Wakefield has since been branded 'dishonest, unethical and callous' by the General Medical Council and removed from the medical register. Unfortunately, the full impact of his fraudulent report will only become evident over the coming decade as public health physicians identify the impact the associated drop in vaccination rates has had on herd immunity (Godlee, 2011). Possibly, more significant to consider is the impact on the academic community, the time and finances lost in attempts to replicate findings and the stigma and fear consequently attached to autism spectrum disorder.

Early this century, Wing and Potter (2002a) were quite clear that 'not one of the possible environmental causes has been confirmed'. Given the current lack of general consensus among researchers and the clear retraction of certain proposed aetiologies their deduction is likely to remain valid into the future.

1.5 Clinical Presentation of Autism Spectrum Disorder

Autism spectrum disorder is the most common disorder in the group of conditions known as the neurodevelopmental disorders (Vannucchi, 2014a). Other neurodevelopmental disorders include intellectual disability, communication disorders, attention deficit hyperactivity disorder, specific learning disorder and motor disorders

(American Psychiatric Association, 2013). Autism spectrum disorder can be behaviourally defined by diagnostic criteria specifying pervasive qualitative abnormalities in social and communication skills and behaviour. However, as yet, there are no definitive diagnostic tests, biochemical, neuroimaging or otherwise to detect autism spectrum disorder. Hence, diagnosis relies heavily on detailed history and observation of behaviour by a skilled clinician using the ICD-10 and / or DSM-5 criteria.

For decades, there was a lack of officially defined diagnostic criteria for early infantile autism and autistic psychopathy as publications consisted mostly of case studies. Some authors provided their impression of common symptoms across cohorts of case studies (Kanner 1943, Eisenberg 1956, Schain 1960, Creak 1961, Lotter 1966, Ornitz 1968, Rendle-Short 1968, Tinbergen 1972, Wing JK 1976, Wing L 1976, Gillberg 1989). Unfortunately, though somewhat similar, the criteria proposed by each were too diverse to allow accurate comparison of cases or research findings or to provide nosological certainty (Lotter 1966, Rutter 1978). Due to the passage of time, not all original articles could be sourced as part of this literature review. Details of early criteria proposed in available articles are outlined in Table 1.6.

Table 1.6

Defining Criteria for Autism Spectrum Disorder

Author, Year of Publication	**Criteria**
Kanner, 1943	Ten common features: - An inability to develop relationships with people - Delay in speech acquisition - Non-communicative use of speech after it developed - Delayed echolalia - Pronoun reversal - Repetitive and stereotyped activities - Obsessive insistence on sameness - Lack of imagination - Good rote memory - Normal physical appearance
Eisenberg, 1956	2 criteria and limit in age of onset: - Extreme aloneness - Preoccupation with the perseveration of sameness Limit for age of onset at 1 - 2 years

Author, Year of Publication	Criteria
Schain, 1960	3 criteria for diagnosis: - Evidence of a severe personality disorder characterized by extreme preoccupation with self and unrelatedness to people in his environment - Presence of a history indicating the onset of this disorder during the first 2 years of life as manifested by the failure to develop the expected patterns of relationships to the parents or other guardians Absence of a history of serious motor retardation such as is associated with most forms of gross brain defect
Creak, 1961	Five common characteristics: - Marked unevenness in intellectual retardation - Bizarre mobility - Gross anxiety reactions - Clinging social behaviour - Unusual sensory sensitivities
Lotter, 1966	Twenty four features: - Speech not used for communication - Reversal of pronouns - Echolalia - Repetition of phrases - Visual avoidance - Solitary - Ignores children - Aloof and distant - Walks / looks through people - Self-spinning - Jumping - Flapping - Toe walking - Other marked mannerisms - Behaves as if deaf - Covers ears - Distress at noise - Elaborate food fads - Lines and patterns with objects - Spinning objects - Other elaborate ritual play - Carrying, banging, twirling objects - Insistence on sameness (objects) - Insistence on sameness (events)

Author, Year of Publication	Criteria
Rendle-Short, 1969	Requires 7 of 14 behavioural symptoms as a screening test, followed by clinical examination, IQ assessment, EEG and urine amino acid testing to meet criteria for diagnosis.
Gillberg, 1989	All six criteria must be met for diagnosis: Severe impairment in reciprocal social interaction (≥2): - inability to interact with peers - lack of desire to interact with peers - lack of appreciation of social cues - socially and emotionally inappropriate behavior All-absorbing narrow interest (≥1): - exclusion of other activities - repetitive adherence - more rote than meaning Imposition of routines and interests (≥1): - on self, in aspects of life - on others Speech and language problems (≥3): - delayed development - superficially perfect expressive language - formal, pedantic language - odd prosody, peculiar voice characteristics - impairment of comprehension including misinterpretations of literal / implied meanings Non-verbal communication problems (≥1) : - limited use of gestures - clumsy / gauche body language - limited facial expression - inappropriate expression - peculiar, stiff gaze Motor clumsiness: - poor performance on neurodevelopmental examination

The ICD and DSM communities were slow to accept autism-like conditions and to describe them using independent diagnostic categories or criteria. In DSM-I and DSM-II, autism-like illnesses were included under the concept of childhood schizophrenia. In ICD-8, although autism was introduced as a term, it remained a subgroup of schizophrenia (Wing, 2002a). It was not until 1980, that autism was provided with an independent diagnostic category when the DSM-III introduced 'infantile autism'. From DSM-III to DSM-III-TR came the most significant diagnostic advances for autism when criteria became more concrete and measureable (Factor, 1989).

Asperger's syndrome was slower to gain recognition among nosologists as DSM and ICD did not publish diagnostic criteria for Asperger's syndrome until some ten years later when DSM-IV set out five conditions within chapter one's description of pervasive developmental disorders: autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's syndrome and pervasive developmental disorder - not otherwise specified, including atypical autism (American Psychiatric Association, 1994). The evolution of the ICD and DSM autism-related diagnostic criteria are outlined in Table 1.7.

Table 1.7

ICD and DSM: Evolution of Diagnostic Criteria for Autism Spectrum Disorder

Publication	Name of Condition
1952, DSM-I	Childhood schizophrenia
1967, ICD-8	Infantile autism classified as a subgroup of schizophrenia
1968, DSM-II	Childhood schizophrenia
1978, ICD-9	Infantile autism classified as a subgroup of childhood psychosis
1980, DSM-III	Infantile autism as a distinct diagnostic category
1987, DSM-III-R	Pervasive developmental disorders
1992, ICD-10	Pervasive developmental disorders
1994, DSM-IV	Pervasive developmental disorders
2000, DSM-IV-TR	Pervasive developmental disorders
2013, DSM-5	Autism spectrum disorder

The ICD-10 (World Health Organisation, 1992) and DSM-5 (American Psychiatric Association, 2013) now provide clinicians with useable diagnostic criteria, allowing more accurate assessment, diagnosis and research in the area of autism spectrum disorder compared to previously. Currently, the ICD-10 outlines eight conditions under F84: childhood autism, atypical autism, Rett's syndrome, other childhood disintegrative disorder, overactive disorder associated with mental retardation and stereotyped movements, Asperger's syndrome, other pervasive developmental disorders and pervasive developmental disorder, unspecified. Although Rett's syndrome is included in the ICD-10 listing of autism spectrum disorder, its presence on the list is considered controversial and misplaced by many. Gillberg and Billstedt (2000) point out that although some individuals with Rett's syndrome have autism-like symptomatology, the criteria for autism spectrum disorder are not fulfilled by all. Criteria for each subtype of pervasive developmental disorder as per ICD-10 and DSM-5 are outlined in Table 1.8.

Table 1.8

Diagnostic Criteria for Subtypes of Autism Spectrum Disorder

International Classification of Diseases-10 (World Health Organisation, 1992)	
Childhood autism	**A. Abnormal or impaired development is evident before the age of 3 years in at least one of the following areas:** 1. receptive or expressive language as used in social communication 2. the development of selective social attachment or of reciprocal social interaction 3. functional or symbolic play **B. A total of at least six symptoms from (1), (2) and (3) must be present, with at least two from (1) and at least one from each of (2) and (3)** 1. Qualitative Impairment in social Interaction are manifest in at least two of the following areas: a) failure adequately to use eye-to-eye gaze, facial expression, body posture and gestures to regulate social interaction b) failure to develop (in a manner appropriate for mental age, and despite ample opportunities) peer relationship that involve a mutual sharing of interests, activities and emotions

Childhood autism	c) lack of socio-emotional reciprocity as shown by an impairment or deviant response to other people's emotions; or lack of modulation of behaviour according to social context; or a weak integration of social, emotional and communicative behaviours d) lack of spontaneous seeking to share enjoyment, interests or achievements with other people (e.g. a lack of showing, bringing or pointing out to other people objects of interest to the individual) **2. Qualitative abnormalities in communication as manifest in at least one of the following areas:** a) delay in or total lack of development of spoken language that is not accompanied by an attempt to compensate through the use of gestures or mime as an alternative mode of communication (often preceded by a lack of communicative babbling) b) relative failure to initiate or sustain conversational Interchange (at whatever level of language skill is present) in which there is reciprocal responsiveness to the communications of the other person c) stereotyped and repetitive use of language or idiosyncratic use of words or phrases d) lack of varied spontaneous make-believe play or (when young) social imitative play **3. Restricted, repetitive and stereotypes patterns of behaviour, interests and activities are manifested in at least one of the following:** a) an encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content of focus, or one or more interests that are abnormal in their intensity and circumscribed nature though not in their content or focus b) apparently compulsive adherence to specific non-functional routines and rituals stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting or complex whole body movements d) preoccupations with part-objects of non-functional elements of play materials (such as their order, the feel of their surface or the noise or vibration they generate) The clinical picture is not attributable to the other varieties of pervasive developmental disorders, specific development disorder of receptive language with secondary socio-emotional problems, reactive attachment disorder or disinhibited attachment disorder, mental retardation with some associated emotional or behavioural disorders, schizophrenia of unusually early onset and Rett's syndrome

International Classification of Diseases-10 (World Health Organisation, 1992)	
Atypical autism	**A.** Abnormal or impaired development is evident at or after the age of 3 years **B.** There is insufficient demonstrable abnormalities in one or two of the three areas of psychopathology required for the diagnosis of childhood autism (namely reciprocal social interactions, communication or restrictive, stereotyped, repetitive behaviours) **C.** Atypical autism constitutes a meaningfully separate condition from childhood autism
Rett's syndrome	Onset between age 7 and 24 months Loss of purposive hand movements and acquired fine motor manipulative skills Accompanying loss, partial loss or lack of development of language, distinctive stereotyped torturous wringing or 'hand washing' movements with the arms flexed in front of the chest or chin, stereotypic wetting of the hands with saliva, lack of proper chewing of food, hyperventilation, failure to gain bowel and bladder control, excessive drooling and protrusion of the tongue and loss of social engagement Retention of 'social smile', looking at or through people but not interacting socially in early childhood (although social interaction may develop later) Broad-based stance and gait, hypotonic muscles, poorly co-ordinated trunk movements, scoliosis or kyphoscoliosis Spinal atrophy with severe motor disability Rigid spasticity more pronounced in lower than upper limbs Associated epileptic fits, with general onset prior to age 8 years
Asperger's syndrome	**A.** Diagnostic criteria 1 - 3 of B are fulfilled for childhood autism **B.** No evidence of general delay or retardation in language or cognitive development **C.** Generally associated with normal intelligence

Diagnostic and Statistical Manual of Mental Disorders-5 (American Psychiatric Association, 2013)	
Autism spectrum disorder	**A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:** • Deficits in socio-emotional reciprocity • Deficits in non-verbal communicative behaviours used for social interaction • Deficits in developing, maintaining and understanding relationships **B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history:** • Stereotyped or repetitive motor mannerisms, use of objects or speech • Insistence on sameness, inflexible adherence to routines or ritualised patterns of verbal or non-verbal behaviour • Highly restricted, fixated interests that are abnormal in intensity or focus • Hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of the environment **C.** Symptoms must be present in early developmental period **D.** Symptoms cause clinically significant impairment in social, occupational or other important areas of current functioning **E.** These disturbances are not better explained by intellectual or global developmental delay

Clearly, autism spectrum disorder and Asperger's syndrome are more alike than they are different (Wing, 1981). The most recent version of the DSM diagnostic criteria, DSM-5 acknowledges this by combining autism, Asperger's syndrome and pervasive developmental disorder into a single diagnosis and by changing the name of this group from 'pervasive developmental disorders' to 'autism spectrum disorder' (American Psychiatric Association, 2013). Although the category remains broad, with Asperger's syndrome and PDD-nos now encompassed in the term autism spectrum disorder,

DSM-5 no longer divides conditions by criteria, instead a single set of criteria can be used to diagnose each patient.

In DSM-5 also, the triad of symptoms seen in DSM-IV have been reduced to two, combining social and communication deficits into the single category of 'deficits of social communication and social interaction' alongside 'restricted, repetitive patterns of behaviour, interests or activities' (American Psychiatric Association 2013, Vannucchi 2014a). Many agree this is a preferable means of diagnosis as differentiation between subgroups of ASD is clinically problematic and social and communication deficits are so closely linked as to be clinically inseparable (Konstantareas 2001, Wing 2011). It is interesting that DSM have chosen to combine the five diagnostic entities of pervasive developmental delay from DSM-IV into the single diagnosis of autism spectrum disorder in DSM-5. One could presume ICD will follow suit in their revision of the ICD-10 into ICD-11, which is due for publication in 2018.

An ongoing concern relating to the International Classification of Diseases is the strict hierarchical rules on which they are based. ICD assumes certain disorders to be more 'severe', 'basic' or 'pure' than others causing certain major mental illnesses to trump others when providing a clinical diagnosis. Practically, this means that, on occasion, a patient cannot receive a diagnosis reflecting comorbidity as ICD states the co-occurrence of particular illnesses are not permitted. This hierarchical framework can be helpful if researchers wish to study purer forms of autism spectrum disorder, although adherence to the guidelines can limit clinical provision of services and may not truly reflect the issues faced by real-life patients, their clinicians or families (Gillberg, 2000).

Currently, ICD-10 discourages diagnosis of comorbidity in autism spectrum disorder by providing exclusion notes for two of the four subtypes of pervasive developmental disorder, namely childhood autism and Asperger's syndrome. Exclusion notes for childhood autism include autistic psychopathy, referring to Asperger's syndrome by its original title. Exclusion notes for Asperger's syndrome include attachment disorders of childhood, obsessive compulsive disorder, anankastic personality disorder, schizotypal personality disorder and simple schizophrenia (World Health Organisation, 1992). In essence, if strictly adhered to exclusion notes prevent psychiatrists from diagnosing particular co-occurring personality disorders, anxiety spectrum disorders and psychotic disorders in those suffering from Asperger's syndrome.

A considerable need to revise the provision of comorbid psychiatric illness in autism spectrum disorder was proposed by Gillberg as early as 2000. Since that time, many authors have called for revision of the diagnostic criteria to more accurately reflect the socio-communication deficits and high comorbidity rates in autism spectrum disorder (Ghaziuddin 2002a, Stahlberg 2004, Van Os 2009, Gargaro 2011, Lugnegård 2012, Tyson 2012, Mazzone 2012). DSM-5 appears to have considered these recommendations providing only three exclusion criteria to the diagnosis of autism spectrum disorder 'that symptoms must be present in the early developmental period, that symptoms cause clinically significant impairment in functioning and that symptoms are not better explained by intellectual disability or global developmental delay' (American Psychiatric Association, 2013). No longer is there a specification to prevent diagnosis of comorbid Axis I or Axis II psychiatric illness in those with autism spectrum disorder. Likewise, autism spectrum disorder is no longer an exclusion criterion for schizophrenia, bipolar disorder, depressive disorder or anxiety spectrum disorders. However, a complex criterion clash continues for the DSM-5 definition of Cluster A personality disorders. DSM-5 states that paranoid, schizoid and schizotypal personality disorders cannot 'occur exclusively during the course of autism spectrum disorder' (American Psychiatric Association, 2013). As autism spectrum disorder is a lifelong condition, this is in essence an absolute exclusion criterion.

Similar to the provision of diagnoses in the years of early infantile autism and autistic psychopathy, contemporary authors can interpret the clinical symptomatology of ICD-10 and DSM-5 differently. From 1999 to 2013, a wide variation in interpretation can be seen. Janet Lainhart (1999) interpreted the criteria as patients having difficulty reading the thoughts, beliefs, intent and emotions of other people, being unable to see the 'big-picture or gestalt of situations', lacking day-to-day understanding of their world and unable to predict the future from past experience. Gena Barnhill (2007) described individuals with autism spectrum disorder as people who would struggle with the use of pragmatic language, providing the right information at the right time, use of social niceties, reading non-verbal cues and interpreting information literally. These examples highlight the significantly different degree of disability expected by each clinician.

Table 1.9 describes the clinical symptomatology for each ICD-10 criterion expanding on those provided by Garland et al (2013). This is a useful approach as each criterion corresponds to the clinical approach used in tertiary ASD assessment centres. These

criteria, namely the triad of impairments in social and communication skills and repetitive behaviours, are equally applicable to diagnosis in childhood and adulthood (Hofvander, 2009).

Table 1.9

ICD-10 and DSM-5 Diagnostic Criteria with corresponding Clinical History and Mental State Findings

ICD-10 Criterion	Clinical Symptom / Sign
Abnormal or impaired development is evident before the age of 3 years	- Clear delay in use of speech to communicate - No single words by age 2 years - No phrased speech by age 3 years
Qualitative impairment in social interaction	- Few or no sustained relationships - Aloof, awkward interaction with others - Egocentric with limited empathy - Poor awareness of social norms - Lack of direct eye contact - Restricted or inappropriate range of facial expression - Lack of emotional expression - Absence of close sharing friendships or relationships - Dislike of physical contact and impaired ability to comfort others - Lack of social chit-chat or 'small talk' - Abnormal play; dislike of shared play, lack of symbolic use of toys in childhood
Qualitative abnormalities in communication	- Stilted, pedantic use of language - Non-reciprocal, one-sided interaction - Literal interpretation of what is heard - Restricted affect and limited use of gestures - Poor integration of gaze with content of speech - Lack of creativity and fantasy in thought - Lack of emotional response to another's verbal and non-verbal overtures - Impairs use of cadence of speech - Use of echolalia, neologisms and pronoun reversal - Lack of spontaneous conversation or sharing of personal information

ICD-10 Criterion	Clinical Symptom / Sign
Restricted, repetitive and stereotypes patterns of behaviour, interests and activities	- Circumscribed interest of limited practical or social value - Obsessive pursuit of restricted interests - Strict daily routine and schedule - Deviation from daily structure causes distress - Resistance to change - Abnormal play; preoccupation with parts of objects - Lack of spontaneity, initiative and creativity - Lack of spontaneous imitation / mirroring of others - Unusual sensory seeking or avoidance behaviours - Increased sensitivity to noise

1.6 The Importance of Diagnosing Autism Spectrum Disorder

Although, there is no known treatment for the core impairments in autism spectrum disorder, morbidity can be reduced by appropriate management and education (Raja, 2008). In addition, although it cannot be cured, early diagnosis and identification of autism spectrum disorder is central to implementing early interventions in an effective manner. Both children and adults can be helped by thoughtful ways of engaging their deficits and enhancing their strengths. Wing (1981) suggests that individuals with autism spectrum disorder respond best when there is a regular, organised routine, when carers communicate in ways the individual can understand, when supportive techniques are used to modify behaviour, when teachers ensure the child is not teased or bullied by their peers, when adults gain employment supported by sympathetic employers and workmates and when appropriate living conditions are sourced.

Individuals with autism spectrum disorder endorse greater unmet social and healthcare needs than those seen in the general population (Garland, 2013). It is increasingly recognised that such unmet needs are associated with considerable carer burden. Studies looking at influences on carer burden have examined maternal and child variables in mixed age, mixed IQ samples. Factors associated with a reduction in carer burden include positive maternal affect, greater expression of maternal affection, higher maternal warmth, higher maternal self-esteem, lower maternal pessimism, higher reciprocated affection, better child health and fewer child maladaptive behaviours (Orsmond et al 2006). The severity of a child's disability, nature of care

required, presence of behavioural difficulties, financial stress and carer's physical health significantly increase carer burden (Weiss, 2010). Increased worry, stress and responsibility associated with caring for an individual with physical and / or mental illness further exacerbates carer burden (Kring 2010, Cadman 2012). Carer burden and distress can result in parental stress, marital discord, poor child-parent relationships, poor child-sibling relationships, lower quality of life and carer mental illness such as depression (Weiss, 2010).

Increased mortality rates are noted among individuals with autism spectrum disorder compared to the general population (Howlin 2012, Hirvikoski 2016). Mortality rates are between 2 and 5.6 times higher than expected in the autism spectrum disorder population, especially among females, patients with comorbid epilepsy and those with intellectual disability (Howlin 2000, Barnhill 2007, Howlin 2012). Although a higher mortality rate associated with comorbid intellectual disability would be clinically expected, the strong U-shape association between mortality and IQ suggests increased mortality is in fact associated with both severely low and exceedingly high IQ scores in autism spectrum disorder (Barnhill, 2007).

Early referral and diagnosis of individuals with normal IQ autism spectrum disorder is often not achieved despite widespread research indicating improved outcomes and a substantially better prognosis for those receiving earlier and more effective interventions (Constantino, 2015). Failure to recognise problems in individuals with Asperger's syndrome in childhood has been shown to lead to a downward spiral of rejection and low self-esteem which could result in severe emotional and psychiatric problems (Howlin, 2000). Data suggest that appropriate evaluation, pre-drug workup, provision of a specific diagnosis, efficient measures of outcome and use of pharmacotherapy can provide a safe and efficacious means of reducing many symptoms suffered by individuals with autism spectrum disorder (Tsai, 1996). This approach is increasingly promoted in treatment recommendations and in some jurisdictions has become a legal obligation for policy makers (Department of Health UK, 2010).

As many individuals with autism spectrum disorder only present to psychiatric services when they note personal limitations as adults, in areas such as obtaining employment despite high educational achievement, difficulty adjusting to occupational change or relationship failure a large cohort, especially those with Asperger's syndrome, can

remain undiagnosed into adulthood (Tantam 2000, Barnhill 2007, Raja 2008). Some have argued that psychiatrists must accept their responsibility to diagnose autism spectrum disorder beyond the childhood phase and provide diagnostic, psychoeducational, medical and psychological treatments for the emotional and behavioural difficulties experienced by adults with autism spectrum disorder (Tantam 2000, Barnhill 2007). As more adults seek assessment for autism spectrum disorder, corresponding healthcare services should be configured to meet their needs.

1.7 Methods of Diagnosis and Assessment in Autism Spectrum Disorder

When assessing for autism spectrum disorder, clinicians continue to rely on detailed history and observation to reach a diagnosis. A combination of history taking, collateral information taking and use of screening and diagnostic assessment tools is required. Clinical assessment of individuals with autism spectrum disorder can be difficult due to factors such as a reduced ability to describe emotions and symptoms of mental illness, reduced language skills and a tendency to interpret questions literally (Kannabiran, 2009). It has been suggested that a high level of skill is required to ensure accurate assessment of individuals with normal IQ autism spectrum disorder, gathering of a reliable collateral history and competent application of standardised assessment tools (Lord 1989, Lord 1994, Baron-Cohen 2001a, Kannabiran 2009). Expert training and an opportunity to complete a large number of assessments are necessary to ensure clear-cut diagnosis in this complex patient group.

Little specific literature is available on the healthcare needs of and resource utilisation by adults with autism spectrum disorder. One original study, one review paper, one health service report and one piece of legislation were sourced as part of this literature review. Venkat et al (2012) provide a review paper of the quality of healthcare available to individuals with autism spectrum disorder in Pittsburgh, USA. They report dissatisfaction among family and caregivers, quoting a lack of awareness of the condition among healthcare workers and poor quality assessment skills among physicians. Many carers attribute the health service's inability to deliver effective healthcare to those with autism spectrum disorder to these factors (Venkat, 2012). Bruder et al (2012) surveyed 376 primary care physicians in the Northern United States of America. They found that physicians also acknowledge skill and resource deficits,

noting in particular a lack of training in the care of adults with autism spectrum disorder. Primary care physicians reported a desire for workshops and ASD specific conferences as a means of receiving such training (Bruder, 2012).

The Autism Act was passed by the UK parliament in March 2010. It highlights a national shortage of healthcare services for individuals with autism spectrum disorder in the United Kingdom and places legislative responsibility on healthcare organisations to ensure increased awareness and understanding of autism spectrum disorder among all healthcare staff, increased availability of diagnosis for children and adults, a clear pathway for patients transitioning from child to adult healthcare services and increased opportunity for housing and employment for adults with autism spectrum disorder (Autism Act, 2009).

A report commissioned by the Irish Health Service Executive (2012) broadly mirrored the findings of The Autism Act (2009). It highlighted a similar significant shortage of services for adults with autism spectrum disorder. Particularly noted were the lack of a defined pathway between child and adult services for those diagnosed with autism spectrum disorder in childhood, a lack of mental health services to diagnose and treat adults with suspected or confirmed autism spectrum disorder and a lack of training and education for healthcare providers. Probably most fundamental is the evidence from this report that the Irish health service do not have comprehensive information on the number of adults with autism spectrum disorder residing in the Republic of Ireland.

1.7.1 Clinical Assessment of Autism Spectrum Disorder

Individuals with autism spectrum disorder can be difficult to assess and diagnose for a multitude of reasons. This can lead to symptoms of one psychiatric illness being mistaken for another, especially if assessment is undertaken by a clinician superficially familiar with autism spectrum disorder (Raja, 2008). The wide overlap between some features of autism spectrum disorder and those of other mental illness may prevent the correct identification of psychiatric comorbidity in this population (Vannucchi, 2014a). Clinicians may find it difficult to determine whether symptoms can be accounted for by the diagnosis of autism spectrum disorder or reflect a second illness (Geurts, 2010). On occasion, psychiatric illness associated with autism spectrum disorder can be

characterised by atypical presentations leading to diagnostic, prognostic or therapeutic mistakes (Vannucchi, 2014a).

It is important that core symptoms of autism spectrum disorder are not misdiagnosed as an Axis I or Axis II psychiatric illness when a neurodevelopmental diagnosis would be more appropriate (Vannucchi, 2014a). Symptoms such as new onset social withdrawal, interpersonal difficulties, appetite change, fluctuating mood, reduced self-care, reduced adaptive functioning or poor coping could be considered part of the autism spectrum disorder clinical syndrome if not appropriately explored as an affective or psychotic illness. Eccentricity, emotional lability, anxiety, poor social functioning, repetitive behaviours and fixed habits, known to occur in those with autism spectrum disorder could result in unrequired additional diagnoses such as schizophrenia, bipolar affective disorder or obsessive compulsive disorder (Barnhill, 2007). Limited facial expression or emotions that shift quickly with exquisite sensitivity to small changes in the everyday environment, could be misdiagnosed as depression, mania (Lainhart, 1999) or personality disorder. The need for strict rituals and routines could be mistaken for obsessive compulsive disorder (Van Elst, 2013). The core social and communication deficits of autism spectrum disorder could be difficult to differentiate from social phobia (Tyson, 2012). Complex stereotypies could be mistaken for tics leading to an inaccurate diagnosis of Tourette's syndrome (Lainhart, 1999). When under stress, individuals with autism spectrum disorder can exhibit unusual behaviours or odd coping mechanisms that could be confused with psychosis. Bizarre idiosyncratic behaviours, poor expression of emotion or perceptual misunderstandings could be misdiagnosed as schizophrenia-like illness (Van Elst, 2013). 'Disorganising anxiety' could be mistaken for thought disorder of schizophrenia (Barnhill, 2007). Lack of initiating communication or poor socioemotional responses could be mistaken for poverty of speech attributed to schizophrenia (Lainhart, 1999). Likewise, intense preoccupations or magical thinking could be considered a delusion (Lainhart, 1999). Sometimes, due to sensory overload, patients with autism spectrum disorder can engage in deliberate self-harm in an attempt to self-regulate distress and social inadequacy, this could be mistaken for emotionally unstable personality disorder (Van Elst, 2013). Any psychiatrist confronted with a socially-isolated adult with unusual routines, rituals or obsessive pursuits who has not responded to treatment for their initial psychiatric diagnosis should suspect autism spectrum disorder (Tantam, 2003). Of interest, all four cases described by Asperger (1944) presented with behavioural

symptoms that could be classified as distinct psychiatric disorders (Ghaziuddin, 2002a).

Likewise, symptoms which fulfil criteria for an alternative psychiatric diagnosis should not be overshadowed by the diagnosis of autism spectrum disorder. This is probably most commonly seen in the diagnosis of Cluster A and C personality disorders (Wentz-Nilsson, 1999). Longstanding avoidance behaviour, dependant traits or poor anger management could be included as ASD symptoms while a disabling personality disorder is missed. For these reasons, Oldershaw (2011) recommends all autism assessments be carried out by specialist clinicians trained in the area of neurodevelopmental psychiatry.

Lainhart (1999) makes five recommendations for the accurate evaluation, assessment and diagnosis of autism spectrum disorder in high-functioning adults. Although almost 17 years old, these recommendations remain useful in the assessment of those with autism spectrum disorder and comorbid illness today. Some have been reiterated by Constantino and Charman (2015).

1. Assessors must start from the basic premise that psychiatric disorders are conceptually the same in adults with autism spectrum disorder as in those without a neurodevelopmental disorder, in that signs of the full clinical syndrome should be present and meet full diagnostic criteria.

2. Assessors must have a full understanding of the limitations in affect, communication and social functioning which exist at ‘baseline’ for patients with autism spectrum disorder and avoid misdiagnosis of core ASD features as a secondary mental illness.

3. Assessment requires direct evaluation of the patient’s mental state but also collateral information, as observed by others must be taken into account.

4. Care should be taken in posing questions that can be understood by the patient but also time should be taken to accurately understand the reply and importantly the meaning of what the patient is saying.

5. Initial diagnostic impression should be part of a differential diagnosis, inclusive of physical and neurological conditions, until these are carefully ruled out.

The expertise of the assessor in understanding not only autism spectrum disorder but all psychiatric conditions including mood disorders, psychosis, anxiety spectrum

disorders and personality disorders as well as organic and medical conditions is vital in the assessment of patients with autism spectrum disorder. To train solely in identification of ASD features can lead to misinterpretation of symptoms more accurately attributed to other physical or psychiatric illness, while lack of awareness of neurodevelopmental conditions can equally result in misdiagnosis. Even when standardised measurement instruments are used, clinical expertise remains paramount (Lainhart, 1999). Specialist diagnosis by a team familiar with the specificities of autism spectrum disorder allows accurate recognition and clear diagnosis (Van Elst, 2013).

1.7.2 Screening Tools for Autism Spectrum Disorder

Assessment tools fall into two categories; screening and diagnostic. Screening tools are typically completed by the patient prior to the initial assessment by a psychiatrist, psychologist or paediatrician. These are helpful in identifying those patients with a higher probability of receiving a diagnosis of underlying autism spectrum disorder (Baron-Cohen, 2001a) but they do not provide a definitive diagnosis. Diagnostic tools, on the other hand, are considered more reliable in assisting the clinician to reach a definitive diagnosis. These include the Autism Diagnostic Interview - Revised and the Autism Diagnostic Observation Schedule - Generic.

Screening tools were designed and validated as a means for clinicians to quickly, yet reliably identify those at-risk individuals requiring further evaluation for likely autism spectrum disorder. They are also useful in the early stages of epidemiological research looking at very large population groups, as used by Brugha et al (2011) to determine the prevalence of autism spectrum disorder in adults living in households in the United Kingdom. They can also assist non-specialists in determining who best to refer for further assessment and by specialists to provide a baseline of deficits from which to progress further assessment. Many attempts have been made over the past six decades to develop reliable and generalisable assessment tools for autism spectrum disorder. The majority of research in this area was conducted in children, however more recently, tools have been developed for use with the adult population. A great number of assessment tools exist, as outlined in Table 1.10. Constantino and Charman (2015) comment that availability of a large range of screening tools is not necessarily helpful either clinically or in research.

Table 1.10 History of Assessment Tools in Autism Spectrum Disorder	
Author, Year of Publication	**Name of Assessment Tool**
Rimland, 1964	Diagnostic Checklist for Behaviour - Disturbed Children
Freeman, 1978	Behaviour Observation Scale
Krug, 1980	Autism Behaviour Checklist
Sparrow, 1984	Vineland Adaptive Behavioural Scales
Freeman, 1986	Real Life Rating Scale
Schopler, 1986	CARS, Childhood Autism Rating Scale
Le Couteur, 1989	ADI, Autism Diagnostic Interview
Lord, 1989	ADOS, Autism Diagnostic Observation Schedule
Lord, 1994	ADI-R, Autism Diagnostic Interview - Revised
Gilliam, 1995	GARS, Gilliam Autism Rating Scale
Attwood, 1997	ASIS, Australian Scale for Asperger's Syndrome
Ehlers, 1999	ASSQ, Autism Spectrum Screening Questionnaire
Rutter, 1999	ASQ, Autism Screening Questionnaire
Baron-Cohen, 2000	CHAT, Checklist for Autism in Toddlers
Luteijn, 2000	CSBQ, Children's Social Behaviour Questionnaire
Lord, 2000	ADOS-G, Autism Diagnostic Observation Schedule - Generic

Author, Year of Publication	Name of Assessment Tool
Baron-Cohen, 2001	AQ, The Autism Spectrum Quotient
Gillberg, 2001	ASDI, Asperger Syndrome (and high-functioning Autism) Diagnostic Interview
Gilliam, 2001	GADS, Gilliam Asperger's Disorder Scale
Myles, 2001	ASDS, Asperger Syndrome Diagnostic Scale
Nylander, 2001	ASDASQ, Autism Spectrum Disorder in Adults Screening Questionnaire
Robins, 2001	M-CHAT, Modified Checklist for Autism in Toddlers
Baron-Cohen, 2002	CAST, Childhood Autism Spectrum Test, previously known as the Childhood Asperger Syndrome Test
Constantino, 2002	SRS, The Social Responsiveness Scale
Wing, 2002	DISCO, The Diagnostic Interview for Social and Communication Disorders
Baron-Cohen, 2003	SQ, Systematizing Quotient
Krug, 2003	KADI, Krug Asperger Disorder Index
Baron-Cohen, 2004	EQ, Empathy Quotient
Skuse, 2004	3Di, The Developmental, Dimensional and Diagnostic Interview
Baron-Cohen, 2005	AAA, Adult Asperger Assessment
Cohen, 2005	PDDBI, PDD Behaviour Inventory
Baron-Cohen, 2006	SQ-R, Systematizing Quotient Revised
Matson, 2007	ASD-DA, Autism Spectrum Disorder - Diagnostic for Intellectually Disabled Adults
Allison, 2008	Q-CHAT, Quantitative Checklist for Autism in Toddlers

Author, Year of Publication	Name of Assessment Tool
Bryson, 2008	AOSI, Autism Observation Scale for Infants
Ritvo, 2008	RAADS, Ritvo Autism Asperger's Diagnostic Scale
Absoud, 2011	VISS, The Visual Impairment and Social Communication Schedule
Kopp, 2011	ASSQ-REV, Autism Spectrum Screening Questionnaire - Revised Extended Version
Ritvo, 2011	RAADS-R, Ritvo Autism Asperger's Diagnostic Scale
Baron-Cohen, 2012	AAA-2, Adult Asperger Assessment Version 2
Grodberg, 2012	AMSE, Autism Mental State Examination

1.7.3 Diagnostic Tools for Autism Spectrum Disorder

The development of diagnostic instruments has allowed statistically robust measurements to underpin clinical history and observation as a means of assessment in autism spectrum disorder. Le Couteuret al's (1989) publication of the Autism Diagnostic Interview (ADI), allowed for the first time, assessment of developmental history in autism spectrum disorder to be standardised. The original ADI was intended for research purposes, best suited to the assessment of patients aged five years and older, with a minimum intellectual age of two years. Lord et al (1994) reorganised, shortened and linked the ADI to the ICD and DSM criteria forming the Autism Diagnostic Interview - Revised (ADI-R); a semi-structured, investigator-based interview for caregivers and parents of children and adults to assist in the diagnosis of autism spectrum disorder. New social and communication items were added and items considered to be redundant were removed. The order of questions was also adapted to allow caregivers describe positive aspects of their child's behaviour and prevent repeated negative descriptions which could cause distress. Since that time, the ADI-R has become a commonly used clinical tool for evaluation of autism spectrum disorder (Lord, 1994).

Further progress in diagnostic capability came in 2000 when Lord et al published the Autism Diagnostic Observation Schedule - Generic (ADOS-G). The ADOS-G is a descendant of two previous observational instruments, the Autism Diagnostic Observation Schedule (ADOS) originally created by Catherine Lord in 1989 and the Pre-Linguistic Autism Diagnostic Observation Schedule (PL-ADOS) created by DiLavore, Lord and Rutter in 1995. An upgrade was considered necessary as the ADOS and PL-ADOS were not entirely suitable for the assessment of older children or adults or for use outside of the research setting (Lord, 2000). As a second standardised assessment tool, this time of observed behaviour, the ADOS-G was not considered sufficiently robust by its creator to function independently in the diagnosis of autism spectrum disorder. Lord et al (2000) felt it lacked sufficient assessment of restrictive and repetitive behaviours. For that reason, the 'gold standard' tools to clinically assess a patient for possible autism spectrum disorder are recommended to be the ADOS-G coupled with the ADI-R (Rydén, 2008a).

Unfortunately, though effective and reliable, the ADI-R and ADOS-G can be time-consuming and include questions or tasks which are not scored in the final algorithm. They require formal training, are best administered only in a structured setting, are expensive to purchase and train to use, are time-intensive to administer and require practitioners to maintain inter-rater reliability. Furthermore, neither instrument permits early termination and conclusion if the patient is without positive symptoms. Hence, despite their status as the gold standard in diagnosis, these factors limit their use in both clinical practice and epidemiological research. Overall, researchers are agreed that the judgement of the experienced clinician is the most reliable tool in diagnosing autism spectrum disorder (Constantino, 2015).

1.8 Comorbid Illness in Autism Spectrum Disorder

Comorbidity is defined as 'the study of the association between two or more conditions, which may or may not be causally related' (Ghaziuddin, 2002a), 'the simultaneous presence of two chronic diseases or conditions in a patient' (Oxford English Dictionary, 2012) or 'the occurrence of two or more forms of psychopathology in the same person' (Mannion, 2014a). Although the term 'comorbid' is used throughout the literature in this area of research, Gillberg and Billstedt (2000) argue that the term 'comorbidity' is

contentious as it implies either a coincidental or causal link depending on the reader and perhaps the term ‘overlapping condition’ may be more acceptable. Mental disorders that co-occur with other disorders can also be referred to as ‘a dual diagnosis’ (Kronenberg, 2014). This study mirrors the majority of recently published research by using the term comorbid.

As seen in medical clinics, where patients frequently present with a number of physical diagnoses, psychiatric patients including those with autism spectrum disorder are also susceptible to comorbid illness. Therefore, it is important to remain cognisant of the likelihood of comorbid illness when assessing adult patients with normal IQ autism spectrum disorder. Comorbid psychiatric illness can include any diagnosis as outlined by the ICD-10 or DSM-5. For the purposes of this study, the following conditions are considered:

- Mood disorders including depression, dysthymia and bipolar affective disorder
- Anxiety spectrum disorders including agoraphobia, social phobia, generalised anxiety disorder, obsessive compulsive disorder, specific phobia, somatoform disorder and post-traumatic stress disorder
- Psychotic disorders including schizophrenia, delusional disorder and brief psychotic disorder
- Attention deficit hyperactivity disorder and Tourette’s syndrome
- Eating disorders including anorexia nervosa and bulimia nervosa
- Personality disorders including paranoid, schizoid, schizotypal, antisocial, emotionally unstable, histrionic, anankastic, anxious-avoidant, dependent and narcissistic
- Addiction including alcohol dependency syndrome and illicit drug use

Comorbid physical illness can include any medical condition diagnosed by a general practitioner or medical consultant. For the purposes of this study, the following conditions are considered:

- Cardiac conditions
- Dermatological conditions
- Ear, nose and throat conditions
- Endocrine conditions

- Gastrointestinal conditions
- Genitourinary conditions
- Neurological conditions
- Orthopaedic conditions
- Respiratory conditions

Co-occurrence of illness is an important area of research due to a number of factors:

- To assess functional impact
- To determine if each set of disorders are truly comorbid, namely that they co-occur or if they are in actual fact a single condition, along a severity spectrum
- To assess whether comorbid conditions present with the same symptomatology as each condition in its true form
- To determine if comorbidity alters the course or prognosis of either condition
- To determine if there is a causal link between conditions
- To determine which, if any, is the primary condition
- To determine the probability of suffering from a pure form of the illness, compared to presenting with comorbidity
- To allow formulation of appropriate and targeted treatment plans
- To investigate for biological risk factors for co-occurrence
- To assess for environmental risk factors for co-occurrence

In the clinical setting, to accurately understand the needs of those with comorbid illness, current comorbidity is considered more important than lifetime comorbidity (Kronenberg, 2014). For this reason, over the course of this study, the prevalence of current comorbidity is more frequently referred to than lifetime illness rates.

1.8.1 Limited Research in Comorbidity of Autism Spectrum Disorder

Thirty years ago, neurodevelopmental conditions were rarely, if at all, diagnosed among adult psychiatric patients (Nylander 2013, Van Elst 2013). Research on comorbidity focused on children, adolescent or intellectual disability groups (Ghaziuddin, 2008). As approximately 70% of individuals with autism spectrum disorder have an IQ in the learning disability range (Ghaziuddin 2002b, Newschaffer 2003, Kannabiran 2009) and child and adolescent psychiatrists consider ASD diagnosis part for their general skills repertoire compared to their general adult

counterparts, research on both groups is prolific compared to adults with normal IQ. It is likely that adult comorbidity rates, outcomes and morbidity cannot be accurately extrapolated from childhood, adolescent or intellectual disability research as psychiatric disorders in childhood and adolescence can differ considerably from psychiatric illness in later life (Taurines, 2010). Although, there was a considerable increase in awareness of neurodevelopmental disorders and consequently identification of patients with the illness by adult psychiatrists from 1990 to 2000 (Hofvander 2009, Nylander, 2013) very few research studies were completed on adults with autism spectrum disorder and normal intellectual ability (Barnhill 2007, Hofvander 2009, Lugnegård 2011, Joshi 2013).

One area highlighted by authors as particularly neglected is patterns of comorbidity as relatively little has been published on the topic (Ghaziuddin 1998, Gillberg 2000, Howlin 2000, Ghaziuddin 2002a, Ketelaars 2008, Ghaziuddin 2008, Nylander 2008, Rydén 2008a, Hofvander 2009, Skokauskas 2010, Strunz 2014). Though a number of particular conditions have been linked to autism spectrum disorder in child and learning disability populations (Van Elst, 2013), the true prevalence of such disorders among the adult, normal IQ, ASD population remains unknown. Lugnegård et al (2011) noted that their literature search was unable to source a single article looking at psychiatric comorbidity in adults with normal IQ clinically diagnosed with Asperger's syndrome.

A number of theories exist to explain the deficit of research in this area. For many years, psychiatrists appeared divided on the possible existence of comorbid psychiatric illness in patients diagnosed with autism spectrum disorder. Some suggest that comorbid psychiatric illness is highly prolific (Kanne, 2009) while others would argue that a comorbid illness, such as schizophrenia, obsessive compulsive disorder or certain personality disorders preclude a diagnosis of autism spectrum disorder (World Health Organisation, 1992). The presence of divided opinion has for many years restricted research in the area.

Overall, it is now generally agreed that comorbid psychiatric illness is an important research question in psychiatry. As annual diagnosis rates are now exceeding those for juvenile diabetes, cancer and HIV/AIDS (Cheak-Zamora, 2014), it is becoming clearer that autism spectrum disorder is an important research and clinical issue for practitioners and policy makers alike. Interest in the area appears to be growing since the 1980's (King, 2006) with the need for further clinical research in the area of

comorbidity highlighted in numerous publications (Gillberg 2000, Stahlberg 2004, Hofvander 2009) and researchers have called the deficit of available research an 'urgent need' (Ghaziuddin, 2008).

In more recent years, it has become more evident that autism spectrum disorder is not a singular condition and ASD patients actually suffer from a variety of mental health problems with more than one comorbid condition frequently occurring - autism spectrum disorder alone is no longer considered sufficient to account for every symptom and difficulty experienced by the ASD patient (Tsai 1996, Tantam 2000, Mouridsen 2008b, Kannabiran 2009). Some have even suggested that comorbidity is not only common but 'indeed the rule' in autism spectrum disorder (Gillberg, 2000). Previous studies comprised mainly of case reports or follow-up studies of adults diagnosed in childhood (Ghaziuddin, 2008) and many recommend further research to understand the nature of psychiatric comorbidity in ASD populations and its impact on outcome (Gargaro 2011, Buck 2014, Mannion 2014a, Vannucchi 2014a).

If comorbidity is almost to be expected when making a diagnosis of autism spectrum disorder each psychiatrist working in the area of general adult psychiatry requires a working knowledge of the co-existence of autism spectrum disorder and psychiatric illness (Gillberg 2000, Mouridsen 2008a, Vannucchi 2014a). If rates were more accurately defined perhaps it would explain why adults with a diagnosis of autism spectrum disorder tend to make excessive use of psychiatric services (Lehnhardt, 2012). As targeted health services are severely lacking for adults with autism spectrum disorder (Toal, 2005) such information, if made available, could also facilitate healthcare provision.

1.8.2 The Importance of Diagnosing Comorbidity in Autism Spectrum Disorder

Psychiatric and physical comorbid conditions, due to their associated functional impairment, have considerable impact on mental health, quality of life and psychosocial adaptation in adults with autism spectrum disorder (Howlin 2000, Stewart 2006, Raja 2008, Taurines 2010, Buck 2014). Caution should be taken not to misdiagnose true comorbid psychiatric illness as simple exacerbations of ASD symptomatology (Davis, 2011). Defining and describing the range and magnitude of psychiatric comorbidity in adults with autism spectrum disorder can facilitate disorder-

specific treatments in this vulnerable population (Joshi 2013, Nylander 2013). Superimposed psychiatric illnesses should be treated appropriately and positive outcomes are associated with timely diagnosis, treatment of comorbidity and appropriate access to support (Hare, 2014). Diagnosis of comorbid conditions in autism spectrum disorder is important because psychiatric comorbidity not only worsens the core symptoms of autism spectrum disorder but can have a greater impact on functioning and outcome than the core symptoms alone (Ghaziuddin 2008, Levy 2009). Some authors also propose that comorbid psychiatric illness impacts on the success of psychosocial interventions in autism spectrum disorder (Joshi, 2013), although this has not been replicated in other studies (Huke, 2014).

Currently, it is not possible to rely on measurement instruments to assess psychiatric comorbidity in those with autism spectrum disorder as tools have not been adequately validated (Tyson, 2012) or focus on minority groups within the ASD population. No measurement tool designed for the detection of comorbid psychiatric illness in adults with normal intelligence could be identified as part of this literature review. Six general tools for the detection of comorbidity in autism spectrum disorder were found, however two are designed for use in intellectually disabled adults while the other four are for use in child cohorts. These assessment tools are outlined in Table 1.11.

Table 1.11

Assessment Tools for Comorbid Psychiatric Illness in Autism Spectrum Disorder

Author, Year of Publication	Name of Assessment Tool	Suitable Population	Description
Hansson, 2005	A-TAC, Autism - Tics, ADHD and other Comorbidities	Children, IQ not specified	A 178 item telephone interview conducted with parents. Questions include all symptoms listed in the DSM-IV for childhood onset neuropsychiatric conditions, a selection of other psychiatric illness and the Gillberg and Gillberg criteria for Asperger's syndrome. Inter-rater reliability: 'very good' Test-retest reliability: 'very good' Internal consistency: not reported

Author, Year of Publication	Name of Assessment Tool	Suitable Population	Description
Leyfer, 2006	ACI-PL, Autism Comorbidity Interview - Present and Lifetime Version	Children with normal IQ or intellectual disability	Modelled on the Kiddies Schedule for Affective Disorders and Schizophrenia (KSADS). Uses DSM-IV-TR diagnostic criteria for all psychiatric disorders. Inter-rater reliability: 0.70 - 0.80 Test-retest reliability: 0.61 - 0.75 Internal consistency: not reported
Matson, 2007	ASD-CA, The Autism Spectrum Disorders - Comorbidity for Adults	Adults with intellectual disability	37 items over 5 subscales: • Anxiety / repetitive behaviours • Conduct problems • Irritability / behavioural excesses • Attention / hyperactivity / impulsivity • Depressive symptoms Inter-rater reliability: 0.30 - 0.77 Test-retest reliability: 0.59 Internal consistency: 0.91
Helverschou, 2009	PAC, The Psychopathology in Autism Checklist	Adults with intellectual disability	42 items over 5 subscales: • Psychosis • Depression • Anxiety spectrum disorders • Obsessive compulsive disorder • General adjustment problems Inter-rater reliability: 0.53 - 0.67 Test-retest reliability: not reported Internal consistency: 0.78 - 0.89
Matson, 2009a	BISCUIT-Part 2, Baby and Infant Screen for Children with Autism Traits - Part 2	Infants and toddlers, with normal IQ or intellectual disability	65 items assessing for 5 comorbid conditions: • Attention deficit hyperactivity disorder • Tic disorder • Obsessive compulsive disorder • Specific phobia • Feeding difficulties Inter-rater reliability: 0.98 Test-retest reliability: not reported Internal consistency: 0.97

Author, Year of Publication	Name of Assessment Tool	Suitable Population	Description
Matson, 2009b	ASD-CC, Autism Spectrum Disorders - Comorbidity for Children	Children, IQ not specified	49 items assessing for 7 comorbid conditions: • Depression • Conduct disorder • Attention deficit hyperactivity disorder • Tic disorder • Obsessive compulsive disorder • Specific phobia • Feeding difficulties Inter-rater reliability: 0.89 Test-retest reliability: 0.96 Internal consistency: 0.95

1.8.3 Variable Prevalence Rates of Comorbid Psychiatric Illness in Autism Spectrum Disorder

Variation in rates of detected comorbid psychiatric illness in ASD populations has been attributed to inconsistency in study sample, methodology and reporting methods by various authors (Buck, 2014). Lainhart (1999), Ghaziuddin et al (2002) and Stewart et al (2006) identified selection bias, use of clinically referred samples, differences in sample selection, small sample size, varying methods of inquiry, varying clinical experience of the interviewers, uncertainty regarding the degree of reliability and validity of standardised instruments and the flexible application of ASD diagnostic criteria as reasons for inconsistently reported rates.

Although not outlined by previous researchers, other reasons for variations in reported rates became apparent over the course of this literature review. Some studies examine comorbidity rates among individuals diagnosed with autism spectrum disorder while others examine rates of autism spectrum disorder among individuals diagnosed with an Axis I or Axis II psychiatric illness or examine autism spectrum disorder and attention deficit hyperactivity disorder groups in unison. Some studies examine only current rates of psychiatric illnesses, namely diagnoses detected as part of the research assessment while others looked at both current rates and lifetime diagnoses.

This mixed reporting of lifetime prevalence and current comorbidity rates without clear distinction in the literature as to which is being reported offers conflicting conclusions as to how closely comorbidity rates in autism spectrum disorder relate to those of the general population. The heterogeneous limitations evident in published research not only distort the available information on comorbidity rates but also prevent accurate assimilation of available information due to an inability to separate the adult / normal IQ portion of each sample.

Despite the varying approaches to research and the dual reporting method of current and lifetime illness, authors are generally agreed that psychiatric comorbidity rates are high among adults with autism spectrum disorder and normal range intellectual functioning (Hofvander 2009, Davis 2011, Howlin 2012, Joshi 2013, Van Elst 2013, Chen 2015). Estimated rates of comorbid psychiatric disorders in those with autism spectrum disorder, incorporating all ASD subtypes, vary from 9% to 84% (Hofvander 2009, Howlin 2012). Reported comorbid conditions in normal IQ autism spectrum disorder include depression, anxiety, obsessive compulsive disorder, attention deficit hyperactivity disorder, tic disorder, psychotic symptoms and emotionally unstable personality disorder (Howlin 2012, Van Elst 2013). Typically depression and obsessive compulsive disorder are reported as most prevalent, followed by bipolar affective disorder and mania, while psychosis and schizophrenia-like illnesses are considered rare (Howlin, 2012). Paediatric literature identifies comorbid disruptive and hyperactive conditions such as attention deficit hyperactivity disorder as the most prevalent psychiatric comorbidity in childhood while depressive conditions are more common in adolescence (Ghaziuddin, 1998 and 2002a).

Comparison between rates of psychiatric illness in those with autism spectrum disorder and the general population varies depending on whether one is comparing current comorbid conditions or lifetime prevalence. Examples of papers showing comparable current comorbidity rates but significantly increased lifetime rates include Joshi et al (2013) and Rydén and Bejerot (2008a). Both note lifetime prevalence rates to be significantly higher among high-functioning patients with autism spectrum disorder compared to their neurotypical counterparts, however, point prevalence or current rates were broadly similar (Joshi, 2013).

Only a limited number of studies relating to rates of comorbid psychiatric illness in normal IQ adults with autism spectrum disorder could be identified as part of this

literature review and each study examined clinically recruited samples. The details of these studies are outlined in Table 1.12. To my knowledge, there are no published epidemiological studies looking at incidence or prevalence rates of comorbid psychiatric illness in normal IQ autism spectrum disorder.

Table 1.12

Prevalence Rates of Current Comorbid Psychiatric Illness in Autism Spectrum Disorder

Author, Year of Publication	Country of Origin	Sample Characteristics	Psychiatric Comorbidities
Russell, 2005	London, England	40 adults attending an adult neurodevelopmental clinic: 19 - 36 years	Obsessive compulsive disorder 25%
Anckarsäter 2006	Gothenburg, Sweden	113 adults attending a child neuropsychiatric clinic: 19 - 60 years	Obsessive-compulsive PD 46% Avoidant PD 34% Schizoid PD 32% Paranoid PD 26% Schizotypal PD 23% Borderline PD 11% Dependent PD 9% Narcissistic PD 6% Antisocial PD 0% Histrionic PD 0%
Cath, 2008	Amsterdam, Netherlands	12 adults attending an adult anxiety clinic: 24 - 44 years	Obsessive compulsive disorder 50% Social phobia 50% Depression 50% Dysthymia 8%

Author, Year of Publication	Country of Origin	Sample Characteristics	Psychiatric Comorbidities
Ketelaars, 2008	Groningen, Netherlands	15 adults attending an adult neurodevelopmental clinic: 18 - 24 years	Comorbid Axis I or II disorder 53% Mood disorder 26% Social phobia 20% Substance abuse 20% Agoraphobia 13% Obsessive compulsive disorder 7% Schizoid PD 7% Borderline PD 7% Avoidant PD 7%
Rydén, 2008a	Stockholm, Sweden	130 adults attending neurodevelopmental inpatient treatment centre: 20 - 40 years	Personality disorder 40% Attention deficit hyperactivity disorder 37% Suicide attempt 17%
Hofvander, 2009	Gothenburg, Sweden and Paris, France	122 adults attending two adult neuropsychiatric clinics: 16 - 60 years	Mood disorder 53% Attention deficit hyperactivity disorder 43% Obsessive-compulsive PD 32% Avoidant PD 25% Obsessive compulsive disorder 24% Schizoid PD 21% Tic disorder 20% Paranoid PD 19% Substance abuse 16% Generalised anxiety disorder 15% Dyslexia 14% Schizotypal PD 13% Social phobia 13%

Author, Year of Publication	Country of Origin	Sample Characteristics	Psychiatric Comorbidities
			Psychotic disorder 12% Panic disorder 11% Borderline PD 9% Specific phobia 6% Somatoform disorder 5% Eating disorder 5% Dependent PD 5% Narcissistic PD 5% Antisocial PD 5% Histrionic PD 0%
Lugnegård, 2011	Karlstad, Sweden	54 adults attending an adult neurodevelopmental clinic and child neuropsychiatric clinic: 23 - 31 years	Recurrent depressive disorder 50% Attention deficit hyperactivity disorder 30% Social anxiety disorder 22% Generalised anxiety disorder 22% Agoraphobia 15% Panic disorder 13% Recurrent hallucinations 13% Bipolar II 9% Past alcohol dependence 7% Past drug dependence 7% Past bulimia nervosa 4% Tourette's syndrome 2% Schizophrenia 0%

Author, Year of Publication	Country of Origin	Sample Characteristics	Psychiatric Comorbidities
Lugnegård, 2012	Karlstad, Sweden	54 adults attending an adult neurodevelopmental clinic and child neuropsychiatric clinic: 23 - 31 years	Comorbid Axis II disorder 48% Schizoid PD 26% Obsessive-compulsive PD 19% Avoidant PD 13% Schizotypal PD 2% Paranoid PD 0% Antisocial PD 0% Histrionic PD 0% Borderline PD 0% Narcissistic PD 0% Dependent PD 0%
Joshi, 2013	Massachusetts, USA	63 adults attending an adult neurodevelopmental clinic: 18 - 63 years	Lifetime major depression 77% Social phobia 40% Depression 31% Generalised anxiety disorder 29% Lifetime bipolar I 25% Agoraphobia 24% Specific phobia 18% Obsessive compulsive disorder 16% Substance abuse 14% Psychosis 8% Bipolar I 6% Post-Traumatic stress disorder 5% Tourette's disorder 5% Antisocial PD 5%

Author, Year of Publication	Country of Origin	Sample Characteristics	Psychiatric Comorbidities
Strunz, 2014	Berlin, Germany	118 adults attending an adult neurodevelopmental clinic: 21 - 43 years	Comorbid Axis I disorder 36% Mood disorder 24% Social phobia 14%

1.8.4 Comorbid Axis I and Axis II Psychiatric Illness in Normal IQ Adults with Autism Spectrum Disorder

Mood Disorders

Although population based studies are lacking, research reporting on child, adolescent and adult, normal IQ and intellectual disability samples, suggests mood disorders as the most prevalent comorbid condition in autism spectrum disorder (Gillberg 2000, Ghaziuddin 2002b, Stahlberg 2004, Ketelaars 2008, Mouridsen 2008b, Munesue 2008, Hofvander 2009, Lugnegård 2011, Ragunath 2011, Strunz 2014, Vannucchi 2014b).

Research in depression is more widely available than reports on bipolar affective disorder (Skokauskas, 2010). In a case series by Raja and Azzoni (2008), bipolar affective disorder was noted in three adult patients with normal IQ newly diagnosed with Asperger syndrome. The authors stress the importance of monitoring for bipolar II in patients with autism spectrum disorder and depression as well as highlighting a propensity towards antidepressant induced bipolarity (Raja, 2008). Vannucchi et al (2014b) highlight the risk of underdiagnosing bipolar I in adults with autism spectrum disorder as features of mania expressed by this population, including irritability, hostility, restlessness, perplexity, aggression, insomnia, hallucinations, psychotic interpretations and delusional ideas could easily be mistaken for schizophrenia. The authors also emphasise the difficulty in accurately identifying bipolar II in this population as excessive mood reactivity, irritability, increased activity and difficulty

modulating arousal could be attributed to core ASD symptoms such as insistence on sameness or difficulty in transitioning between tasks (Vannucchi, 2014b).

Risk factors suggested for comorbid mood disorder in adults with autism spectrum disorder include less social impairment, higher cognitive abilities, higher rates of other psychiatric illness, better awareness of their difference from others and negative life events such as bereavement (Wing 1981, Ghaziuddin 2002b, Sterling 2008). Risk factors associated with childhood onset depression in those with Asperger's syndrome also include better social awareness, higher level of intelligence and negative life events such as parental divorce (Ghaziuddin 2002b, Sterling 2008). This is relevant for both populations as those with higher IQ and better social skills are likely to be more aware of their differences from peers (Sterling, 2008), suffer greater emotional impact from peer victimisation or bullying (Hannon, 2013) and experience poor self-esteem and frustration (Tantam, 2000), each contributing to increased vulnerability to depression. Detection of depression in those with normal IQ autism spectrum disorder is important it has been shown to contribute to increased suicidal behaviour (Hannon, 2013).

It is suggested that depression and autism spectrum disorder share a common aetiology as both are highly heritable and share biological similarities such as reduced serum melatonin, disturbance of sleep and altered circadian rhythm (Munesue, 2008). Ragunath et al (2011) explored the genetic links between bipolar affective disorder and autism spectrum disorder. They reported high commonality between genes implicated in the two disorders which they refer to as the 'Neuroactive Ligand Receptor Interaction Pathway'. The genes involved regulate mood and stress through neurotransmitters such as glutamate, dopamine, serotonin and noradrenaline (Ragunath, 2011). The authors speculate that disruption in this pathway due to genetic abnormality increases an individual's risk for both autism spectrum disorder and bipolar affective disorder. However, identification of the common chromosome / gene marker remains elusive.

Anxiety Spectrum Disorders

Methodological approaches affect the recording of prevalence in anxiety spectrum disorders and factors such as gender, age, culture, urbanicity, conflict and economic status are felt to strongly influence rates in different populations, in different regions

and across the globe (Baxter, 2013). It is estimated that anxiety spectrum disorders affect between 0.9% and 28.3% of the general population (Baxter, 2013). Literature relating to individuals with autism spectrum disorder is much rarer. Only one article was identified as part of this literature review, Lugnegård et al (2011), which noted a rate of approximately 50% in 54 normal IQ Swedish adults with normal IQ autism spectrum disorder.

Social phobia, sometimes referred to as social anxiety disorder, has a lifetime prevalence in the general population of 8% - 12% (Cath 2008, Tyson 2012). Growing evidence from mixed age, mixed IQ and trait studies indicates a considerable overlap between social anxiety disorder and high-functioning autism spectrum disorder (Tantam 2000, Gillott 2007, Cath 2008, Ghaziuddin 2008, Mazefsky 2008, Davis 2011, Kanai 2011, Lugnegård 2011, Howlin 2012, Tyson 2012, White 2012, Van Elst 2013, Buck 2014, Hare 2014, Hirvikoski 2014, Vannucchi 2014a). Areas of overlapping symptoms between autism spectrum disorder and social phobia include impaired eye contact, poor non-verbal communication, reduced social cognition, reduced emotional processing, difficulty relating in a social context and difficulty communicating in a social context (Tyson, 2012).

Six studies recorded prevalence rates of social phobia in normal IQ adults with autism spectrum disorder. Five reported ‘social phobia’ rates between 13% and 50% (Cath 2008, Ketelaars 2008, Hofvander 2009, Joshi 2013, Stunz 2014). One study termed the condition ‘social anxiety disorder’ and reported a prevalence rate of 22% (Lugnegård, 2011). Commonality in dysfunction within the fusiform face area, amygdala activity and the serotonin-transporter gene have been suggested as a reason for co-expression of autism spectrum disorder and social phobia (Tyson, 2012).

Generalised anxiety disorder is a disabling illness, noted to be the most frequently presenting anxiety disorder in primary care with prevalence rates of 1.9% - 5.1% in the general population (Wittchen, 2002). Higher rates of generalised anxiety disorder have been noted in adults with autism spectrum disorder ranging from 15% - 29% (Hofvander 2009, Lugnegård 2011, Joshi 2013).

Specific phobia is known to occur in 7.1% - 9.4% of the general population (Stinson, 2007). Although Kanner (1943) did not highlight the prevalence of social phobia among his case studies, this literature review notes him to be the first to describe specific

phobia in individuals with autism spectrum disorder. Kanner noted specific phobias in five of the eleven children he reviewed. Donald T seemed to 'almost have a horror of' tricycles, Frederick W was 'afraid of [the] eggbeater, perfectly petrified of [the] vacuum cleaner and elevators were a simply terrifying experience to him', Herbert B was 'tremendously frightened by running water, gas burners and many other things', Alfred L feared 'a dog's barking' while Elaine C was also 'afraid of the vacuum cleaner'. Rates of specific phobia reported in the literature pertaining to adult ASD populations range from 6% - 18% (Hofvander 2009, Joshi 2013).

Obsessive compulsive disorder is another highly debilitating disease (Russell, 2005), considered by the World Health Organisation to be among the ten most disabling medical conditions worldwide (Anholt, 2010). Its lifetime prevalence in the general population lies between 1.5% and 3% (Cath 2008, Anholt 2010). It has been argued that high-functioning autism spectrum disorder and obsessive compulsive disorder have many symptoms in common (Råstam, 2008). Many also determine it difficult to distinguish certain features of obsessive compulsive disorder from the clinical symptoms of autism spectrum disorder (Bejerot, 2007). Obsessive compulsive disorder can be missed in those with autism spectrum disorder and likewise autism spectrum disorder can be missed in those with obsessive compulsive disorder if comorbidity is not adequately explored. However, with careful history taking and assessment, clinicians can distinguish the two disorders. The clinical picture of obsessive compulsive disorder typically shows relapse and remission whereas the repetitive and ritualistic behaviour of autism spectrum disorder is constant and unremitting (Jones, 2000). Adults with autism spectrum disorder also show higher frequencies of sexual obsessions (Anholt, 2010), fewer somatic obsessions and fewer checking compulsions compared to those with obsessive compulsive disorder alone (Russell, 2005). Such identification is important as co-existence of these conditions is linked to poorer outcome with comorbidity resulting in more severe and treatment resistant obsessive compulsive disorder (Bejerot, 2007). Correct identification of obsessive compulsive disorder, if comorbidity exists, is vital to ensure adequate treatment planning and prevent adverse outcomes (Russell 2005, Bejerot 2007, Cath 2008, Anholt 2010). Studies looking at comorbid obsessive compulsive disorder in the ASD population have found that adults of average IQ with a diagnosis of autism spectrum disorder report a high frequency of both obsessions and compulsions as defined in standard nomenclature, i.e. experienced as intrusive, distressing and time-

consuming (Russell, 2013). Prevalence rates are up to forty times higher than in the general population (Rydén, 2008a) varying from 7% - 50% (Russell 2005, Cath 2008, Ketelaars 2008, Hofvander 2009, Joshi 2013). While Lord et al (1994) differentiated between obsessive compulsive disorder and autism spectrum disorder by comparing ritualised behaviours, noting significant difference in quality of compulsions, Russell noted common deficits between the two disorders. Lord et al (1994) clarified that a compulsion, as seen in obsessive compulsive disorder, is a sequence of events towards an endpoint, different to the repetitive non-functional behaviours and resistance to change seen in autism spectrum disorder. Russell et al (2005) noted executive function deficits and a preference for local rather than global information in both conditions. Although a genetic link between obsessive compulsive disorder and autism spectrum disorder has not been established (Russell, 2005), Anholt et al (2010) describe obsessive compulsive disorder and autism spectrum disorder, along with attention deficit hyperactivity disorder, as a group of developmental basal ganglia disorders due to strong symptom overlap, suggesting common aetiology.

Agoraphobia and panic disorder are reported to occur in less than 2% of the general population (Goodwin, 2005). Rates are significantly higher in adults with normal IQ autism spectrum disorder ranging from 15% - 24% for agoraphobia (Lugnegård 2011, Joshi 2013) and 11% - 13% for panic disorder (Hofvander 2009, Lugnegård 2011). Somatoform disorder is reported to be 2.7% among the general population (Lieb, 2000). Its equivalent rate in adults with normal IQ autism spectrum disorder was reported by a single study, as 5% (Joshi, 2013).

It is not feasible to determine a reliable prevalence rate for post-traumatic stress disorder among the general public given the significant number of confounding variables which impact reporting. These factors include gender, location of the study, recent occurrence of natural disaster or war, study of civilian or military participants, capacity for psychological adjustment and availability of post trauma support networks. One article provides a prevalence rate for post-traumatic stress disorder in normal IQ adults with autism spectrum disorder. Joshi et al (2013) report a figure of 5%, however they do not address the possible confounding factors outlined above.

Psychotic Disorders

Autism spectrum disorder and psychotic disorders, particularly schizophrenia, have a complex and entangled history. The term ‘autism’ was originally used by Bleuler to refer to social withdrawal and progressive loss of communication in patients with schizophrenia praecox (Bleuler 1911, Vannucchi 2014a). Kanner’s use of the term was in reference to deficits in affective contact (Kanner, 1943). Unfortunately, Kanner’s choice of a term already recognised in medical terminology to refer to schizophrenia led to infantile autism being viewed as an early-onset variant of schizophrenia for many decades (Volkmar 1991, Stahlberg 2004). It was not until the DSM-III in 1980 that autism was designated a distinct diagnostic category (American Psychiatric Association, 1980). Over the decades, between Kanner’s misnomer and DSM-III’s inclusion of pervasive developmental disorder, many researchers worked diligently to separate the conditions, investigating presenting characteristics, intellectual functioning, gender distribution, organicity, socioeconomic status, age of onset and family history (Konstantareas, 2001). Unfortunately, these significant efforts again led to bias as the wedge between the conditions was over-estimated, this time naming schizophrenia as a specific exclusion criterion for autism spectrum disorder (American Psychiatric Association, 1980). With time, it is increasingly recognised that autism spectrum disorder does not protect against schizophrenia and although rare the conditions can co-present (Dykens 1991, Ghaziuddin 1998, Jones 2000, Nylander 2008, Lugnegård 2011, Vannucchi 2014a).

While autism spectrum disorder and schizophrenia with marked positive symptoms are clearly distinguishable, differentiation between the two conditions when negative symptoms are more pronounced can be difficult. Some features of autism spectrum disorder could be misidentified as negative symptoms of schizophrenia including diminished emotional expression and avolition, while other symptoms such as poor social skills, impairment in interpersonal relationships, language / communication abnormalities, deficits in abstract reasoning and poor problem-solving overlap (Goldstein 2002, Nylander 2008, Raja 2010). Poor stress tolerance resulting in disorganised behaviour could resemble a brief psychotic disorder (Nylander, 2008) while repetitive narrowly-focused ideas could resemble delusional disorder.

Cognitive deficits are recognised in both autism spectrum disorder and schizophrenia (Nylander, 2008). Dysfunction in attention, memory, executive function and theory of

mind have been shown in both cohorts (Baron-Cohen 2001b, Happé 2001a, Hill 2004a, Nylander 2008). Likewise, language abnormalities are often noted in autism spectrum disorder including poverty of speech, reduced content of speech, perseveration and lack of reciprocity which could reflect negative features of schizophrenia (Dykens 1991, Nylander 2008, Raja 2010). Features of positive thought disorder as seen in schizophrenia including derailment, illogicality and loss of goal are rarer in autism spectrum disorder (Dykens, 1991).

Konstantareas et al (2001) examined 28 adult males, 14 with autism spectrum disorder and 14 with schizophrenia to determine the features which best differentiate between the two conditions. The authors noted far greater difficulties among the ASD group in the areas of stereotypical and repetitive behaviour, resistance to environmental change, visual preoccupations and deficits in non-verbal communication.

Van Os and Kapur (2009) suggest that genomic variants (copy number variants) occur at a higher rate in autism spectrum disorder and schizophrenia compared to controls, suggesting a shared neurodevelopmental pathway. Further evidence supporting this hypothesis stems from genetic studies into velocardiofacial syndrome or 22q11 deletion syndrome, which is often comorbid with autism spectrum disorder and schizophrenia (Murphy KC, 2002). Other shared genetic anomalies include microdeletions and microduplications of chromosome 16p and deletions, disruptions and missense mutations in Neurexin 1 (Raja 2010, Hallerbäck 2012). An MRI imaging study by Toal et al (2009) comparing adults with autism spectrum disorder, with and without psychosis, to healthy controls, showed that subjects with autism spectrum disorder differed from controls in brain regions common to schizophrenia. The authors suggest developmental brain abnormalities common to the two disorders.

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder is a neurodevelopmental disorder with onset in childhood which persists into adulthood for up to 60% of patients (Taurines, 2010). Symptoms include failure to give close attention to details or making careless mistakes in schoolwork, at work, or with other activities, having trouble holding attention on tasks or play activities, not appearing to listen when spoken to directly, not following through on instructions and failing to finish schoolwork, chores or duties in the workplace,

having trouble organising tasks and activities, avoiding, disliking or being reluctant to do tasks that require mental effort over a long period of time, often losing things necessary for tasks and activities, being easily distracted, being forgetful in daily activities, fidgeting with or tapping hands or feet, or squirming in seat, often leaving one's seat in situations when remaining seated is expected, running or climbing in situations where it is not appropriate (adolescents or adults may be limited to feeling restless), unable to play or take part in leisure activities quietly, often "on the go" acting as if "driven by a motor", talking excessively, blurting out an answer before the question has been completed, having trouble waiting his / her turn and often interrupting or intruding on others (American Psychiatric Association, 2013). The worldwide prevalence of adult attention deficit hyperactivity disorder is estimated to be 5.29% (Polanczyk, 2007).

Although ICD states that attention deficit hyperactivity disorder and autism spectrum disorder cannot be diagnosed in a single individual, many agree that considerable overlap exists between the two conditions with comorbid prevalence rates as high as 14% - 78% (Stahlberg 2004, Anholt 2010, Gargaro 2011, Chen 2015). Gargaro et al (2011) examined the anatomical, neuroimaging, executive function and clinical similarities between attention deficit hyperactivity disorder and autism spectrum disorder and showed a strong biological basis for their co-existence. Chen et al (2015) also showed a strong shared genetic susceptibility between the disorders as well as a link to depressive disorder, bipolar affective disorder and schizophrenia. Both studies successfully argue that the diagnostic criterion excluding comorbidity between the two conditions is groundless.

In fact, attention deficit hyperactivity disorder was the second most prevalent lifetime condition in a group of normal IQ adults with autism spectrum disorder studied by Joshi et al (2013), who noted a lifetime prevalence rate of 47% - 68%. Studies of current prevalence places estimates between 37% and 43%, considerably higher than rates seen in the general population (Rydén 2008a, Hofvander 2009). A thorough assessment looking for dual diagnosis is strongly advised as patients with both autism spectrum disorder and attention deficit hyperactivity disorder suffer higher interpersonal, school, family and cognitive difficulties, compromised ability to learn and interpret their environment and considerable functional and psychosocial impairments (Ghaziuddin 1998, Taurines 2010, Roy 2013, Chen 2015).

Eating Disorders

In 1985, when researching autism spectrum disorder and eating disorders in children, Christopher Gillberg suggested a possible common aetiology to the two conditions, proposing hereditary genetic vulnerabilities interacting with environmental factors to cause anorexia nervosa in females and autism spectrum disorder in males. Since then, research in the field has taken two directions. Some authors interested in autism spectrum disorder have looked at comorbid eating disorders in individuals with autism spectrum disorder, while other authors with an interest in eating disorders have examined the comorbidity rates of autism spectrum disorder in those with anorexia nervosa and / or bulimia nervosa. Despite this combined approach, research on eating disorder in adults with normal IQ autism spectrum disorder is scarce (Råstam, 2008).

As part of this literature review, only a single study could be identified listing a prevalence rate for eating disorder in normal IQ autism spectrum disorder, namely Hofvander et al (2009), who quoted the current rate of eating disorder as 5%. Two research papers reporting on prevalence rates of autism spectrum disorder in adults with a previously diagnosed eating disorder were identified. Wentz-Nilsson et al reported an 18% comorbidity rate in 1999. In 2005 the same research group noted a rate of 23% in females with severe and enduring eating disorder. Given the low population prevalence of autism spectrum disorder and a known male predominance for the condition, this rate of comorbid autism spectrum disorder in a group of female patients is extremely high. Interestingly, only anorexia nervosa patients endorsed features of autism spectrum disorder, no patients with bulimia nervosa reached diagnostic criteria.

An overlap between anorexia nervosa and autism spectrum disorder was initially proposed in the 1980's on the basis of clinical and behavioural observations (Oldershaw, 2011). Autism spectrum disorder and anorexia nervosa share some characteristics including obsessiveness, insistence on sameness, social skills deficits, refusal of particular foods, dislike of texture or certain types of food, unusual behaviours at mealtimes, weaknesses in empathising, executive dysfunction and an inability to observe the bigger picture (Råstam 2008, Oldershaw 2011). However, individuals with autism spectrum disorder and anorexia nervosa differ in their ability to problem solve and form relationships. In a study of 22 adult females with anorexia nervosa and normal IQ, Hambrook et al (2008) noted that anorexia nervosa patients did not differ

significantly from healthy controls on the Systemizing Quotient questionnaire or the Empathy Quotient questionnaire. This indicated that their drive to analyse problems and construct systematic relationships in non-social domains was similar to healthy controls. Wentz-Nilsson et al (1999) speculate that autism spectrum disorder and obsessive compulsive personality disorder could be premorbid conditions, enhancing one's risk of developing an eating disorder. It is important to identify comorbid ASD and anorexic symptoms in order to prevent poor outcomes among this population (Wentz-Nilsson 1999, Wentz 2005). Young people with autism spectrum disorder and eating disorder could benefit from a tailored treatment programme designed to meet their ASD-related needs compared to receiving treatments targeted at individuals suffering from an eating disorder alone (Wentz-Nilsson, 1999).

Personality Disorders

A personality disorder is an 'enduring, inflexible and pervasive pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture, manifesting in deficits in cognition, affectivity, interpersonal functioning or impulse control, of stable and long duration, leading to clinically significant distress or impairment, not better attributable to another mental, medical or physiological disorder' (American Psychiatric Association, 2013). There are currently ten defined personality disorders, falling into three clusters: Cluster A - paranoid, schizoid and schizotypal; Cluster B - antisocial, borderline / emotionally unstable, histrionic and narcissistic; and Cluster C - anxious-avoidant, dependent and anankastic / obsessive-compulsive.

There is considerable overlap between characteristic symptoms of autism spectrum disorder and those of some personality disorders. Schizoid, schizotypal, avoidant, anankastic, narcissistic and emotionally unstable personality disorders have many features which can overlap with autism spectrum disorder (Råstam 2008, Rydén 2008b, Vannucchi 2014a, Strunz 2015). The division of psychiatry into child and adult specific teams has hindered true understanding of the link between the developmental aspects of personality formation occurring in childhood and the expression of personality disorder as diagnosed in adulthood (Anckarsäter, 2006). Less again is known about co-occurring personality disorders and autism spectrum disorder in adulthood (Strunz, 2015). Up to the year 2000, no studies existed on the incidence of

personality disorder in autism spectrum disorder (Gillberg, 2000). However, the current concept of personality disorder in autism spectrum disorder could possibly explain some of the noted ‘odd’ engagement style (Rydén, 2008a).

Studies on personality characteristics in individuals with autism spectrum disorder have elicited distinct temperament profiles. Autism spectrum disorder is associated with a more introverted and inhibited interaction style, lower novelty seeking, lower openness to new experience, inner feelings and emotions, lower reward dependence, poorer self-directedness, unco-operativeness and lower agreeableness, lower levels of sentimentality, lower altruism and poorer attachment to others, stronger harm avoidance, improved emotional regulation, increased self-transcendence, higher degrees of personal organisation, compulsivity and conscientiousness along with greater straight-forwardness and honesty (Anckarsäter 2006, Sizoo 2009, Strunz 2015). Given the high degree of associated personality traits in autism spectrum disorder, care should be taken as the condition, if not diagnosed in childhood, could be misdiagnosed as a personality disorder in adulthood (Rydén, 2008a).

Personality traits are important comorbid symptoms in adults with autism spectrum disorder as these characteristics represent poorly matured character and could be considered risk factors for personality disorder, anxiety spectrum disorders, social detachment and increased resistance to change (Tani 2003, Sizoo 2009).

Self-injurious and Suicidal Behaviour

Suicidal behaviour refers to deliberate self-harm (any deliberate non-lethal act of self-injury), suicidal ideation (thoughts of how to commit suicide), suicide attempt and completed suicide (Hannon, 2013). Deliberate self-harm is commonly referred to as self-injurious behaviour in the literature examining individuals with autism spectrum disorder, possibly due to the crossover between general population and intellectual disability nomenclature in this group. Global rates of suicidal behaviour have increased consistently over recent decades with a recent World Health Organisation publication quoting lifetime prevalence figures for suicidal ideation and attempts as 9% and 3% respectively (Borges, 2010). Research shows the association with comorbid psychiatric illness to be considerable and autism spectrum disorder is now considered one of these conditions (Phillips 2010, Raja 2011).

Studies examining rates of suicidal behaviour in normal IQ adults with autism spectrum disorder are rare (Bennett, 2015). However, the condition is recognised and examples include head banging, self-biting, self-hitting, hair pulling and eye-poking (Gillberg, 2000). Care should be taken to differentiate between deliberate self-harm, self-injurious behaviour, core symptoms of autism spectrum disorder and catatonic symptoms such as motor stereotypies when a patient with autism spectrum disorder presents with injury to avoid diagnostic overshadowing and under-reporting (Hannon, 2013).

Within the general population, accepted risk factors for attempted and completed suicide include male gender, unmarried, unemployment, low educational attainment, low income, presence of psychiatric illness or chronic physical illness, childhood adversity, vulnerability and stressful life events (Balfe 2010, Crump 2014). High prevalence for each of these factors has been identified among the ASD population. When reporting on 587 adults admitted via the Emergency Department for attempted suicide, Kato et al (2013) identified 7.3% of patients with autism spectrum disorder. They noted that this subgroup of psychiatric admissions were more likely to be younger, single and living alone, with higher rates of comorbid adjustment disorder, requiring longer hospitalisation and to have used more lethal methods (jumping from a height, cutting / stabbing and carbon monoxide poisoning) when attempting suicide. ASD patients were also less likely to attribute their suicide attempt to a stressor occurring in the preceding 24 hours. Takara and Kondo (2014) examined a group of 336 adults with mood disorders following attempted suicide and noted that 11% fulfilled diagnostic criteria for autism spectrum disorder on the SCID-I. They noted agitation, history of suicidal behaviour and high-functioning autism spectrum disorder to be significantly associated with increased rates of suicide attempt. They also confirmed Kato et al's (2013) finding relating to use of more lethal methods.

Other risk factors for suicidal behaviour in autism spectrum disorder have been identified through case studies, including low self-esteem, interpersonal difficulties, social isolation, lack of peer support, life stresses, life changes and comorbid depression, anxiety and substance misuse (Hannon 2013, Richa 2014). Child and adolescent studies have also noted normal IQ, poor problem solving, impulsivity, lack of emotional awareness, history of physical and / or sexual abuse and bullying as relevant risk factors (Hannon, 2013). Although rates of suicidal behaviour fluctuate

depending on the study population, it would appear that both suicidal ideation and suicide attempts are considerably higher in adults with autism spectrum disorder than the general population. Matthew Bennett (2015) stresses the importance of discussing these experiences with adult ASD patients to ensure a clearer understanding among clinicians and to test the effectiveness of proposed treatment approaches.

Substance Use Disorder

Recent prevalence rates for alcohol and drug dependence among the general population are difficult to ascertain as studies in recent years focus on particular ethnicities or age groups. Although almost 26 years old, Regier et al (1990) published prevalence rates of 13.5% for alcohol dependence and 6.1% for drug dependence. In 2005, Harford et al reported much lower alcohol dependency rates, with a 2.5% prevalence in males and 1.4% in females. More recent literature focusing on the general population is difficult to locate. Research published as recently as 2012 continues to refer to prevalence rates from the 1990s (Miles, 2012). Likewise substance and alcohol abuse in those with autism spectrum disorder is an under-researched area (Sizoo 2010, Singh 2012, Kronenberg 2014, Van Wijngaarden-Cremers 2014).

Known risk factors for substance use disorder in the psychiatric population include early onset of smoking, disruptive behaviour in childhood and a parental history of substance misuse (Sizoo, 2010). Specific risk factors relating to those with normal IQ autism spectrum disorder are not widely researched. Sizoo et al (2010) were the first to examine whether these risk factors also applied to the ASD population. They noted that early onset smoking and parental substance misuse were also relevant risk factors for those with autism spectrum disorder. However, contrary to other psychiatric cohorts, childhood maltreatment did not increase risk of substance use disorder in adults with normal IQ autism spectrum disorder. Miles and McCarthy (2012) later identified a maternal history of alcohol addiction as a significant risk factor for alcohol dependency in adults with autism spectrum disorder.

As substance use disorder and autism spectrum disorder do not share common clinical features, it has been difficult to elucidate possible common aetiological factors (Miles, 2012). Possible links in maternal dopamine β-hydroxylase alleles and dysregulation of

the neurotransmitter systems for GABA have been suggested but not replicated (Miles, 2012). Possibly, a more robust finding is the proposed link to genes regulating neural cell adhesion (Neurexin 1 and 3) and to dysregulation of the 'cognitive' cortico-striatal loop regulating inhibition and impulse control in both disorders (Miles 2012, Van Wijngaarden-Cremers 2014).

Tic Disorders, including Tourette's syndrome

Tic disorders include Tourette's syndrome, persistent (chronic) motor or vocal tic disorder and provisional tic disorder (American Psychiatric Association, 2013). Knight et al (2012) reported a prevalence of childhood Tourette's syndrome, following a large systematic review and meta-analysis as 0.77%. Wentz et al (2005) suggested the prevalence rate among adults in the general population to be one tenth that of the child rate, approximately 0.1%. The condition has been reported to occur in association with many neurological and psychiatric illnesses including autism spectrum disorder (Kumar, 1997) with the estimated prevalence rate for comorbid Tourette's syndrome in adults with normal IQ autism spectrum disorder ranging from 2% - 20% (Hofvander 2009, Joshi 2013).

Distinguishing tics from stereotyped repetitive behaviours in autism spectrum disorder can be difficult but historical paediatric research has provided a number of insights that remain helpful in distinguishing the two disorders. This research suggests (Lainhart, 1999):

- Tics tend to be more sudden, rapid and brief and have an involuntary quality compared to stereotyped movements
- Complex stereotypies are rhythmical while complex tics are usually spasmodic
- Stereotyped movements commonly involve the hands, fingers or whole body while tics usually involve the face, neck, shoulders and arms
- Those with stereotypies may appear preoccupied or amused while children with tics are more likely to appear distressed
- Stereotyped movements are less variable than tics and less influenced by psychosocial factors
- Tics tend to wax and wane while stereotypies are more regular in pattern of occurrence

It has not yet been established if tic disorder, Tourette's syndrome and autism spectrum disorder are associated or predisposing conditions. Researchers hypothesise that genetic inheritance plays a significant role in the co-expression of these disorders and that a pre-existing diagnosis of autism spectrum disorder could lend causality to the development of a tic disorder following minor head trauma (Lainhart, 1999).

Catatonia

Catatonia was first described by Karl Kahlbaum in 1873 as a distinct disease expressed as cyclical symptoms of melancholia, mania, stupor, confusion and dementia (Realmuto 1991, Tandon 2013). In the early 1900s, it was linked with hebephrenia and dementia paranoids, renaming its clinical manifestation 'dementia praecox' (Tandon, 2013). As the diagnostic criteria for schizophrenia evolved, catatonia became a subtype of the illness. This reduced the ability of many clinicians to recognise the illness in the absence of psychotic symptoms. It was not until the DSM-IV that catatonia was again recognised as potentially occurring in the context of a major mood disorder or a physical / neurological illness as well as schizophrenia (Tandon, 2013). Currently, it is agreed that catatonia can manifest in association with many illnesses including neurodevelopmental disorders, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, conversion reactions, Tourette's syndrome, anti-NMDA encephalitis, Parkinson's disease, neurosyphilis, tuberculosis, tetanus, typhoid fever, rabies, lupus erythematosus, epilepsy, viral encephalopathy, cerebral arterial malformation, cerebral infarction, posterior fossa atrophy, midbrain abnormality, Wernicke's encephalopathy, subdural haematoma, hyperparathyroidism, myxoedema, Addison's disease, hypocalcaemia and use of recreational drugs (Realmuto 1991, Fink 2009, Venkat 2012, American Psychiatric Association 2013). To my knowledge, the only exclusion disorder is delirium (American Psychiatric Association, 2013).

Catatonia is defined as a motor dysregulation syndrome in which patients are unable to move normally, despite absence of physical incapacity, occurring in 7% - 15% of acutely hospitalised psychiatric patients (Fink, 2009). Current diagnostic criteria for catatonia outline a clinical picture dominated by three or more of the following symptoms; stupor, cataplexy, waxy flexibility, mutism, negativism, posturing,

mannerism, stereotypy, agitation, grimacing, echolalia and echopraxia (American Psychiatric Association, 2013). This combination of symptoms is frequently under-recognised by clinicians (Tandon, 2013). Literature suggests the presence of mutism, akinesia and cataplexy indicates severe catatonia while increased slowness, difficulty initiating or completing actions, reliance on prompting, passivity, reversal of day / night, parkinsonian features, excitement, agitation and repetitive behaviour suggests a milder variant (Wing 2000, Wing 2006).

Many symptoms of catatonia overlap with the clinical features of autism spectrum disorder. These include odd hand posture, interruption, freezing of movement, difficulty completing tasks, catatonic excitement, motor stereotypies, mannerisms, rituals, echolalia and negativism (Realmuto 1991, Dhossche 1998, Wing 2000, Hare 2004, Nylander 2008). Some authors even suggested catatonia could be misdiagnosed as autism spectrum disorder (Mazzone, 2014).

Although there is increasing recognition of catatonia as a comorbid syndrome of autism spectrum disorder (Ghaziuddin 2005, Nylander 2008, Mazzone 2014), prevalence estimates are difficulty to determine. Studies located as part of this literature review refer to child and adolescent populations, mixed age and mixed IQ populations or case reports on adults. To my knowledge, there are no published studies examining the prevalence rate of catatonia in adults with normal IQ autism spectrum disorder. Prevalence rates as reported in mixed age and mixed IQ populations are possibly the closest estimate to prevalence in normal IQ adults. This would suggest a general estimate ranging from 6% - 18% (Wing 2000, Bailine 2007, Kakooza-Mwesige 2008, Ghaziuddin 2012).

The presence of catatonic symptoms increases the severity of ASD symptomatology, increases carer burden and is a frequent cause of deteriorating skills and behaviour (Wing 2000, Ghaziuddin 2005, Fink 2009). Many authors advise care in assessing for comorbid physical, neurological or psychiatric conditions which could increase the risk of catatonia in patients with autism spectrum disorder (Realmuto, 1991). However, no true identifiable risk factors have been repeatedly reported in the literature (Wing, 2006). A single study suggesting a link between catatonia and low IQ was identified as part of this literature review (Wing 2000).

1.8.5 Comorbid Physical Illness in Normal IQ Adults with Autism Spectrum Disorder

Epilepsy

Epilepsy, as defined in the ASD literature, requires the occurrence of two or more unprovoked seizures of any type (Tuchman, 2002). Seizures in the course of illness, trauma or due to an underlying metabolic disorder cannot be considered when assessing for comorbid epilepsy in autism spectrum disorder. In this context, a history of febrile convulsions does not constitute a history of epilepsy, rather existing as an exclusion criterion (Bolton, 2011). Furthermore, almost all information noted as part of this literature review related to epilepsy as seen in child or young adult populations, intellectual disability or mixed IQ cohorts. A significant deficit in normal IQ adult literature was noted.

The association between autism spectrum disorder and epilepsy has been noted from as early as Kanner's first publication on early infantile autism when two of his original eleven children developed seizures (Kanner, 1943). Consistently throughout the intervening decades, an association between epilepsy and autism spectrum disorder has been reported. Rutter (1967, 1973 and 1978) found that those with a diagnosis of autism spectrum disorder frequently developed epilepsy. Lainhart (1999) reported a 'seizure disorder' prevalence rate of 25% - 30% and Wing and Potter (2002a) noted 'epileptic fits' to be common. Reporting has continued into the 21st century as researchers note prevalence rates from 11% - 39% (Bolton 2011, Howlin 2012). This variation in prevalence rates is considered by many authors to be due to the heterogeneous nature of the samples studied. When individuals at increased risk of comorbid epilepsy are included in a study the prevalence is noted to be higher and likewise when these individuals are excluded the prevalence is lower. Factors which increase the prevalence of comorbid epilepsy include gender, age, intelligence level, degree of language skill deficits, associated neurological conditions, medication use and presence of behavioural disturbance. The prevalence is highest amongst females, adolescents and young adults, those with moderate to profound intellectual disability, those with severe receptive language deficits particularly verbal auditory agnosia, individuals with Rett's syndrome, childhood disintegrative disorder or cerebral palsy,

those on prescribed antipsychotic medication and individuals with increased rates of behavioural disturbance (Tuchman 2002, Canitano 2007, Bolton 2011, Howlin 2012).

Although epilepsy can be diagnosed at any age, seizure onset is considered to have a bimodal distribution in those with autism spectrum disorder, typically peaking in two age brackets; those aged under 5 years (early childhood) and those aged 10 - 15 years (adolescence) (Tuchman, 2002). Bolton et al (2011) reported a third peak in a group of 150 mixed IQ adults, noting an increase in onset aged 20 - 25 years. All seizure types have been linked to autism spectrum disorder with mixed reports as to the most commonly occurring. As a result, researchers advise observation for simple or complex partial seizures, atypical seizures, tonic-clonic seizures and myoclonic seizures as no single seizure type can be expected (Canitano, 2007).

Epilepsy is not considered a causal condition for autism spectrum disorder rather a comorbid disorder due to common brain dysfunction (Mouridsen, 2011). Several markers on chromosome 15q11-13 have been linked independently to both epilepsy and autism spectrum disorder strengthening the argument for common aetiology (Canitano, 2007). However, as yet, the mechanism underlying comorbidity of the two conditions remains unclear (Bolton, 2011).

As seizures can influence emotional and behavioural expression, evidenced by poorer outcomes for those with epilepsy, the illness should be routinely considered and investigated (Billstedt 2005, Canitano 2007). Factors indicating a new seizure disorder in adults with autism spectrum disorder include deterioration in language skills, social skills, cognitive function, mood or behaviour, new onset hallucinations or new onset stereotyped repetitive movements (Lainhart, 1999). Treatment of epilepsy in autism spectrum disorder parallels treatment options in the neurotypical population, namely prescription of antiepileptic medication. Further to seizure control, other beneficial effects seen in those with autism spectrum disorder include reduced affective instability, impulsivity and aggression (Tuchman, 2002).

Sleep Difficulties

Sleep is defined as *'a condition of body and mind which typically recurs for several hours every night, in which the nervous system is inactive, the eyes closed, the postural muscles relaxed and consciousness practically suspended'* (Oxford English Dictionary,

2012). It is one of the human circadian rhythms, alongside body temperature, allergy susceptibility, hormone production and general activity (Hare, 2006b). One's sleeping pattern is gradually established as one ages, graduating from infancy into early childhood. In infancy, it is recognised that sleep occurs in a polyphasic manner with multiple naps and a more sustained period of sleep overnight, by age three months the infant sleeps more regularly availing of two naps per day and from toddlerhood to age three years a single daytime nap is required (Richdale, 1999). From early childhood into adulthood a stable sleep pattern is established that will hold unless disrupted by physical illness, psychiatric illness, medication or environmental disturbances. Aging, in turn, is associated with a deterioration in sleep quality, increased sleep fragmentation, early morning waking and reduced slow wave sleep (Crowley, 2011).

'Sleep problems' is defined as sleep behaviour that is disturbing to the individual, their sleep partner, family or others, these can include settling difficulties and night waking. 'Sleep disturbance' is a collective term used to describe difficulties relating to sleep attributed to factors other than aging (Richdale 1999, Reynolds, 2011). 'Sleep disorder' refers to sleep disturbance due to underlying physiological dysfunction, including insomnia and parasomnias (Richdale, 1999). Insomnia is defined by DSM-5 as the complaint of dissatisfaction with sleep quality or quantity associated with difficulty initiating sleep, difficulty maintaining sleep or early morning waking (American Psychiatric Association, 2013). Sleep parasomnias include non rapid eye movement (NREM) and rapid eye movement (REM) sleep disorders. NREM sleep parasomnias include sleep walking, sleep terrors, sleep talking and nightmares while REM parasomnia is defined as repeated episodes of arousal during sleep associated with vocal or motor movements due to absence of normal REM sleep atonia (American Psychiatric Association, 2013).

Sleep is an important clinical parameter to measure. Chronic sleep impairment in neurotypical children is associated with inattention, hyperactivity, maternal stress, parental sleep disruption and parental depression (Reynolds 2011, Mannion 2014b). In neurotypical adults it is linked to increased daytime sleepiness, poor memory, executive dysfunction, inattention, learning difficulty, impaired emotional control and poorer social functioning (Hare 2006a, Crowley 2011). In those with intellectual disability it has been associated with challenging behaviour and communication difficulties (Galli-Carminati, 2009). In individuals with autism spectrum disorder, sleep

disturbance has been put forward as the third marker of abnormal neural function, following epilepsy and intellectual disability, and connected to higher overall autism severity scores, increased repetitive behaviours and stronger insistence on sameness (Limoges 2005, Reynolds 2011).

Findings of research in normal IQ individuals with autism spectrum disorder from 1999 to 2015 are outlined in Table 1.13.

Table 1.13

Sleep Disturbance in Normal IQ Autism Spectrum Disorder

Author, Year of Publication	Country of Origin	Sample Characteristics	Sleep Disturbance Described
Godbout, 2000	Montréal, Canada	8 patients attending a specialised ASD clinic Mixed age (7 - 53 years) Normal IQ	Difficulty initiating sleep Difficulty maintaining sleep ↑ shifts into REM sleep from waking epoch ↑ REM sleep disruption Pathological index of PLMS ↓ sleep time in first ⅔ of the night ↓ sleep spindles on EEG Normal REM sleep rapid eye movements Normal K complexes on EEG
Tani, 2003 and 2004	Helsinki, Finland	20 patients attending a specialised ASD clinic Adults (19 - 34 years) Normal IQ	Insomnia - initial, middle and terminal ↑ variation in night-to-night sleep parameters ↑ θ power in slow wave sleep ↓ sleep quality ↓ Δ power in slow wave sleep

Author, Year of Publication	Country of Origin	Sample Characteristics	Sleep Disturbance Described
Limoges, 2005	Québec, Canada	27 patients attending a specialised ASD clinic Adults (16 - 27 years) Normal IQ	Insomnia Earlier bed and rise times ↑ Sleep latency ↑ Nocturnal awakenings ↓ Sleep efficiency ↓ NREM sleep ↓ slow wave sleep ↓ Stage 2 sleep spindles ↓ rapid eye movements during REM sleep Normal K complexes on EEG No evidence of daytime napping No difference in sleep apnoea No difference in periodic leg movement syndrome (PLMS)
Hare, 2006a	North-West England	10 patients attending a specialist independent service for ASD Adults (23 - 38 years) Normal IQ	Delayed circadian rhythm of 24½ hours Less stable circadian rhythm Less link between circadian rhythm and environmental synchronisers (zeitgebers) ↑ sleep latency ↑ sleep fragmentation ↓sleep efficiency

Eating Disturbance

Eating disturbance is a change in eating pattern which is similar to but less severe than an eating disorder and does not reach diagnostic criteria for anorexia nervosa or bulimia nervosa. It is considered common in all individuals, neurotypical as well as those with autism spectrum disorder, from age two to six years and typically resolves from middle childhood (Kuschner, 2015). In autism spectrum disorder however, it is noted to frequently persist into adulthood. Eating disturbance in autism spectrum

disorder is a wide ranging symptom with many phenotypes and constitutes a research question that is largely unanswered (Whiteley 2000, Råstam 2008, Mannion 2014a).

Detection of eating disturbance in adults with a normal IQ autism spectrum disorder is clinically relevant due to the associated physical complications including gastric acid erosion of tooth enamel, malnutrition, vitamin and mineral deficiencies, oesophageal disease, diarrhoea and constipation (Råstam 2008, Venkat 2012). It is also psychosocially relevant as eating disturbance can lead to limited social engagement, poorer social skills and obesity with associated low self-confidence.

Eating disturbance in autism spectrum disorder can include (Lainhart 1999, Råstam 2008, Venkat 2012):

- Food neophobia, the fear of new foods
- Food refusal
- Low body weight
- Pica, the eating inedible non-food substances
- Requirement for supervision to ensure nutritionally balanced dietary intake
- Rumination, the repetitive regurgitation of ingested food into the mouth with subsequent spitting, remastication or swallowing
- Selective eating, the restriction of food by number, colour, texture or brand
- Vomiting

Although, the aetiology of eating difficulties in autism spectrum disorder remains unclear, it is most likely multifactorial and linked to the core symptoms of the condition itself including hyper- or hypo- sensitivity to smell, taste, feel or the visual appearance of food, sensory processing difficulties, oral and fine motor impairments, rigid routines, restricted interests and insistence on sameness. Furthermore, it has been suggested that social and communication deficits reduce the ASD individual's ability to engage in the social ritual of dining leading to poorer dietary intake (Råstam 2008, Kuschner 2015).

Motor Skills

Although, motor skill deficits in autism spectrum disorder appear to be present from early infancy (Fournier 2010, Fabbri-Destro 2013) and persist into adulthood (Gowen 2012, Bejerot 2013) the condition is wide ranging and difficult to define. Available literature uses a variety of terms when referring to motor skill deficits, complicating both research methodologies and research findings. A selection of terms includes clumsiness, disorders of locomotion, poor motor co-ordination, movement disorder, motor dysfunction and sensory-motor skill deficits. Apraxia is generally reserved for acquired neurological movement disorders of adulthood while dyspraxia is used to refer to a less severe developmental impairment often seen from childhood (Miller, 2014). Fine motor skills refers to manual dexterity and visuomotor control while gross motor skills include walking, throwing, posture and balance (Gowen, 2012). Over the decades, 'motor skill deficit' in autism spectrum disorder has become a far reaching term to include absence of facial expression, poor fine motor co-ordination, lack of fluency in locomotion, poorly co-ordinated movements, odd posture, hypotonia, postural instability, muscle rigidity, akinesia and bradykinesia (Raja 2009, Weiss 2013).

Early literature believed motor skill deficits in autism spectrum disorder to be sufficiently common as to warrant inclusion in the diagnostic criteria. Researchers noted an abnormal pattern of righting and lack of protective reflexes in infancy, abnormal limb and hand posturing, marked asymmetry in crawling, delayed onset of walking and ultimately an abnormal gait, reduced range of motion at the ankle and in some studies features in common with Parkinson's disease such as slow gait, short steps and stooped posture (Hallett 1993, Hardan 2003, Nayate 2005). The multifaceted nature of these findings led researchers to hypothesise neurological aetiology in the cerebellum, frontal lobe and basal ganglia strengthening the argument for a neurological basis to autism spectrum disorder (Hallett 1993, Hardan 2003, Nayate 2005).

In 2003, the possible link between basal ganglia pathology, specifically focusing on the caudate nucleus and putamen was ruled out by Hardan et al in a neuroimaging study of 40 normal IQ individuals (aged 8 - 45 years) with autism spectrum disorder. They concluded the only possible remaining neuroanatomical aetiology was that of the cerebellum and frontal lobes. More recently, research has focused on motor skill deficits in the areas of gesture imitation, gesture to command and tool-use, with reports

of associated lack of empathy and deficits in theory of mind (Dziuk 2007, Fabbri-Destro 2013). This has led researchers to propose a link between autism spectrum disorder and the mirror neuron system. Mirror neurons are found in the inferior frontal, precentral and inferior parietal cortex. These neurons fire when an individual is undertaking an action or when observing another perform an action, allowing one to experience the thoughts and feelings required to effectively understand the event taking place. This understanding is based on receiving and interpreting information and on the ability to experience empathy and utilise social communication. Increased activity in one's mirror neuron system is linked with increased ability to empathise and socialise. By extension, reduced firing in one's mirror neuron system is linked to reduced empathy, reduced theory of mind and deficits in social skills (Society for Neuroscience, 2013). Impaired mirror neuron functioning has been demonstrated in empathy and non-verbal communication tasks in individuals with autism spectrum disorder (Roy, 2013).

Although no longer viewed as a core deficit of autism spectrum disorder, it is acknowledged that motor problems can impact on multiple facets of an ASD individual's life from infancy through to old age (Fournier, 2010). The finding that motor skill deficits are present before the onset of social and communication skill deficits supports this argument (Nayate 2005, Fabbri-Destro 2013). In childhood, gross and fine motor skills such as walking, running, jumping, climbing and cycling a bicycle are required to allow a child to interact with their world. Fine motor skills such as grasping, speaking, writing and typing facilitate cognitive development and social interaction. Impaired motor skills can impact on one's ability to engage in meaningful activity, effect mood, enjoyment and the formation of relationships. A link between poor motor skills and peer victimisation or bullying in childhood, most notably in girls, has been established by Bejerot and Humble (2013) when looking at 277 patients with pervasive developmental delay in Stockholm, Sweden. Simple skills such as using a knife and fork, cycling, driving or engaging in recreational activity, use of hand gestures, facial expressions, chewing and hand-eye co-ordination can be limited for adults with autism spectrum disorder. Limited ability to interact with one's physical and social environment could result in poor social communication, reduced occupational performance and impaired relationship development for individuals with autism spectrum disorder over and above that experienced by neurotypical individuals.

Smoking

Smoking is an established risk factor for physical and psychiatric illness. It has been associated with depression, alcohol and drug abuse, personality disorder and anxiety spectrum disorders, particularly agoraphobia, cancer, coronary heart disease, myocardial infarction, cerebrovascular accident, peripheral vascular disease, chronic obstructive pulmonary disease, pneumonia and infertility (Bejerot 2003, NHS Choices 2015). Prevalence rates for smoking among the general population in the United Kingdom were last reported in 2012 as males 22%, females 19% and total population 20% (OECD, 2012). Smoking rates have been measured among the psychiatric population also and were noted to be at least double that of the general population for all types of psychiatric illness and particularly higher in patients with schizophrenia (El-Guebaly 2002, Lê Cook 2014).

By contrast, available research on smoking rates in those with autism spectrum disorder is sparse (Mattila, 2010). Bejerot and Humble (2013) reported smoking rates of 15.8% and Joshi et al (2013) reported a rate of zero percent. Interestingly, both rates are lower than rates seen in the respective general population for each nation under study.

Gastrointestinal Disease

Considerable controversy exists in relation to the association between autism spectrum disorder and gastrointestinal disease. Studies vary by age and IQ cohort but also by definition of gastrointestinal disease. Although practicing physicians would generally use the term to refer to disease involving any portion of the gastrointestinal tract from the oesophagus to the anus, this literature review noted a tendency for ASD literature to use the term to refer solely to diarrhoea and constipation. One particularly controversial paediatric gastroenterologist, Arthur Krigsman has dedicated a large portion of his career to proving a link between gastrointestinal disorders and autism spectrum disorder. His 2007 paper outlines thirteen different gastrointestinal lesions noted on endoscopic examination of children with autism spectrum disorder, including lymphonodular hyperplasia, eosinophil-laden oesophagitis, gastroesophageal reflux disease, Barrett's oesophagitis, gut hypomobility, inflammatory gastric polyps, nodular

gastritis, non-specific duodenitis, colitis, colonic ulceration, inflammatory colonic polyps, ulcerative colitis and Crohn's disease.

Probably the most controversial association between gastrointestinal disease and autism spectrum disorder was proposed by Wakefield et al (1998). Wakefield and colleagues proposed a 'real' and 'unique' gastrointestinal disease process leading to abdominal pain, diarrhoea, bloating and food intolerance in twelve children aged 6 - 10 years following receipt of the MMR vaccine in infancy. These findings were clearly refuted by later research, the article redacted by its publishing journal and Wakefield removed from the medical register by the General Medical Council ruling (Godlee, 2011). Paediatric studies which could possibly be considered more robust note a prevalence rate of 9% - 91% for gastrointestinal disease in children with autism spectrum disorder with a narrower prevalence rate of 24% - 42% for chronic diarrhoea and constipation (Venkat 2012, Mannion 2014c).

This literature review sourced two published studies relating to rates of gastrointestinal disease in adults with autism spectrum disorder. Both included adults with intellectual disability. No study relating to normal IQ adults could be identified. Galli-Carminati et al (2006) investigated rates of gastrointestinal disease in 75 adults (age 26 - 48 years) with an intellectual disability compared to 43 adults with intellectual disability alone, reporting higher rates of upper gastrointestinal symptoms such as dyspepsia, gastroesophageal reflux disease, oesophagitis and gastritis. Mouridsen et al (2010) compared 118 adults (age 27 - 57 years) with autism spectrum disorder, 71% of whom had an intellectual disability, to 336 healthy controls in Copenhagen, Denmark. Findings showed equal rates of gastrointestinal disease in both groups. Only dental problems were statistically more likely in the group with autism spectrum disorder. Of interest, when dental problems were excluded, individuals with autism spectrum disorder were noted to suffer from less gastrointestinal disease than their neurotypical counterparts. Dental problems have been shown to correlate highly with intellectual disability, reducing the significance of their finding.

Overall, the nature and frequency of gastrointestinal disease in both children and adults with autism spectrum disorder remains undecided. Research findings are inconsistent and significant controversy in the area has prevented the drawing of reliable conclusions. On balance, this literature review was unable to establish a reliable link between normal IQ autism spectrum disorder and gastrointestinal disease.

1.9 Aims and Hypotheses of the Study

Despite the significant psychiatric and physical comorbidities associated with autism spectrum disorder, as outlined above, there is a notable lack of literature referring to adults with a normal IQ suffering from the disorder. This study was undertaken to determine if further clarification could be made in relation to comorbid illnesses in this specific population. The aims of this study are:

1. To determine the frequency of Axis I and Axis II comorbid psychiatric illness in adults with normal IQ autism spectrum disorder

2. To determine the frequency of reported physical illness in adults with normal IQ autism spectrum disorder

3. To determine the frequency of psychiatric and physical illness by specific ASD subgroup

4. To determine the frequency of psychiatric and physical illness by gender

5. To draw comparison between the rates of psychiatric and physical illness among the ASD population and reported rates among the general population

This study tested the following hypotheses:

1. In a sample of adults with normal IQ suffering from autism spectrum disorder the rate of comorbid psychiatric illness will be higher compared to the general population

2. In a sample of adults with normal IQ suffering from autism spectrum disorder the rate of comorbid physical illness will be higher compared to the general population

1.10 Summary of Introduction

Autism spectrum disorder is a pervasive neurodevelopmental disorder characterised by deficits in social skills, impaired communication style and characteristic repetitive and ritualised behaviours. It was first described almost simultaneously by Leo Kanner and Hans Asperger in the 1940s. From that time, autism spectrum disorder has undertaken many evolutionary steps to reach the illness as understood today.

Current prevalence rates estimate up to 1% of the population suffer from autism spectrum disorder with a larger, as yet undefined, population falling into the wider phenotype. Much progress has been made in determining the aetiology of autism spectrum disorder, especially in the areas of genetic and neuroanatomical research. However, given the significant heterogeneity of the disorder, research continues to search for the definitive causative factor.

Criteria for diagnosis of autism spectrum disorder are outlined by both the ICD-10 and DSM-5. These are enhanced by a wide array of screening tools and two gold standard diagnostic instruments now available to diagnosticians. Despite the low volume of literature in the area, works are emerging showing adults with autism spectrum disorder most likely suffer from disorders of mood, thought and behaviour at significantly higher rates that those seen in the general population. Relatively few studies investigate the rates of psychiatric and physical comorbidity in normal IQ adults with autism spectrum disorder. It is as yet unclear if particular comorbid conditions are more prevalent in adults with autism spectrum disorder, whether a gender imbalance is present or if conditions are seen more frequently in certain subtypes of autism spectrum disorder.

Awareness of the potential for diagnostic overshadowing in this area is crucial to ensure accurate diagnosis, formulation, care planning and treatment. If psychiatric and physical comorbidity is shown to commonly occur in those with autism spectrum disorder, care must be taken to ensure accurate diagnosis of autism spectrum disorder in those suffering from a psychiatric or physical illness and likewise diagnosis of comorbid psychiatric and physical illness in patients diagnosed with autism spectrum disorder.

Internationally, legislation has been required to increase diagnostic services and improve treatment options for those with autism spectrum disorder. Closer to home,

the increase in public awareness has yet to translate into government policy or increased healthcare services and it is frequently shown that access to crucial treatment opportunities for individuals with autism spectrum disorder, wanes significantly after the age of 18 years. It is hoped, that as support for those with autism spectrum disorder improves among both clinicians and the general public, so too will funding and policy driven care by health service providers. Further research will assist access to diagnosis and treatment and lead to better outcomes for those with this highly debilitating illness.

Chapter 2: Materials and Methods

2.1 Overview

This chapter outlines the methods used to undertake a literature review on the subject of autism spectrum disorder in adults with normal range intellectual functioning, development of an SPSS dataset and codebook and sourcing of the clinical sample. It outlines the preassessment screening process and diagnostic tools used in this study, ethical approval, data gathering methods, inclusion and exclusion criteria, methods of statistical analysis and methods of reporting.

The timeline for this study is outlined in Table 2.1

Table 2.1 **Ghant Chart**	
Date	**Activity**
August 2012 - October 2012	Initial literature review
October 2012 - December 2012	Application for MD student placement Development of SPSS codebook
January 2013 - March 2013	Data gathering from chart records
March 2013 - August 2013	Manual review of 364 reports
September 2013	Publication: Garland J, O' Rourke L, Robertson D (2013) Autism spectrum disorder in adults: clinical features and the role of the psychiatrist. *Advances in Psychiatric Treatment,* 19(5):378-391.
August 2013 - February 2014	Off books, due to maternity leave

Date	Activity
February 2014 - September 2015	Manual review of remaining 96 reports Upload of 96,140 variables to SPSS
February 2015 - July 2016	Literature review Data analysis Writing of thesis
July 2016	Thesis submission

2.2 Literature Review

The literature review for this study was performed by the author in August 2012 and repeated in February 2015. Databases searched included Medline Pubmed, Google Scholar, PsychInfo and PsychNet. Terminology was defined for each search using terms related to the research question. Terms were expanded using clinical synonyms, psychiatric nomenclature, medical nomenclature and medical literature. Search terminology is listed in Table 2.2. The author searched each term individually and repeated searches using combinations of search terms. When a new synonym or phrase was identified from sourced literature, it was added to the search terms. Reference lists for each article were manually searched for related articles by the author.

Certain topics which the autor wished to address in the literature review were under-researched with few published articles available for review. In these circumstances, the author broadened the search criteria to include child cohorts and mixed IQ populations. These references are explicitly named in the text. No intellectual disability only studies were included. To allow a comprehensive search of the literature all study designs were included and the search was not limited by publication date. Studies in all languages were considered relevant. The author accessed the abstracts of these articles in the English language and where available the full article was accessed. When more than one paper was published relating to the same study sample, the

author reviewed all papers and included each separately. Examples include Brugha et al (2007 and 2011), Lugnegård et al (2011 and 2012) and Tani et al (2003 and 2004).

Articles are referenced using the Harvard Referencing System. On occasion, books or articles that could no longer be sourced are cited. In each case reference is made to the original author, as found in the more recent publication. Online articles, summaries and presentations are referenced by web address and date of access.

Table 2.2

Terminology of Literature Review

Search Topic	Search Terms
ASD Terminology	• Asperger • Asperger's syndrome • Autism • Autism spectrum disorder • Childhood autism • PDD • Pervasive developmental delay
Intelligence Quotient Terminology	• High-functioning • Intellectual functioning • Intelligence • Intelligence quotient • IQ
Comorbid Terminology	• Comorbid • Comorbidity • Co-occurring
Age Terminology	• Adult • Adulthood
Psychiatric Illness Terminology	• Psychiatric illness • Mental illness • Mood • Affective • Bipolar • Depression • Hypomania • Mania • Anxiety spectrum disorders • Generalised anxiety • Hypochondriasis • Obsessive compulsive disorder • Panic disorder • Post-Traumatic stress disorder

Psychiatric Illness Terminology	• Social anxiety • Social phobia • Somatisation • Somatoform • Psychotic • Psychosis • Delusional • Schizoaffective • Schizophrenia • Eating disorder • Anorexia • Bulimia • Personality • Anankastic • Antisocial • Dissocial • Anxious-avoidant • Dependent • Borderline • Emotionally-unstable • Histrionic • Narcissistic • Paranoid • Schizoid • Schizotypal • Neurodevelopmental • Attention deficit hyperactivity disorder • Tic disorder • Tourette's syndrome • Gender identity disorder • Addiction • Substance use disorder • Alcohol • Catatonia • Self-harm • Self-injury • Suicide • Suicidal behaviour • Sleep • Sleep difficulties • Insomnia • Appetite • Diet • Eating disturbance • Eating behaviours • Eating habits

Search Topic	Search Terms
Physical Illness Terminology	• Physical illness • Medical illness • Medical condition • Motor skills • Clumsiness • Dyspraxia • Dyslexia • Epilepsy • Gastrointestinal • Head injury • Hypertension • Smoking • Medication • Sedative • Hypnotic • Allergy • Food
Other Terminology **Other Terminology**	• Assessment • Causality • Epidemiology • Prevalence • Age • Gender • Genetics • History of autism spectrum disorder • MMR vaccine • Mortality • Neuroimaging • Outcomes • Prevalence • Stress

2.3 Development of an SPSS Codebook

The author uploaded, stored and analysed data using Statistical Package for Social Science (SPSS), version 22. The key to the SPSS dataset and codebook are outlined in Table 2.3. The original dataset included 51 variables. This was extended to 209 variables over the course of data entry to allow for accurate recording of particular psychiatric and physical conditions and to allow detailed data analysis. For all variables, 777 reflects unanswered questions, 888 for nonapplicable questions and 999 for 'do not know' replies.

Table 2.3

Key to SPSS Codebook

Variable	Type of Data	Codes
Assessment Information:		
Initials of consultant completing assessment	Categorical	0. CM 1. DM 2. DR 3. IJ 4. JZ 5. MC 6. MCA 7. QD
Date of assessment	Continuous	Dates ranged from 22.09.2009 to 21.10.2012
Referring clinician	Categorical	1. General practitioner 2. Consultant psychiatrist 3. Clinical psychologist
Accompanying person	Categorical	0. Alone 1. Parents 2. Mother 3. Father 4. Sister 5. Brother 6. Spouse / partner 7. Carer / CMHT member 8. Interpreter 9. Friend 10. Child 11. Grandparent 12. Aunt

Variable	Type of Data	Codes
Assessment Information:		
Date of birth	Continuous	Dates ranged from 09.02.1939 to 08.12.1995
Age at assessment	Continuous	Age ranged from 14 - 70 years
Gender	Categorical	0. Male 1. Female
Marital status	Categorical	0. Single 1. Partner 2. Engaged 3. Married 4. Separated 5. Divorced 6. Widowed
Parental marital status	Categorical	0. Single 1. Partner 2. Engaged 3. Married 4. Separated 5. Divorced 6. Widowed
Employment status	Categorical	0. No 1. Yes
Accommodation status	Categorical	0. Alone 1. Parents 2. Mother 3. Father 4. Sister 5. Brother 6. Spouse / partner 7. Carer / supported accommodation 8. Sibling(s) 9. Friend 10. Child(ren) 11. Grandparents 12. Homeless

Variable	Type of Data	Codes
Assessment Information:		
History of delay in motor milestones	Categorical	0. No 1. Yes
History of delay in speech milestones	Categorical	0. No 1. Yes
Type of schooling	Categorical	1. Mainstream 2. Mainstream with statement 3. Special needs school 4. Mainstream with SNA 5. Home-schooled
Bullying in school	Categorical	0. No 1. Yes
Third level education	Categorical	0. No 1. Yes
Psychiatric Information:		
Prior contact with community mental health team	Categorical	0. No 1. Yes
Past psychiatric history	Categorical	0. No 1. Yes
Previous diagnosis of autism spectrum disorder	Categorical	0. No 1. Yes
History of deliberate self-harm	Categorical	0. No 1. Yes
History of self-injurious behaviour	Categorical	0. No 1. Yes
Diagnosis of autism spectrum disorder given at assessment	Categorical	0. No 1. Yes
ICD-10 ASD diagnosis	Categorical	0. No 1. Yes

Variable	Type of Data	Codes
Psychiatric Information:		
Diagnosis of other psychiatric disorder at assessment	Categorical	0. No 1. Yes
Neurodevelopmental disorder diagnosed at assessment	Categorical	0. No 1. Yes
Mood disorder diagnosed at assessment	Categorical	0. No 1. Yes
Anxiety spectrum disorder diagnosed at assessment	Categorical	0. No 1. Yes
Psychotic disorder diagnosed at assessment	Categorical	0. No 1. Yes
Personality disorder diagnosed at assessment	Categorical	0. No 1. Yes
Addictive disorder diagnosed at assessment	Categorical	0. No 1. Yes
Other psychiatric disorder diagnosed at assessment	Categorical	0. No 1. Yes
Learning disability diagnosed at assessment	Categorical	0. No 1. Yes
Family history of autism spectrum disorder	Categorical	0. No 1. Yes
Family history of psychiatric illness	Categorical	0. No 1. Yes
Medical Information:		
Past medical history	Categorical	0. No 1. Yes
History of sleep difficulties	Categorical	0. No 1. Yes
History of eating disturbance	Categorical	0. No 1. Yes

Variable	Type of Data	Codes
Medical Information:		
Current medications	Categorical	0. No 1. Yes
Allergies	Categorical	0. No 1. Yes
Weekly alcohol intake	Continuous	Units consumed per week
Illicit drug use	Categorical	0. No 1. Yes
Family history of medical illness	Categorical	0. No 1. Yes
Questionnaires:		
Autism Quotient - self	Continuous	Total result entered numerically
Autism Quotient - other	Continuous	Total result entered numerically
Obsessive Compulsive Inventory, Revised	Continuous	Total result entered numerically
Hospital Anxiety and Depression Scale	Continuous	Total result entered numerically
Barkley Screening Questionnaire - self	Continuous	Total result entered numerically
Barkley Screening Questionnaire - other	Continuous	Total result entered numerically
Autism Diagnostic Interview, Revised	Continuous	Total result entered numerically
Autism Diagnostic Observational Schedule, Generic	Continuous	Total result entered numerically
Full scale IQ	Continuous	Total result entered numerically

2.4 The Behavioural Genetics Clinic

This study involved access to case records of patients attending The Behavioural Genetics Clinic (BGC) in the outpatient department of the Maudsley Hospital, London. The BGC is a purpose designed clinic for the assessment and diagnosis of adults with suspected autism spectrum disorder. The clinic functions as the outpatient assessment unit of the Autism Assessment and Behavioural Genetics Service within the South London and Maudsley Trust. The clinic has 'pioneered the development of specialist services for assessment and treatment of autism spectrum disorder and other neurodevelopmental disorders in adults' (National Services NHS, 2015) offering single day assessments to patients from across the United Kingdom. It accepts referrals from consultant psychiatrists, general practitioners and clinical psychologists. Self-referrals are not accepted.

Each referral is triaged by a consultant psychiatrist and offered an assessment appointment if appropriate. Inclusion criteria include age over 17 years and 4 months, male or female, suspected or confirmed autism spectrum disorder, possible genetic / chromosomal abnormalities or psychiatric comorbidity, engaged with a local community mental health team or forensic psychiatry service and in receipt of funding for assessment. Exclusion criteria include referral reports of current use of street drugs or not engaged with a local community mental health team / forensic psychiatry service (National Services NHS, 2015).

Outpatient assessments are a half-day procedure consisting of a detailed psychiatric interview by a trained non-consultant hospital doctor, the Autism Diagnostic Observation Schedule - Generic (ADOS-G) and / or the Autism Diagnostic Interview - Revised (ADI-R) by a trained and accredited clinical psychologist or psychiatric nurse practitioner, consensus meeting with a consultant psychiatrist and provision of a diagnosis, formulation and treatment recommendations. When required, patients also undergo genetic screening, blood testing, neuroimaging and neuropsychological assessment depending on suspected comorbid illness.

The detailed psychiatric examination consists of clinical observation and a semi-structured diagnostic interview by a psychiatric registrar with training in the assessment of autism spectrum disorder in a normal IQ adult population. Some registrars will have further experience in intellectual disability or inpatient care of adults with autism

spectrum disorder and comorbid psychiatric illness. Diagnosis is based on the ICD-10 criteria. For the duration of this study, version 10 of the International Classification of Diseases was used. No new criteria were devised / revised over this period, providing stable diagnostic criteria throughout. A structured ADI-R and / or ADOS-G is undertaken by a qualified psychologist or psychiatric nurse practitioner with training in both ADI-R and ADOS-G assessment and previous clinical and research experience in using both diagnostic tools. The ADI-R is completed with the patient's primary caretaker or parent.

Once the clinical interview, collateral history and initial impressions are complete, a 30 minute to 1 hour meeting takes place involving the registrar, psychologist / psychiatric nurse practitioner and consultant general adult psychiatrist, specialising in the assessment of autism spectrum disorder and mental illness, to reach a consensus diagnosis. Diagnoses include a primary diagnosis of autism spectrum disorder or neurotypical development where applicable and secondary diagnoses of comorbid psychiatric illness. Following discussion of the team's findings, the patients and carer are further interviewed by the consultant psychiatrist, in the company of the registrar and psychologist / psychiatric nurse practitioner, to confirm any points of disagreement or discrepancies allowing a consensus to be reached regarding diagnosis.

The consensus team use a combination of preassessment screening questionnaires including the Obsessive-Compulsive Inventory - Revised (OCI-R), the Hospital Anxiety and Depression Scale (HADS), the Barkley Adult ADHD Rating Scale (BAARS), ICD-10 diagnostic criteria, the Autism Diagnostic Interview - Revised, the Autism Diagnostic Observation Schedule - Generic, collateral information from a parent or caregiver, a comprehensive psychiatric history, mental state examination and clinical expertise to arrive at a confirmed diagnosis. This diagnostic strategy exceeds methods employed to diagnose autism spectrum disorder in previous studies on autism spectrum disorder identified as part of the literature review for this study for rigour and completeness.

Interviewers are not blinded to the preassessment screening tool results but are blinded to the findings of their colleagues as the psychiatric assessment and collateral history plus ADI-R are completed simultaneously. Although, ICD-10 diagnostic criteria provide exclusion notes for childhood autism and Asperger's syndrome as well as other psychiatric illnesses consultant psychiatrists at the Behavioural Genetics Clinic are unanimous in their decision to opt for the non-hierarchical approach to diagnostic

criteria and provide named diagnoses for each condition meeting diagnostic criteria. This allows for more comprehensive assessment and accurate recording of comorbidity rates.

A BGC medical report is compiled by the consensus team including all acquired information and forwarded to the referrer following assessment. Reports are inclusive documents following a standard template consisting of: Opening Summary, Background History, History of Presenting Complaint, Reciprocal Social Interaction, Language and Communication, Interests and Routines, ADHD Symptoms, Anxiety Symptoms, OCD Symptoms, Mood Symptoms, Psychotic Symptoms, Past Psychiatric History, Past Medical History, Family History, Personal and Developmental History, Current Social Situation, Educational History, Forensic History, Drug and Alcohol History, Mental State Examination including subheadings of Appearance and Behaviour, Mood, Speech, Thoughts, Perceptions, Cognitions, Insight and Risk to self, to others and from others, Summary, Formulation and Recommendations.

Each BGC medical report includes the ICD-10 criteria for the autism spectrum disorder subtype diagnosis received by the patient and for each individual psychiatric comorbidity highlighting in bold the symptoms present to support the diagnosis. The ADI-R report and / or the ADOS-G report are included as appendices. Each report is signed by the NCHD, clinical psychologist / psychiatric nurse practitioner and consultant psychiatrist involved in the assessment. An anonymised report has been attached to this thesis as Appendix 6.1 to show the detail in which each report is written and the availability of required data to complete data extraction for this study. This assessment method has been revised and developed over the lifetime of the Behavioural Genetics Clinic by practising clinicians who ensure it is sufficiently sensitive to differentiate between disorders.

All assessments included in this study were completed in the above format and undertaken from September 2009 to October 2012. Eight consultant psychiatrists, thirty two non-consultant hospital doctors and thirteen clinical psychologists or psychiatric nurse practitioners worked in the clinic during this time. Each patient was assessed by two or three practitioners, as on occasion a consultant completed the NCHD history or the ADOS-G / ADI-R. While working in the Behavioural Genetics Clinic, from July 2011 to July 2012, the author completed one assessment per week, totally approximately 40 assessments. Each patient is approached regarding consent

to participate in research and varying numbers agree. A full list of practitioners and the number of patients assessed by each who consented to research is outlined in the results section of this thesis, the author's input is listed among the thirty two NCHDs.

2.4.1 Preassessment Screening Tools used in this study

The Autism Spectrum Quotient (AQ); Baron-Cohen, 2001

The AQ was designed by the University of Cambridge as a brief, self-administered instrument aimed at measuring the degree to which adults with normal intelligence have the traits associated with autism spectrum disorder (Baron-Cohen 2001a, Hambrook 2008). It was designed to serve as a 'short, easy to use, easy to score and useful instrument in identifying the extent of autistic traits shown by an adult of normal intelligence'. Baron-Cohen et al (2001a) propose its use in identifying persons in distress who warrant a referral to expert clinicians for full diagnostic assessment.

The AQ is available is three forms, the AQ-50, AQ-21 and AQ-10. The AQ-50 as used in this study is the original format and generally referred to as the AQ. It is a 50 item, self-administered questionnaire allowing patients of normal intelligence to rate their preferences in five domains corresponding to the autism triad (Baron-Cohen 2001a, Hambrook 2008, White 2012, Roy 2013). Ten questions are used per domain assessing social skill, attention switching, attention to detail, communication and imagination. Participants score items on a four point Likert scale, as 'definitely agree', 'slightly agree', 'slightly disagree' or 'definitely disagree'. This four point scale is then collapsed to two categories, as a binary manner of rating, such that a score of one is given for responses indicating ASD traits and a score of zero is given for responses which are not consistent with autism spectrum disorder (Baron-Cohen 2001a, Hurst 2007, White 2012). A maximum score of 50 is possible and Baron-Cohen et al (2001a) have suggested that a score of 32 or greater in a person suffering distress merits referral to an expert clinician for a full diagnostic assessment. Higher scores indicate more severe symptomatology, lower scores trend towards the neurotypical, inferring where an individual can be placed in the continuum from neurotypical to autism spectrum disorder (Hambrook 2008, White 2011, Roy 2013).

Researchers publishing on their experience of using the AQ demonstrate excellent test-retest reliability, moderate to high internal consistency, good diagnostic validity, good inter-rater reliability, reasonable face validity and reasonable construct validity (Hurst 2007, Roy 2013). Hambrook et al (2008) showed the internal consistency of the AQ to be high (α=0.82). The suggested cut-off score of $\geq$32 has been identified as sufficiently sensitive to capture over 79% of those with autism spectrum disorder and sufficiently specific in that only 2% of those without autism spectrum disorder are erroneously captured (White 2012, Roy 2013). In summary, the AQ has been shown to strongly predict diagnosis of autism spectrum disorder (Roy, 2013).

Barkley Adult ADHD Rating Scale (BAARS-IV); Barkley, 2011

The Barkley Adult ADHD Rating Scale is a behavioural assessment of symptoms of attention deficit hyperactivity disorder designed for use in adults (Barkley, 2011). It is based on the DSM-IV-TR criteria for attention deficit hyperactivity disorder. Its authors describe the BAARS-IV as 'empirically-based, reliable, valid and exceptionally convenient to use' (Barkley, 2011). The tool is most useful as an initial screening tool, identifying individuals at high risk of attention deficit hyperactivity disorder, prompting more detailed clinical assessment.

The Barkley Adult ADHD Rating Scale consists of 18 items based on the DSM diagnostic criteria for attention deficit hyperactivity disorder. The items alternate from inattentive to hyperactive-impulsive symptoms covering nine of each. Patients self-report difficulties pertaining to each item on a four point Likert scale of never / rarely, sometimes, often and very often. Items marked often and very often are rated one point each. Items marked never / rarely and sometimes are scored as zero. Scoring is completed by adding each point scored on inattentive items and each point scored for hyperactivity items. A score greater than six relating to difficulties in childhood and four relating to difficulties in adulthood suggest further assessment of attention deficit hyperactivity disorder is warranted.

The Barkley Adult ADHD Rating Scale shows good internal consistency (0.72 - 0.94) and reasonable test-retest reliability (0.66 - 0.88) (Barkley, 2011).

Hospital Anxiety and Depression Scale (HADS); Zigmond, 1983

The Hospital Anxiety and Depression Scale is a 14-item measure of anxiety and depressive symptoms in individuals to determine the severity of an individual's symptom experience. The HADS is recommended as a screening questionnaire not as a case identifier (Spinhover, 1997). Anxious and depressed feelings are rated on a four point Likert scale and a cut-off score of eight indicates anxiety or depressive feelings which warrant further investigation (Hare, 2014). The HADS is quick to administer and patient friendly, it can be completed in two to six minutes and scored within one minute. It is accessible to and useable by both psychiatrists and non-psychiatric medical and nursing staff alike (Herrmann, 1997).

Internal consistency is good to excellent (0.78 - 0.93), with sensitivity and specificity of over 0.80 and test-retest reliability of 0.86 (Herrmann 1997, Spinhoven 1997, Mykletun 2001, Bjelland 2002, Hansson 2009).

Obsessive-Compulsive Inventory - Revised (OCI-R); Foa, 2002

The OCI-R is a brief, self-report measure devised from the Obsessive-Compulsive Inventory, as designed by Foa et al in 1998. Foa et al (2002) adapted their original assessment tool by reducing the number of assessment items from forty two to eighteen, removing the frequency scale, eliminating overlap between items and simplifying the scoring mechanism. The OCI-R differentiates between individuals with and without obsessive compulsive disorder using eighteen items across six subscales (Foa, 2002). Subscales include washing, checking / doubting, obsessing, mental neutralising, ordering and hoarding assessed by three questions each.

The OCI-R boasts good internal consistency (0.34 - 0.72), good to excellent test-retest reliability (0.74 - 0.91) and correlates strongly with the long version of the OCI (Foa, 2002). Its authors recommend the OCI-R replace the OCI in clinical use.

2.4.2 Diagnostic Tools used in this study

Autism Diagnostic Interview - Revised (ADI-R); Lord, 1994

The ADI-R is a standardised, semi-structured, investigator-based interview conducted with parents, caregivers or carers of an individual with suspected autism spectrum disorder. The original format, the Autism Diagnostic Interview (ADI), was designed for research purposes but came to be used in clinical work, prompting its revision to the ADI-R (Lord 1994, Wing 2002b). The ADI-R interview contains 93 questions on early development, language, social interest, play and behaviours across five sections: opening questions, communication, social development and play, repetitive and restricted behaviours and general behaviour. Answers are coded as 0 indicating no abnormality, 1 for possible abnormality, 2 for definite abnormality or 3 for severe abnormality. Cut-off scores in each domain of social, communication and repetitive behaviour allow for diagnosis (Lord, 1989). This diagnostic algorithm was generated by selecting items which most closely matched diagnostic criteria as set out by the ICD-10 and DSM-IV (Lord, 1994).

The ADI-R is designed for use as part of a multidisciplinary assessment and has adequate test-retest reliability, proven inter-rater reliability (0.64 - 0.89) and good internal consistency (0.69 - 0.95) (Lord, 1994). Intra-class correlations were also shown to be very high. The ADI-R is suitable for use with persons aged 18 months to adulthood, is a comfortable experience for parents / caregivers and with practice, administration time can be reduced to 1 - 1½ hours (Lord 1994, Baron-Cohen 2001a, Wing 2002b).

The Autism Diagnostic Observation Schedule - Generic (ADOS-G); Lord, 2000

The ADOS-G is a semi-structured, standardised assessment of communication, social interaction, play and imaginative use of materials (Lord, 2000). It contains schedules of activities designed to highlight social deficits pertaining to autism spectrum disorder through direct one-to-one engagement between assessor and patient and through observation of the patient's social, communication and other behaviours. Each specifically designed social occasion is called a 'press' designed to elicit spontaneous social, communication or repetitive behaviours which can be rated in a standardised

manner (Lord, 2000). Four modules were designed, each for use with a particular age group of differing cognitive ability. Module 1 for those who are preverbal or use single words, module 2 for those with phrased speech, module 3 for children and adolescents with fluent speech and module 4 for adolescents and adults with phrased speech. Module 4 differs from module 3 in that it assesses high-functioning adolescents and adults, who are not interested in playing with toys, for ASD features. Module 4 rates ASD features through 31 questions across five domains and cut-off scores allow for diagnosis (Lord, 2000).

The ADOS-G demonstrates good to excellent inter-rater reliability (0.41 - 0.66), test-retest reliability (1.19 - 1.78), internal consistency (0.47 - 0.91) and agreement between assessors (88%) (Lord, 2000). Efficient use of the ADOS-G relies on the skill of the examiner and requires practice and consensus rating of the assessor's ability (Lord, 2000). Coupled with the 45 minutes required for each assessment, the 30 - 40 minute report writing time, on-going training and inter-rater reliability consensus meetings, testing can be time consuming.

2.5 Ethical Approval

The BGC is attached to The Department of Forensic and Neurodevelopmental Sciences (FANS) for research purposes. The FANS department specialises in research in autism spectrum disorder from neuroimaging and neuropsychiatric disorders through to clinical research in symptomatology and new treatment opportunities. Patients and healthy controls are recruited through both advertising campaigns in UK media and from the patient group attending the Behavioural Genetics Clinic.

As part of their preassessment questionnaire pack, patients awaiting assessment at the BGC receive a postal invitation to join research projects underway within the Department of Forensic and Neurodevelopmental Sciences. This includes a written consent form, a participant information sheet and an invitation letter requesting permission for clinical information collected at assessment to be included in a data bank within the research department.

The Clinical Research of Developmental Disorders Database is a list of all patients who agree to contribute data to research projects within the FANS department. It

identifies patients by initials and medical record number. Ethical approval was granted by the National Research Ethics Service, Health Research Authority, London. All forms associated with this recruitment process were devised in 2012 by Dr SW under the supervision of Professor DM. Parties interested in undertaking research with the department can request access to The Clinical Research of Developmental Disorders Database.

2.6 Data Collection

In late 2012, the author was granted access to The Clinical Research of Developmental Disorders Database for the purposes of this research. At the time of access, the dataset dated from 08.04.2003 to 21.10.2012. The most recent 460 participants were selected. Patient records were accessed through the Electronic Medical Records System at the Behavioural Genetics Clinic by two researchers, the author and my colleague JG (who was undertaking research on the same population group relating to a different project). BGC medical reports, as described above, were sourced on each of the 460 participants. These reports were stored on a password protected desktop computer for the duration of the study.

The author reviewed each report systematically, phrase by phrase, and extracted data by hand. A total of 23,460 data items were extracted in the initial phase. These were expanded to 96,140 data items over the course of data gathering, by means of redefining string to numerical data and by repeat review of reports to include extra variables which became evident over the course of the study. These data items were then entered into the newly devised SPSS Codebook by the author.

2.7 Inclusion and Exclusion Criteria

Inclusion criteria for this study:

- Male and female patients attending the Behavioural Genetics Clinic who consented to their data being available on The Clinical Research of Developmental Disorders Database
- Participants aged over 18 years
- Participants with an intelligence quotient greater than 70

Exclusion criteria for this study:

- Participants with known or likely genetic disorders which have been linked to ASD symptomatology (for example Tuberous Sclerosis, Fragile X syndrome and Neurofibromatosis)
- Participants with known or likely intellectual disability
- Participants aged under 18 years

2.8 Statistical Analysis

Data recording, processing and statistical analysis was conducted using Statistical Package for Social Science (SPSS), version 22. All analysis was undertaken by the author. This included thirteen demographic data items, forty seven psychiatric illness data items and eighty one physical illness data items. Descriptive analysis was used to provide results relating to demographic data. Comparisons were made using cross-tabulation and Pearson's chi-squared testing. Data were tested by diagnostic group and for difference using Pearson's chi-squared tests for independence. For tables larger than 2 by 2, Cramer's V was reported to show effect size. Values of 0.10 denote a small effect size, 0.30 a medium effect size and 0.50 a large effect size (Cohen, 1988). Mann-Whitney U testing was undertaken on all continuous variables, namely age and alcohol intake. Where a p-value was statistically significant, it was corrected for multiple comparisons using the Bonferroni Correction method. The Bonferroni critical value was calculated by adjusting for the number of tests carried out at each analysis.

Rates of psychiatric and physical illness were determined for the participants with autism spectrum disorder, participants without autism spectrum disorder, between subtypes of autism spectrum disorder, by age and by gender. A p-value of <0.05 was regarded as a statistical difference between groups. The sample size was sufficiently large to allow division of the participant group by age, by gender and by ASD subtype. Age profile was divided in three ways: a median split (at age 29 years) to compare younger adults to older adults (Davis, 2011), at age 50 years to determine rates of comorbid psychiatric illness in the 'older' adult (Howlin 2012, Gray 2012, Mannion 2014a) and at age 30 years to determine rates of physical illness in younger versus older adults (Howlin, 2012). Comparison was undertaken between genders to

determine gender differences in comorbidity. Group comparisons were undertaken according to subtype of autism spectrum disorder to assess outcome and rates of psychiatric and physical comorbidity in individuals with less severe forms of autism spectrum disorder such as Asperger's syndrome, PDD-nos and atypical autism compared to more severely symptomatic cases of childhood autism (Howlin, 2000).

2.9 Reporting Methods

The prevalence of psychiatric and physical comorbidity is reported as percentages instead of rates per thousand. Reporting as percentages was chosen as it was felt to read better throughout the text. Due to rounding of decimal points, percentages in the tables or figures may not add exactly to 100%. Rounding was upward if the percentage was greater than or equal to 0.5 and down if it was below 0.5. Likewise, cumulative figures within the text may not match equally to figures if added from the tables or figures, due again to the use of rounding or the presence of missing data. Percentages are quoted to a single decimal place, which is rounded up or down as above. The term 'significance' is used in two ways, to represent statistical significance and to represent clinical significance. Attempts are made throughout the text by the author to clearly differentiate which meaning is intended.

Missing values occurred for four reasons; the patient may not have known the information when asked by the Behavioural Genetics Clinic interviewer, the screening or assessment tool may not have been completed by the patient, the Behavioural Genetics Clinic medical report may have not contained the information or the report may have described the information in an ambiguous manner that could not be clearly categorised during data collection.

2.10 Summary of Materials and Methods

This study is a cross-sectional survey examining the prevalence of comorbid psychiatric and physical illness in adults with normal IQ autism spectrum disorder. Participants were selected from a list of consenting adult males and females on The Clinical Research of Developmental Disorders Database. Patients contributing to this database each attended the Behavioural Genetic Clinics at the Maudsley Hospital,

London. There each completed a semi-structured interview and mental state examination with a registrar in psychiatry, an ADOS-G and / or ADI-R with a psychologist or psychiatric nurse practitioner and was reviewed by a consultant psychiatrist specialising in the diagnosis of autism spectrum disorder in adults with normal IQ.

Patients also completed screening questionnaires including the AQ, BAARS-IV, HADS and OCI-R. All clinical information and consensus diagnoses was reported as a standardised medical report varying in length from 14 to 26 pages and saved to the patient's electronic medical record. The author worked as a registrar in psychiatry with the BGC for a one year period undertaking mental state and clinical assessment of patients, participating in two clinics per week.

For the purposes of this study, initials and MRN information relating to 460 clinic attendees were selected from the database. The author, along with my colleague, sourced the BGC medical reports for each patient through the electronic medical records system. The author read each medical report phrase by phrase and extracted 51 data variables from each to answer the research questions. The author found it necessary to expand this number to 209 variables for each of the 460 participants to allow clarification of detail prior to entering all data for analysis into SPSS, version 22. Descriptive analysis provided demographic data while comparisons were made using cross-tabulation, Pearson's chi-squared tests and Mann-Whitney U testing. The author used the data to test the hypothesis that rates of psychiatric and physical illness among adults with a normal range IQ and autism spectrum disorder would be greater than rates reported in the literature for the general population.

Chapter 3: Results Chapter

3.1 Overview

The following chapter describes the variables analysed by the author and outlines the demographic data relating to the study sample as a single group followed by demographics of the sample of participants diagnosed with autism spectrum disorder and then those who did not meet criteria for autism spectrum disorder.

The chapter goes on to outline the rates of psychiatric illness in the study sample. Results are reported for the study sample as a whole and those individuals with autism spectrum disorder. Results for individuals with autism spectrum disorder are further reported by ASD subtype, age and gender.

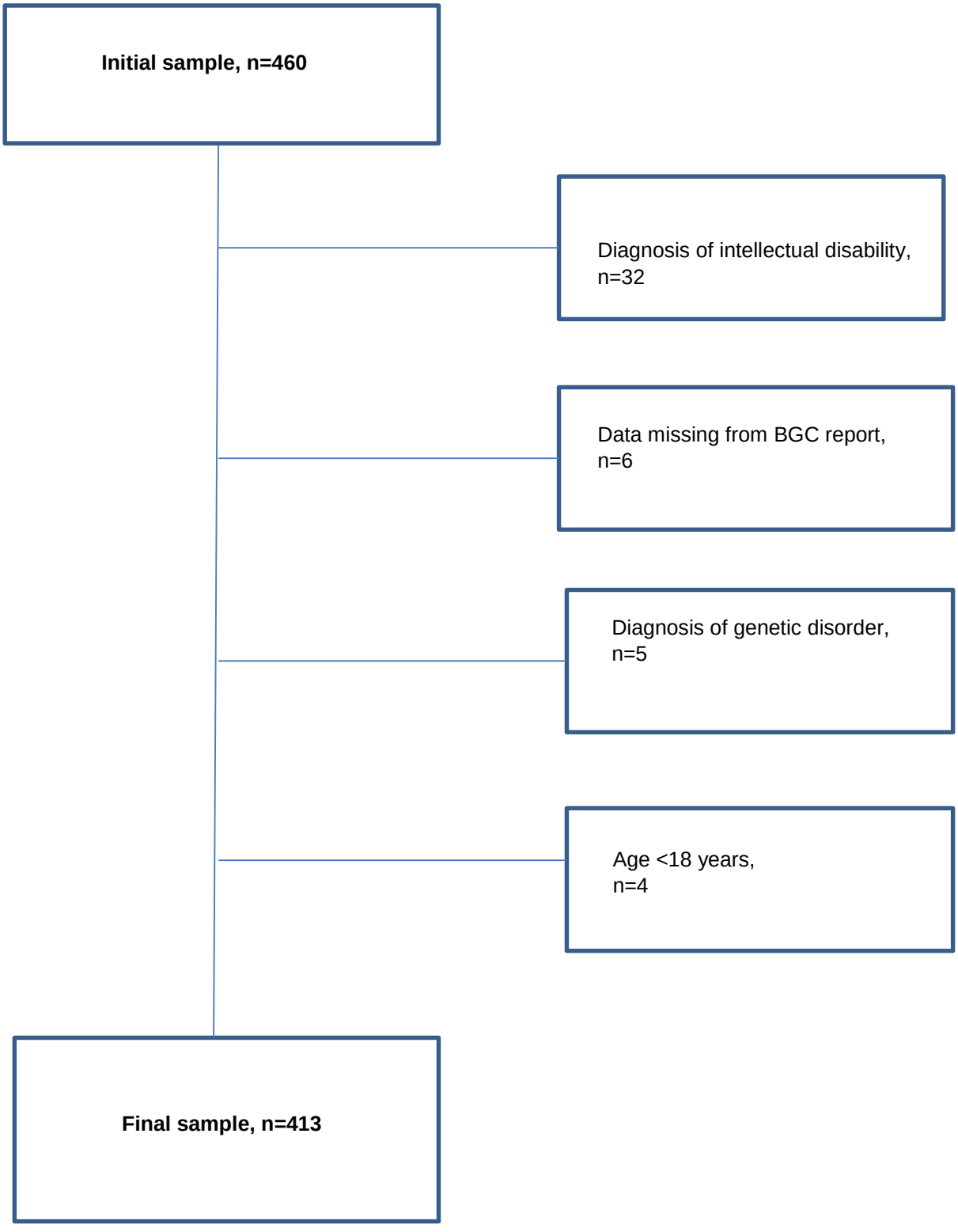
Lastly, the chapter describes the rates of physical illness in the study sample. Results are reported for the study sample as a whole and those individuals with autism spectrum disorder. Results are further reported by ASD subtype, age and gender. Other physical ailments reported include rates of sleep difficulty, appetite disturbance, allergies and use of prescribed medication.

3.2 Data Relating to Study Sample

Behavioural Genetic Clinic medical reports for four hundred and sixty serial clinic attendees provided the basis for this study. These clinic attendees / study participants were selected by two data collectors (LOR (myself) and JG) from the Clinical Research of Developmental Disorders Database. The first identified participant was the most recent clinic attendee recorded on the database. Each preceding participant was included until a total of 460 participants was reached. Following completion of the dataset, the author reviewed all data and excluded 47 participants from the final dataset; 32 due to a suspected or confirmed diagnosis of comorbid intellectual disability, 5 with suspected or confirmed chromosomal / genetic abnormality, 6 as their BCG medical reports lacked vital data such as diagnosis and 4 further participants as they were aged less than eighteen years. The sample profile is outlined in Figure 3.1.

Figure 3.1

Sample Profile



A final sample of four hundred and thirteen participants were included in this study. As each BGC medical report was written to a standardised template, the quality of information available in the analysed reports was very high. This resulted in good to high availability of the data needed to address the questions posed by this study. Acquisition rates for demographic, psychiatric and medical information are outlined in Table 3.1.

Table 3.1

Study Variables and Missing Data

Variable	Type of Data	Percentage of Data Acquired
Assessment Information:		
Initials of consultant completing assessment	Categorical	100%
Initials of NCHD completing assessment	Categorical	100%
Date of assessment	Continuous	100%
Referring clinician	Categorical	100%
Accompanying person	Categorical	99%
Demographic Information:		
Date of birth	Continuous	99%
Age at assessment	Continuous	100%
Gender	Categorical	100%
Marital status	Categorical	94%
Parental marital status	Categorical	70%
Employment status	Categorical	97%
Accommodation status	Categorical	91%

Variable	Type of Data	Percentage of Data Acquired
Childhood Information:		
A history of delay in motor milestones	Categorical	94%
A history of delay in speech milestones	Categorical	94%
Type of schooling	Categorical	98%
A history of being bullied in school	Categorical	89%
Progress to third level education	Categorical	93%
Psychiatric Information:		
Prior contact with a community mental health team	Categorical	99%
Details of past psychiatric history	Categorical	98%
Record of previous diagnosis of autism spectrum disorder by another service	Categorical	99%
A history of deliberate self-harm	Categorical	99%
A history of self-injurious behaviour	Categorical	99%
If a diagnosis of autism spectrum disorder was given following BGC assessment	Categorical	100%
The ICD-10 ASD diagnostic code	Categorical	100%
If a diagnosis of other psychiatric disorder was given following BGC assessment	Categorical	99%
If a diagnosis of neurodevelopmental disorder was given following BGC assessment	Categorical	99%
If a diagnosis of mood disorder was given following BGC assessment	Categorical	99%

Variable	Type of Data	Percentage of Data Acquired
Psychiatric Information:		
If a diagnosis of anxiety spectrum disorder was given following BGC assessment	Categorical	99%
If a diagnosis of psychotic disorder was given following BGC assessment	Categorical	99%
If a diagnosis of personality disorder was given following BGC assessment	Categorical	99%
If a diagnosis of substance use disorder was given following BGC assessment	Categorical	99%
If a diagnosis of another psychiatric disorder was given following BGC assessment	Categorical	99%
Was a learning disability suspected following BGC assessment	Categorical	100%
A known family history of autism spectrum disorder	Categorical	87%
A known family history of psychiatric illness	Categorical	92%
Medical Information:		
Past medical history	Categorical	97%
A history of sleep difficulties	Categorical	79%
A history of eating disturbance	Categorical	96%

Variable	Type of Data	Percentage of Data Acquired
Medical Information:		
List of current medications	Categorical	89%
Documented allergies	Categorical	69%
Weekly alcohol intake in units	Continuous	93%
Current or history of illicit drug use	Categorical	93%
A known family history of medical illness	Categorical	93%

As not all patients attending the BGC undergo both an ADI-R and AGOS-G assessment, acquisition rates for those variables appear falsely low. However, when examining rates of participants who completed either the ADI-R, the ADOS-G or both, acquisition rates rise to 97%. Only 3% (14 participants) did not undergo an ADI-R or ADOS-G assessment. Acquisition rates for data relating to the ADI-R and ADOS-G are outlined in Table 3.2.

Table 3.2

Acquisition Rates for Data Relating to Diagnostic Tools

Variable	Type of Data	Percentage of Data Acquired
Autism Diagnostic Interview, Revised (ADI-R) only	Continuous	42%
Autism Diagnostic Observational Schedule, Generic (ADOS-G) only	Continuous	51%
ADI-R or ADOS-G or both	Continuous	97%

Assessments in the BGC were undertaken by eight consultant psychiatrists (CM, DM, DR, IJ, JZ, MC, MCA and QD), thirty two non-consultant hospital doctors (AK, AM, AV, BS, BSR, CM, CO, FM, FO, GMA, IJ, JJ, JK, JKH, JZ, KL, LOR (myself), MAM, MF, MP, PB, PJ, RA, RT, SC, SK, SM, SS, ST, SW, TL and WK) and thirteen psychologists / clinical nurse practitioners (CM, DS, DW, EW, GR, HD, HH, HQ, MJD, NG, PJ, TC and TL), as outlined in Figure 3.2, 3.3 and 3.4. There was no relationship between the consultant psychiatrist assessing each participant in the BGC and receipt of a diagnosis of autism spectrum disorder, a comorbid psychiatric or rates of reported physical illness.

Figure 3.2 Pie Chart Representing Number of Participants Assessed by each Consultant Psychiatrist

Figure 3.3 Pie Chart Representing Number of Participants Assessed by each Non-consultant Hospital Doctor

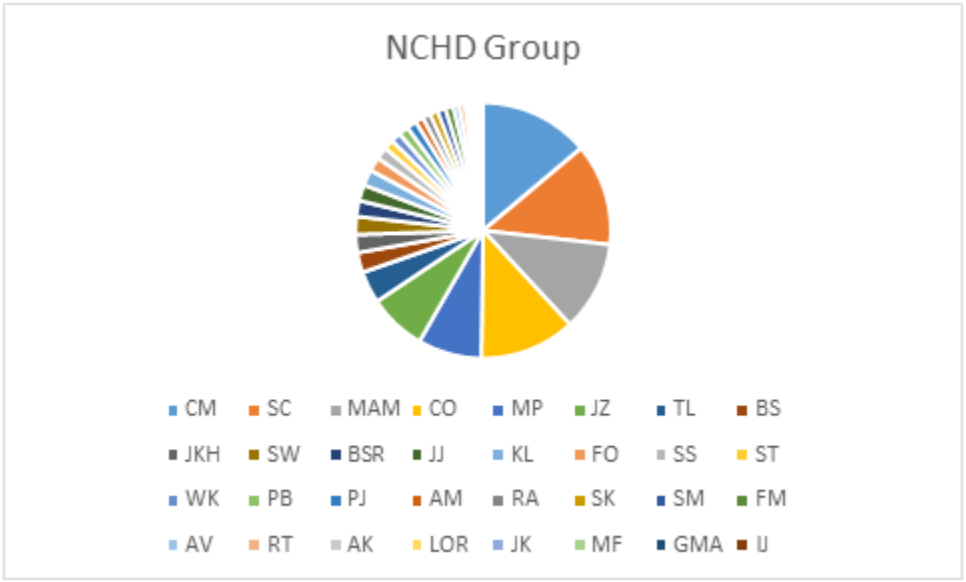
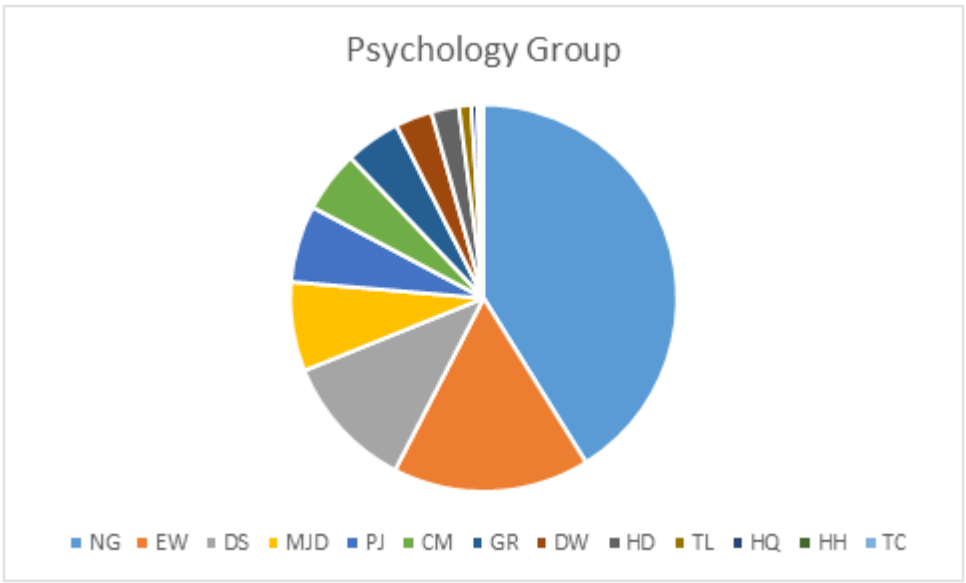


Figure 3.4 Pie Chart Representing Number of Participants Assessed by each Psychologist or Clinical Nurse Practitioner



3.3 Results of Analysis of Demographic Variables

3.3.1 Characteristics of Study Sample

The study group, of 413 participants, consisted of 299 (72%) males and 114 (28%) females, with a male-to-female ratio of 2.6:1. Demographic results are outlined in Table 3.3. The study group comprised of adults only, ranging in age from 18 - 70 years (mean age 32 years, SD 11.6 years). Of these, 253 (61%) were single, 115 (28%) were in a relationship (partner, engaged or married), 20 (5%) were separated, divorced or widowed and marital status was unavailable for 25 (6%). Two hundred and five (50%) participants were unemployed, 122 (30%) were recorded as in gainful employment, 52 (13%) were in education, 18 (4%) were active volunteers and 1 participant was retired.

Study participants were referred to the assessment clinic by their community mental health team (67%) or general practitioner (33%) for assessment of autism spectrum disorder. Two hundred and ninety four (71%) attended their assessment with a companion, typically a first degree relative (58%) while 112 (27%) participants attended alone.

A previous diagnosis of autism spectrum disorder, provided by another clinical team, was noted for 56 individuals in the study group, 50 of which were upheld and 6 were refuted. Two hundred and thirty seven participants received the diagnosis of autism spectrum disorder for the first time at the Behavioural Genetics Clinic, that is they were diagnosed for the first time in adulthood.

Three hundred and twenty four (79%) participants in the total study group were found to have a comorbid psychiatric illness at the time of assessment. Three hundred and thirty three (81%) participants reported a previously diagnosed physical illness, 165 (40%) reported sleep difficulties and 87 (21%) described appetite disturbance. A total of 223 (54%) participants were taking medication to treat a psychiatric or physical illness. Two hundred and sixty five (64%) participants had a family history of other psychiatric illness while 110 (27%) were noted to have a positive family history of autism spectrum disorder.

Table 3.3 Characteristics of Study Sample	
Characteristic	**Study Group**
Total number	413
Age in years	Range 18 - 70 Mean 32 (SD 11.6)
Gender ratio; M:F	2.6:1
Referral source	CMHT 67.3% GP 32.7%
Marital status	Single 61.3% Relationship 27.8%
Accommodation; Participant living with…	Alone 19% Family 55.6% Partner 17.6% *Other 7.8%
Employment status	Unemployed 49.6% In fulltime education 12.6% Volunteer 4.4% Employed 29.5%
Bullied in school	Yes 61.3% No 38.7%
Progressed to third level education	Yes 33.2% No 59.8%
Forensic history	Yes 31% No 62%
Smoking status	Smoker 15.3% Non-smoker 63.2%

Characteristic	Study Group
Alcohol intake per week in standard unit measures	Range 0 - 280 units Mean 7.8 (SD 26.3)
Current use of illicit substances	Current drug user 9%
Historical use of illicit substances	Previous drug user 36.8%

*Other accommodation includes: psychiatric inpatient unit, supported accommodation, living with friends or homeless accommodation

3.3.2 Characteristics of Participants with Autism Spectrum Disorder

Two hundred and eighty eight (70%) individuals in the study group were confirmed to have autism spectrum disorder following assessment at the Behavioural Genetics Clinic. They are referred to as the 'ASD group' throughout this results chapter. The 288 individuals under study as the ASD group consisted of 212 (74%) males and 76 (26%) females; the male-to-female ratio was 2.8:1. Age ranged from 18 - 67 years (mean age 31 years, SD 11.1 years).

Asperger's syndrome was the most frequent diagnosis, at 144 participants (35%), followed by 77 participants with atypical autism (19%), 35 with childhood autism (9%) and 32 with pervasive developmental delay-not otherwise specified (8%). No patient received a diagnosis of Rett's syndrome or childhood disintegrative disorder.

One hundred and eighty four (64%) participants with autism spectrum disorder were single, 77 (27%) were in a relationship (partner, engaged or married), 10 (3%) were separated or divorced and 1 participant was widowed, marital status was unavailable for 16 (6%) participants. One hundred and fifty one (52%) participants in the ASD group were unemployed, 78 (27%) were recorded as in gainful employment, 38 (13%) in fulltime education, 13 (5%) participants were active volunteers and 1 individual was retired.

Participants in the ASD group were referred for assessment by their community mental health team consultant psychiatrist (65%), general practitioner (33%) or community mental health team psychologist (2%).

Two hundred and nineteen (76%) participants in the ASD group were found to have a comorbid psychiatric illness at the time of assessment. Two hundred and forty one (84%) participants reported a previously diagnosed physical illness. One hundred and twenty one (42%) reported sleep difficulties while 71 (25%) described appetite disturbance. One hundred and sixty four (57%) participants were taking a medication to treat a psychiatric or physical illness. Eighty six (30%) participants were noted to have a positive family history of autism spectrum disorder while 186 (65%) had a family history of other psychiatric illness.

3.3.3 Comparing Characteristics by Autism Spectrum Disorder Subtype

Participants with autism spectrum disorder received definitive ICD-10 subtype diagnoses following assessment by the multidisciplinary team. Of the 288 participants with autism spectrum disorder, 144 (35%) received a diagnosis of Asperger's syndrome, 77 (19%) were identified as atypical autism, 35 (9%) as childhood autism and the remaining 32 (8%) with PDD-nos.

There were no statistically significant differences between the four groups in terms of age, gender, source of referral, marital status, living conditions and progression to third level education. At initial analysis, they did however show statistical differences in employment rates, likelihood of being bullied in school, smoking status and forensic history. Individuals with childhood autism were least likely to be smokers, those with Asperger's syndrome were more likely to be in employment and least likely to have a forensic record and those with PDD-nos were most likely to have a forensic record. Due to the large number of tests involved in calculating differences between ASD subtypes across 13 variables, Bonferroni correction reduced the statistically significant p-value to 0.009. Following correction for multiple testing, statistical significance was lost for each of these four comparisons.

Characteristics of participants by ASD subtype are outlined in Table 3.4.

Table 3.4

Characteristics of Participants by ASD Subtype

Characteristic	Asperger's Syndrome	Atypical Autism	Childhood Autism	PDD-nos	*p-value* BFC: n=52, p<0.009
Total	144	77	35	32	-
Age in years	Range 18-65 mean 31 (SD 10.8)	Range 18-65 mean 29 (SD 10.9)	Range 18-50 mean 30 (SD 9.7)	Range 19-67 mean 37 (SD 12.7)	0.03
Gender ratio, M:F	2.2:1	4.1:1	4:1	2.6:1	0.29
Referral source	CMHT 65.3% GP 34.7%	CMHT 64.9% GP 35.1%	CMHT 71.5% GP 28.6%	CMHT 75% GP 25%	0.84
Marital status	Single 66% Relationship 30.5%	Single 64.9% Relationship 26%	Single 71.4% Relationship 25.7%	Single 43.8% Relationship 46.8%	0.37
Accommodation; Participant living..	Alone 35.4%	Alone 29.9%	Alone 28.6%	Alone 43.8%	0.27
Employment status	Unemployed 66% Employed 32.6%	Unemployed 71.4% Employed 24.7%	Unemployed 82.9% Employed 17.1%	Unemployed 78.1% Employed 15.6%	0.04 (Cramer's V 0.16, small effect size)
Bullied in school	Yes 63.2% No 26.4%	Yes 66.2% No 22.1%	Yes 54.3% No 37.1%	Yes 59.4% No 31.3%	0.17
Progressed to third level education	Yes 31.3% No 62.5%	Yes 36.4% No 50.6%	Yes 28.6% No 65.7%	Yes 40.6% No 53.1%	0.62

Characteristic	Asperger's Syndrome	Atypical Autism	Childhood Autism	PDD-nos	*p-value* BFC: n=52, p<0.009
Forensic history	Yes 22.9% No 70.8%	Yes 55.8% No 33.8%	Yes 37% No 57%	Yes 43.8% No 50%	0.02 (Cramer's V 0.20, small effect size)
Smoking status	Smoker 13.9% Non-smoker 68.1%	Smoker 9.1% Non-smoker 66.2%	Smoker 11.4% Non-smoker 68.6%	Smoker 15.6% Non-smoker 56.3%	0.89
Alcohol intake per week in standard unit measures	Range 0-210 Mean 8.10 (SD 24.86)	Range 0-280 Mean 10.84 (SD 41.17)	Range 0-32 Mean 2.06 (SD 5.78)	Range 0-24 Mean 3.37 (SD 6.45)	0.01
Current use of illicit substances	Current drug user 4.2%	Current drug user 11.7%	Current drug user 5.7%	Current drug user 12.5%	0.13
Historical use of illicit substances	Previous drug user 28.5%	Previous drug user 35.1%	Previous drug user 28.6%	Previous drug user 43.8%	0.29

3.3.4 Characteristics of Participants without Autism Spectrum Disorder

One hundred and twenty five (30%) individuals in the study group did not fulfil diagnostic criteria for autism spectrum disorder. These individuals are referred to as the 'nonASD group' in this results chapter. The nonASD group consisted of 87 (70%) males and 38 (30%) females; ratio of males to females was 2.3:1, ranging in age from 18 - 70 years (mean age 34 years, SD 12.7 years).

Sixty nine (55%) participants in the nonASD group were single, 38 (30%) were in a relationship (partner, engaged or married), 9 (7%) were separated or divorced and marital status was unavailable for 9 (7%) participants. Fifty four (43%) participants in the nonASD group were unemployed, 45 (36%) were recorded as in gainful employment, 14 (11%) in fulltime education and 5 (4%) participants were active volunteers.

Participants were referred for assessment by their community mental health team consultant psychiatrist (63%), general practitioner (33%) or community mental health team psychologist (4%).

Although no participant in the nonASD group was diagnosed with autism spectrum disorder, 105 (84%) received a diagnosis of an alternative psychiatric illness, 19 (15%) were not diagnosed with a psychiatric illness and data were missing in relation to one participant. Forty eight (38%) individuals were diagnosed with an anxiety spectrum disorder, 37 (30%) with attention deficit hyperactivity disorder, 26 (21%) with a mood disorder, 17 (14%) with a personality disorder, 10 (8%) with schizophrenia, 5 (4%) with a substance use disorder, 2 with an eating disorder and one each for attachment disorder, cognitive impairment, gender identity disorder and psychosexual disorder.

Ninety two (74%) participants reported a previously diagnosed physical illness. Forty four (35%) reported sleep difficulties while 16 (13%) described appetite disturbance. Fifty nine (50%) participants were taking medication to treat a psychiatric or physical illness. Twenty four (19%) participants were noted to have a positive family history of autism spectrum disorder and 79 (63%) had a family history of other psychiatric illness.

3.3.5 Comparison between the ASD and NonASD Groups

Comparing the ASD to nonASD samples, demographics between the groups were largely similar. However, there was a statistical difference in employment rates, likelihood of being bullied in school, smoking status and historical use of illicit substances. Participants with autism spectrum disorder were statistically more likely to report a history of childhood school-yard bullying and statistically less likely to have a history of illicit drug use. There was also a non-significant trend among the ASD group towards being unemployed, living in the company of others and non-smoking. Characteristics of ASD and nonASD groups are outlined in Table 3.5.

Table 3.5 Characteristics of ASD and NonASD Groups			
Characteristic	**ASD group**	**NonASD group**	***p-value*** **BFC: n=13, p<0.004**
Total	288	125	-
Age in years	Range 18 - 67 Mean 33 (SD 11.1)	Range 18 - 70 Mean 31 (SD 12.7)	0.09
Gender ratio, M:F	2.8:1	2.3:1	0.40
Referral source	CMHT 67.4% GP 32.6%	CMHT 67.2% GP 32.8%	0.68
Marital status	Single 63.9% Relationship 26.8%	Single 55.2% Relationship 30.4%	0.11
Accommodation; Participant living with…	Alone 19% Family 57% Partner 16.5% Other 7.5%	Alone 19.3% Family 52.3% Partner 20.1% Other 8.3%	0.08
Employment status	Unemployed 52.4% In education 13.2% Volunteer 4.5% Employed 27%	Unemployed 43.2% In education 11.2% Volunteer 4% Employed 36%	0.03 (Cramer's V 0.11, small effect size)
*Bullied in school	Yes 62.5% No 27.1 %	Yes 36% No 51.2%	<0.001* (Cramer's V 0.27, small to medium effect size)

Characteristic	ASD group	NonASD group	*p-value* **BFC: n=13, p<0.004**
Progressed to third level education	Yes 33.3% No 58.7%	Yes 32.8% No 62.4%	0.74
Forensic history	Yes 30.6% No 62.2%	Yes 32% No 61.6%	0.81
Smoking status	Smoker 12.5% Non-smoker 66.3%	Smoker 21.6% Non-smoker 56%	0.01 (Cramer's V 0.14, small effect size)
Alcohol intake per week in standard unit measures	Range 0 - 280 Mean 7.64 (SD 28.2)	Range 0 - 140 Mean 8.17 (SD 21.4)	0.85
Current use of illicit substances	Current drug user 7.3%	Current drug user 12.8%	0.68
*Historical use of illicit substances	Previous drug user 31.9%	Previous drug user 48%	0.001* (Cramer's V 0.17, small effect size)

* Statistically significant results after correction for multiple testing are marked with an asterisk

3.4 Results of Analysis of Psychiatric Illness Variables

3.4.1 Results for Comorbid Psychiatric Illness in Study Sample

A total of 324 participants in the overall study group were diagnosed with a comorbid psychiatric illness by the BGC consensus group. Two hundred and nineteen (76%) participants in the ASD group received a diagnosis of comorbid psychiatric illness. Comparatively, 105 (84%) of the nonASD participants were diagnosed with a psychiatric illness. One hundred and thirty six (62%) ASD group participants received a single comorbid diagnosis alongside the diagnosis of autism spectrum disorder, 65 (30%) participants were diagnosed with two comorbid psychiatric illnesses, 14 (6%) with 3 psychiatric illnesses, 2 (1%) with 4 psychiatric diagnoses and 1 participant received 7 comorbid psychiatric diagnoses. At initial analysis a statistical difference

was noted in rates of comorbid psychiatric illness between the groups with individuals with autism spectrum disorder statistically more likely to suffer from comorbid psychiatric illness compared to those without an ASD diagnosis. On correction for multiple testing this statistical significance was lost. However OCD remained statistically more likely in participants with autism spectrum disorder. Interestingly, this was the only psychiatric illness to trend towards the ASD group. In fact, participants in the nonASD group, those without a diagnosis of autism spectrum disorder, were more likely to have a comorbid psychiatric illness. Personality disorder was statistically more likely among the nonASD group. Psychotic disorder also trended towards the neurotypical participants, however this finding did not retain statistical significance following correction for multiple testing.

Rates of current psychiatric illness as seen in the study group of adults with and without autism spectrum disorder are outlined in Table 3.6 and Figure 3.5.

Table 3.6

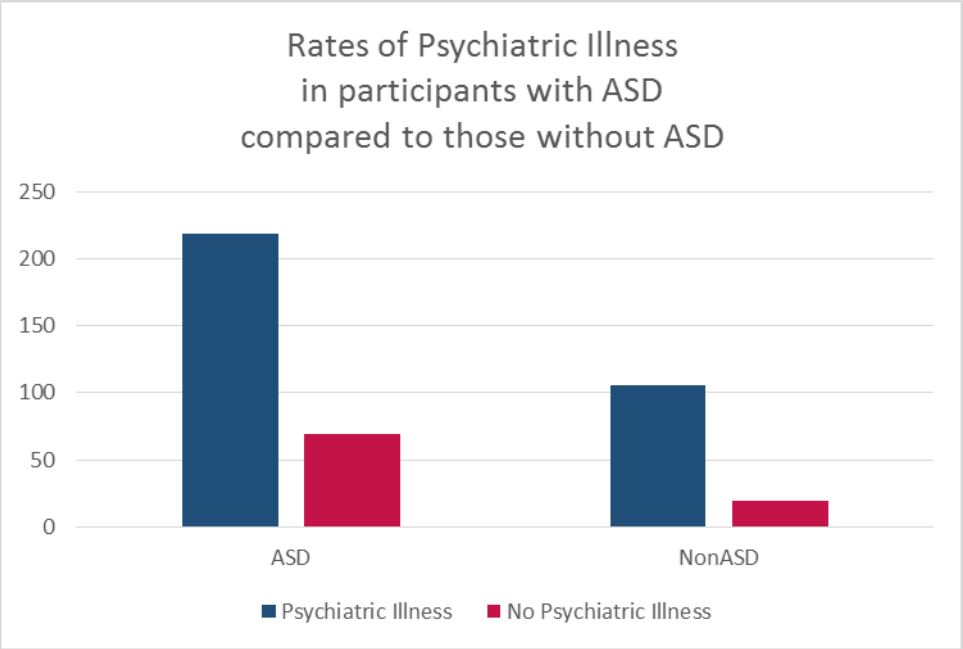
Current Comorbid Psychiatric Disorders in Adults with and without Autism Spectrum Disorder

Diagnosis	**ASD group n (%)**	**NonASD group n (%)**	***p-value*** **BFC: n=9, p<0.006**
Comorbid psychiatric illness	219 (76%)	105 (84.4%)	0.05
*Anxiety spectrum disorders	142 (49.3%)	48 (38.4%)	Agoraphobia 0.09 Social phobia 0.77 GAD 0.17 OCD 0.001* (Cramer's V 0.16, small effect size) Specific phobia 0.29 Somatoform disorder 0.91 PTSD 0.35
Attention deficit hyperactivity disorder	79 (27.4%)	37 (29.6%)	0.65

Diagnosis	**ASD group** **n (%)**	**NonASD group** **n (%)**	***p-value*** **BFC: n=9, p<0.006**
Mood disorder	72 (25%)	26 (20.8%)	Depression 0.43 Bipolar 0.59
History of deliberate self-harm	71 (24.7%)	34 (27.2%)	0.59
History of self-injurious behaviour	44 (15.3%)	17 (13.6%)	0.46
Psychotic illness	11 (3.8%)	10 (8%)	0.05
*Personality disorder	7 (2.4%)	17 (13.6%)	<0.001* (Cramer's V 0.23, small to medium effect size)
Substance use disorder	6 (2.1%)	5 (4%)	Alcohol dependency 0.87
Tic disorder / Tourette's syndrome	3 (1%)	0%	0.31
Eating disorder	1 (0.3%)	2 (1.6%)	0.17
Catatonia	0%	0%	n/a

* Statistically significant results after correction for multiple testing are marked with an asterisk

Figure 3.5 Diagnosis of Comorbid Psychiatric Illness in Participants with Autism Spectrum Disorder Compared to those without Autism Spectrum Disorder



3.4.2 Results for Comorbid Psychiatric Illness in ASD Group

Anxiety spectrum disorders were the most common comorbid psychiatric diagnosis in participants with autism spectrum disorder. Almost half of the ASD group (49%) suffered from a comorbid anxiety spectrum disorder. Obsessive compulsive disorder was the most frequent at 23%, followed closely by generalised anxiety disorder (20%), social phobia (19%) and agoraphobia with or without panic disorder was noted in 37 (13%) participants.

Table 3.7 Comorbid Anxiety Spectrum Disorders in ASD Group	
Diagnosis	**ASD Group** **n (%)**
Obsessive compulsive disorder	65 (22.6%)
Generalised anxiety disorder	58 (20.1%)
Social phobia	54 (18.8%)
Agoraphobia	37 (12.8%)
Social anxiety	5 (1.7%)
Specific phobia	3 (1%)
Mixed anxiety and depression	2 (0.7%)
Somatoform disorder	2 (0.7%)
Post-Traumatic stress disorder	2 (0.7%)
Mixed anxiety disorder	1 (0.3%)

Attention deficit hyperactivity disorder was the second most frequent comorbid diagnosis with 79 (27%) participants receiving a diagnosis of childhood attention deficit hyperactivity disorder.

Mood disorder, combining depressive and bipolar illnesses was ranked third. Depressive illness including mild, moderate and severe depression, recurrent depressive disorder (both currently depressed and in remission) and dysthymia was noted in 65 participants (23%). Of the 65 participants with depressive disorders; 12 had current mild depression, 17 had current moderate depression, 1 with current severe depression with psychotic symptoms, 1 with current severe depression without psychotic symptoms, 24 with recurrent depressive disorder (5 in remission), 9 with dysthymia and 1 with moderate depression superimposed on dysthymia. Bipolar affective disorder was diagnosed in 7 (2%) individuals. Of the 7 individuals with bipolar affective disorder examined in this study, 3 were euthymic at the time of assessment, 1 suffering from mild depression, 2 with moderate depression and 1 was noted to be hypomanic.

Table 3.8 Comorbid Mood Disorders in ASD Group	
Diagnosis	**ASD Group** **n (%)**
Recurrent depressive disorder	24 (8.3%)
Moderate depressive episode	18 (6.3%)
Mild depressive episode	12 (4.2%)
Dysthymia	10 (3.5%)
Bipolar affective disorder	7 (2.4%)
Severe depressive episode	1 (0.3%)
Severe depressive episode with psychotic symptoms	1 (0.3%)

For the purposes of this study, deliberate self-harm and self-injurious behaviour were analysed separately. Deliberate self-harm included attempted self-drowning, attempted self-hanging, self-burning, self-cutting, jumping from a height and overdose. Self-injurious behaviour referred to hair pulling, head-banging, self-biting, self-punching, self-scratching, skin picking and damage to property or self.

Deliberate self-harm was noted in 71 (25%) participants with autism spectrum disorder, self-injurious behaviour followed closely at 15%. A number of participants were noted to engage in both deliberate self-harm and self-injurious behaviour while a large proportion engaged in multiple methods of harm / self-injury.

Table 3.9 Comorbid Self-harm and Self-injury in ASD Group	
Method of self-harm / self-injury	**ASD Group** **n (%)**
Self-cutting	42 (14.6%)
Overdose	33 (11.5%)
Head-banging	20 (6.9%)
Attempted self-hanging	14 (4.9%)
Self-scratching	11 (3.8%)
Self-burning	8 (2.8%)
Damage to property and self	7 (2.4%)
Self-biting	6 (2.1%)
Self-punching	6 (2.1%)
Skin picking	5 (1.7%)
Hair pulling	4 (1.4%)
Jump from a height	4 (1.4%)
Attempted self-drowning	2 (0.7%)

A psychotic illness was diagnosed in 11 (4%) participants with autism spectrum disorder. All participants received the diagnosis of schizophrenia. The category divided into paranoid schizophrenia (10 participants, 4%) and treatment resistant schizophrenia (1 participant, 0.3%). Nine of the 11 participants were unwell at the time of assessment with evidence of both positive and negative symptoms of schizophrenia. The most common positive symptoms were paranoid and persecutory delusions. Three participants were experiencing auditory hallucinations and 1 participant was experiencing visual hallucinations.

Personality disorder was the next most frequent comorbid psychiatric diagnosis among the ASD group. A total of 7 (2%) participants were diagnosed with a personality disorder. Personality disorders included paranoid personality disorder (3 participants,

1%), emotionally unstable personality disorder (2 participants, 0.7%), anankastic personality disorder (1 participant 0.3%) and schizotypal personality disorder (1 participant, 0.3%).

Substance use disorder occurred at a rate of 2% in participants with autism spectrum disorder. Alcohol dependence was the most common at 1% (4 participants), followed by 1 participant each for opiate and caffeine addiction.

Eating disorder was diagnosed in a single participant (0.3%). This participant was female with a diagnosis of anorexia nervosa and was noted to be actively unwell at the time of assessment with fasting and binge / purge behaviours.

A trend was noted in the combinations of comorbidities in those with autism spectrum disorder. A notable 56% of the ASD group suffered from co-existing mood disorder and anxiety spectrum disorder. The next most frequent association was between attention deficit hyperactivity disorder and anxiety spectrum disorder at 26%, followed by attention deficit hyperactivity disorder and mood disorder at 16%.

3.4.3 Results for Comorbid Psychiatric Illness in Autism Spectrum disorder - ASD Subtype

There was a statistically higher chance of having a diagnosis of any comorbid psychiatric illness if an individual was diagnosed with Asperger's syndrome compared to the other three subtypes of autism spectrum disorder recorded in this study. Comorbid obsessive compulsive disorder was statistically more likely in those with Asperger's syndrome. Though rare, personality disorder was more likely if the participant suffered from pervasive developmental disorder - not otherwise specified though this did not reach statistical significance. There was also a non-significant trend for self-injurious behaviour in those with childhood autism and atypical autism.

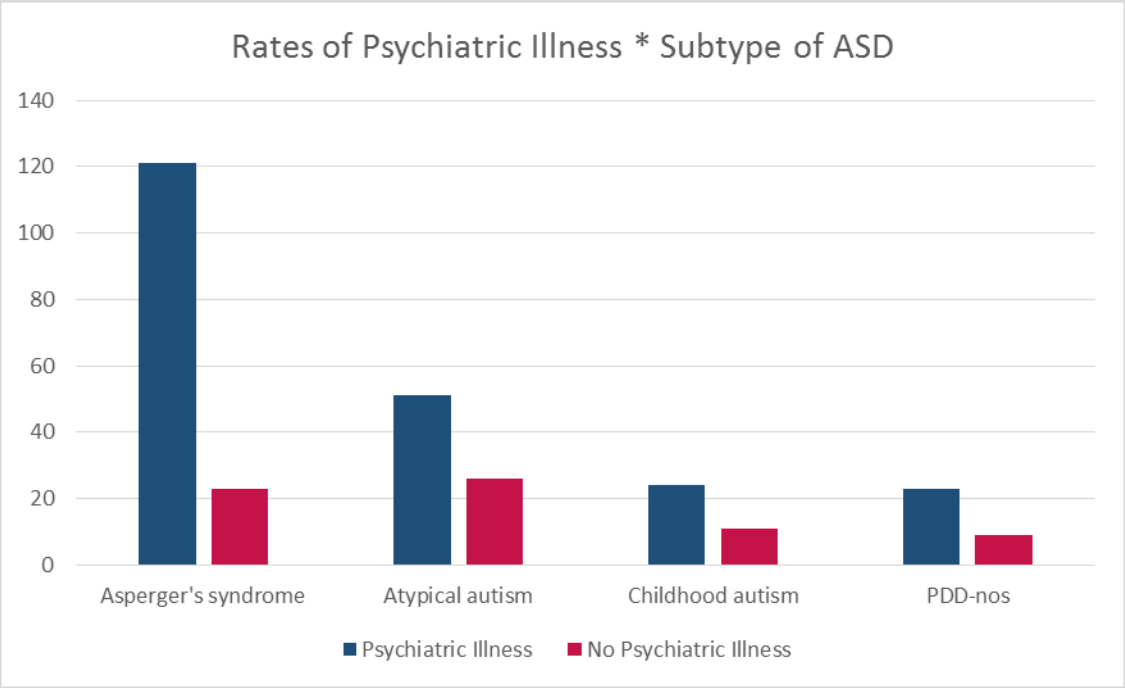
Table 3.10

Comorbid Psychiatric Illness in Adults with Autism Spectrum Disorder - ASD Subtype

Diagnosis	Asperger's Syndrome	Atypical Autism	Childhood Autism	PDD-nos	*p-value* BFC: n=40, p<0.001
Comorbid psychiatric illness	Yes 84% No 16%	Yes 66.2% No 33.8%	Yes 68.6% No 31.4%	Yes 71.9% No 28.1%	0.004
ADHD	Yes 27% No 73%	Yes 32.5% No 67.5%	Yes 20% No 80%	Yes 25% No 75%	0.56
Depression	Yes 25% No 75%	Yes 18.2% No 81.8%	Yes 11.4% No 88.6%	Yes 12.5% No 87.5%	0.16
Agoraphobia	Yes 14.6% No 85.4%	Yes 11.7% No 88.3%	Yes 5.7% No 94.3%	Yes 15.6% No 84.4%	0.51
Social phobia	Yes 23.6% No 76.4%	Yes 10.4% No 89.6%	Yes 17% No 83%	Yes 18.8% No 81.2%	0.12
GAD	Yes 20% No 80%	Yes 18% No 82%	Yes 17% No 83%	Yes 75% No 25%	0.83
*OCD	Yes 30% No 70%	Yes 11.7% No 88.3%	Yes 25.7% No 74.3%	Yes 12.5% No 87.5%	<0.001* (Cramer's V 0.24, small to medium effect size)
History of deliberate self-harm	Yes 21.5% No 78.5%	Yes 30% No 70%	Yes 17.1% No 82.9%	Yes 34.4% No 65.6%	0.21
History of self-injurious behaviour	Yes 13.2% No 86.8%	Yes 18.2% No 81.8%	Yes 28.6% No 71.4%	Yes 6.3% No 93.8%	0.06
Psychotic illness	Yes 2.8% No 97.2%	Yes 2.6% No 97.4%	Yes 2.9% No 97.1%	Yes 9.4% No 90.6%	0.29
Personality disorder	Yes 1.4% No 98.6%	Yes 1.3% No 98.7%	Yes 2.9% No 97.1%	Yes 6.3% No 93.8%	0.33

* Statistically significant results after correction for multiple testing are marked with an asterisk

Figure 3.6 Diagnosis of Comorbid Psychiatric Illness - ASD Subtype



3.4.4 Results for Comorbid Psychiatric Illness in Autism Spectrum disorder - Age

In line with recommendations made by previous literature, two methods were employed to assess rates of comorbid psychiatric illness in the ASD group. Firstly, the ASD group was split at its median age (29 years) into younger adults and older adults. The groups' diagnostic rates of total comorbid psychiatric illness remained equal at 76% each (p = 1.00). If however, psychiatric comorbidity is broken down by illness / diagnosis, there is a statistically higher chance of being diagnosed with self-injurious behaviour (p = 0.03) and attention deficit hyperactivity disorder (p <0.001) if aged less than 29 years and with depression (p = 0.04) and personality disorder (p = 0.04) if aged over 29 years.

Next, 50 years was investigated as the cut-off point from younger adulthood into older adulthood. Again the rates of total comorbid psychiatric illness remained largely equal, 83% and 93%, with no statistical difference between groups (p = 0.64). The only statistically significant illness seen when the groups were analysed by individual

psychiatric illness, where the over 50 age group was statistically more likely to suffer from comorbid generalised anxiety disorder (p = 0.01).

Comorbid psychiatric illness in adults with autism spectrum disorder according to age is outlined in Table 3.11.

Table 3.11

Comorbid Psychiatric Illness in Adults with Autism Spectrum Disorder - Age

Diagnosis	**Age <29 years**	**Age >29 years**	***p-value***
Comorbid psychiatric illness	Yes 114 No 36	Yes 105 No 33	1.00
Diagnosis	**Age <50 years**	**Age >50 years**	***p-value***
Comorbid psychiatric illness	Yes 208 No 67	Yes 11 No 2	0.64

3.4.5 Results for Comorbid Psychiatric Illness in Autism Spectrum disorder - Gender

A comorbid psychiatric illness was diagnosed in 78% of males and 81% of females in the ASD group. There was no statistical difference in overall receipt of a psychiatric illness diagnosis between the groups stratified by gender. However, on initial analysis by individual disorder significantly more females than males with autism spectrum disorder had a diagnosis of comorbid bipolar affective disorder (p = 0.01). This finding did not retain statistical significance on correction for multiple testing as the Bonferroni critical value was p<0.004.

Table 3.12 Comorbid Psychiatric Illness in Adults with Autism Spectrum Disorder - Gender			
Diagnosis	**Males**	**Females**	***p-value*** **BFC: n=14, p<0.004**
Comorbid psychiatric illness	Yes 77.9% No 22.1%	Yes 80.7% No 19.3%	0.82
ADHD	Yes 28.4% No 71.6%	Yes 27.2% No 72.8%	1.00
Depression	Yes 17.7% No 82.3%	Yes 22.8% No 77.2%	0.69
BPAD	Yes 1% No 99%	Yes 5.3% No 94.7%	0.006
Agoraphobia	Yes 11.7% No 88.3%	Yes 9.6% No 90.4%	0.92
Social phobia	Yes 18.4% No 81.6%	Yes 21.1% No 78.9%	0.93
GAD	Yes 18.7% No 81.3%	Yes 17.5% No 82.5%	0.35
OCD	Yes 18.7% No 81.3%	Yes 17.5% No 82.5%	0.31
History of deliberate self-harm	Yes 22.2% No 77.8%	Yes 31.6% No 68.4%	0.14
History of self-injurious behaviour	Yes 15.6% No 84.4%	Yes 15.8% No 84.2%	1.00
Psychotic illness	Yes 5.7% No 94.3%	Yes 2.6% No 97.4%	1.00
Personality disorder	Yes 4.7% No 95.3%	Yes 7.9% No 92.1%	0.07

Diagnosis	Males	Females	*p-value* **BFC: n=14, p<0.004**
Alcohol dependence	Yes 1.7% No 98.3%	Yes 0.9% No 99.1%	1.00
Eating disorder	Yes 0% No 100%	Yes 2.6% No 97.5%	0.59
Historical use of illicit substances	Yes 33.5% No 59%	Yes 29.6% No 69.7%	0.29

* Statistically significant results before correction for multiple testing are marked with an asterisk

3.5 Results of Analysis of Physical Illness Variables

3.5.1 Results for Comorbid Physical Illness in Study Sample

A wide range of lifetime and current physical morbidity was reported by adult participants with normal IQ autism spectrum disorder assessed in this study. Table 3.13 outlines the range of conditions described.

Table 3.13

Physical Illnesses within each System-Related Category

Bodily System	Physical Illness
Neurological Conditions	• Bell's palsy • Cerebral atrophy • Cluster / recurrent headaches • Epilepsy • Febrile convulsion • Head injury • Hydrocephalus • Meningitis • Migraine • Myasthenia gravis • Neuropathic pain • Pituitary adenoma • Recurrent blackouts • Spina bifida • Vertigo

Respiratory Conditions	• Asthma • Bronchitis • Hayfever • Obstructive sleep apnoea • Pulmonary embolism • Recurrent cough • Recurrent lower respiratory tract infection • Sarcoidosis • Tuberculosis
Orthopaedic Conditions	• Accidental bone fracture • Gout • Hip pain • Knee surgery • Kyphoscoliosis • Kyphosis • Osteoarthritis • Polydactyly • Rheumatoid arthritis • Scoliosis • Spondylosis • Traumatic bone fracture
Gastrointestinal Conditions	• Appendicectomy • Cholecystectomy • Cholecystitis • Chron's disease • Coeliac disease • Constipation • Gastritis • Gastroesophageal reflux disease • Haemorrhoids • Hernia • Irritable bowel syndrome • Liver abscess • Pancreatitis • Pilonidal sinus • Primary biliary cirrhosis • Repair of twisted mesentery • Ulcerative colitis
Ear, Nose and Throat Conditions	• Adenoidectomy • Chronic rhinitis • Cleft palate • Hearing impairment • Nasal polyps • Recurrent nose bleeds • Recurrent otitis media • Recurrent tonsillitis

Ear, Nose and Throat Conditions	• Sinusitis • Tinnitus • Tonsillectomy
Genitourinary Conditions	• Amenorrhoea • Benign prostatic hypertrophy • Circumcision • Dysmenorrhoea • Ectopic pregnancy • Endometriosis • Erectile dysfunction • Gender reassignment surgery • Haematuria • Hysterectomy • Menorrhagia • Miscarriage • Nephrectomy • Nocturnal enuresis • Orchidectomy • Orchidopexy • Ovarian cysts • Postpartum haemorrhage • Recurrent renal calculi • Recurrent urinary tract infections • Sterilisation • Termination of pregnancy • Underdeveloped kidneys • Urinary incontinence • Uterine cysts • Uterine fibroids • Uterine prolapse
Cardiac Conditions	• Congenital cardiac defect • Endocarditis • Heart murmur • Hypercholesterolaemia • Hypertension • Hypotension • Intermittent claudication • Kawasaki disease • Myocardial infarction • Myocarditis • Pericarditis • Supraventricular tachycardia • Wolff-Parkinson-White syndrome

Bodily System	Physical Illness
Endocrine Conditions	• Adrenomyeloneuropathy • Diabetes mellitus • Hyperthyroidism • Hypothyroidism • Polycystic ovarian syndrome • Thymectomy
Dermatology Conditions	• Acne • Cold urticaria • Dermatitis • Eczema • Herpes zoster • Psoriasis • Raynaud's disease • Systemic lupus erythematosus • Ulcers
Other Medical Conditions	• Accidental poisoning • Acute lymphoid leukaemia • Anaemia • Beta thalassaemia • Bone cysts requiring chemotherapy • Breast cyst • Clumsiness • Corneal graft • Facial reconstruction • Glaucoma • Hepatitis C • HIV • Lipoma • Obesity • Sciatica • Scotopic photosensitivity syndrome • Seminoma • Septicaemia • Sight Loss • Strabismus

Three hundred and thirty four (81%) participants in the total study sample described a previous or current diagnosis of medical illness, consisting of 237 (71%) males and 97 (29%) females, age range 18 - 70 years (mean age 32 years, SD 11.7 years). Sixty

seven (16%) participants denied a previous history of or current physical illness. Of those who did have a history of physical ill-health or current illness, 33% reported a neurological condition, 22% a respiratory illness, 19% with an orthopaedic condition, 16% with a gastrointestinal diagnosis, 13% an ear nose and throat condition, 12% a genitourinary condition, 11% a cardiac condition, 8% indicated a dermatological diagnosis and 8% an endocrine condition.

Two hundred and forty two (84%) participants in the ASD group endorsed a previous or current medical condition, compared to 92 (74%) of the nonASD group. This difference was not statistically significant. Medical history as reported by the ASD and nonASD groups is outlined in Table 3.14. There was no statistical difference between the groups when assessed for overall or individual physical illness.

Table 3.14

Comorbid Physical Illness in Study Sample

Illness	**ASD group n (%)**	**NonASD group n (%)**	***p-value***
Any comorbid medical condition	242 (84%)	92 (74%)	0.07
Neurological condition	92 (32%)	45 (36%)	0.29
Respiratory condition	61 (21%)	28 (22%)	0.65
Orthopaedic condition	54 (19%)	24 (19%)	0.78
Gastrointestinal condition	52 (18%)	15 (12%)	0.16
ENT condition	43 (15%)	10 (8%)	0.07
Genitourinary condition	40 (14%)	10 (8%)	0.12
Cardiac condition	30 (10%)	15 (12%)	0.55
Dermatological condition	22 (8%)	9 (7%)	0.95
Endocrine condition	27 (9%)	7 (6%)	0.24

3.5.2 Results for Comorbid Physical Illness in ASD Group

Physical illnesses as reported by the ASD group are outlined in Table 3.15. The most commonly reported physical ailments were asthma (16%) and head injury (16%), followed by accidental / traumatic bone fracture (13%), dyspraxia (8%), headache / migraine (7%), recurrent otitis media (7%), hayfever (6%), eczema (5%), hypertension (5%), tonsillitis / tonsillectomy (5%), diabetes mellitus (4%), epilepsy (4%), hernia (4%), irritable bowel syndrome (4%), appendicectomy (3%), hearing impairment (3%), hypothyroidism (3%), obesity (3%), polycystic ovarian syndrome (3%), adenoidectomy (2%), dysmenorrhoea / menorrhagia (2%), constipation / haemorrhoids (2%), hypercholesterolaemia (2%), inflammatory bowel disease (2%), knee surgery (2%), recurrent blackouts (2%), accidental poisoning (1%), arrhythmia (1%), congenital cardiac defect (1%), hyperthyroidism (1%), miscarriage (1%), osteoarthritis (1%), rheumatoid arthritis (1%), recurrent UTI (1%), sight loss (1%), anaemia (0.7%), atopy (0.7%), gout (0.7%), malignant tumour (0.7%), psoriasis (0.7%), Raynaud's disease (0.7%), recurrent renal calculi (0.7%), benign tumours (0.3%), coeliac disease (0.3%), dyslexia (0.3%) and systemic lupus erythematosus (0.3%).

Table 3.15

Comorbid Physical Illness in Adults with Autism Spectrum Disorder

Illness	**Prevalence**
Neurology:	
Head injury	47 (16%)
Headache / Migraine	21 (7%)
Epilepsy	12 (3%)
Recurrent blackouts	6 (2%)
Respiratory:	
Asthma	45 (16%)
Hayfever	16 (6%)

Illness	Prevalence
Orthopaedic:	
Accidental / Traumatic bone fracture	37 (13%)
Knee Surgery	7 (2%)
Osteoarthritis	3 (1%)
Rheumatoid arthritis	3 (1%)
Gout	2 (0.7%)
Gastrointestinal:	
Hernia	12 (4%)
Irritable bowel disease	10 (4%)
Appendicectomy	8 (3%)
Constipation / Haemorrhoids	6 (2%)
Inflammatory bowel disease	5 (2%)
Coeliac disease	1 (0.3%)
Ear, Nose and Throat:	
Recurrent otitis media	19 (7%)
Tonsillitis / Tonsillectomy	13 (5%)
Hearing impairment	9 (3%)
Adenoidectomy	6 (2%)
Genitourinary:	
Dysmenorrhoea / Menorrhagia	7 (2%)
Miscarriage	4 (1%)
Recurrent urinary tract infection	4 (1%)
Recurrent renal calculi	2 (0.7%)

Illness	Prevalence
Cardiac:	
Hypertension	15 (5%)
Hypercholesterolaemia	5 (2%)
Arrhythmia	4 (1%)
Congenital cardiac defect	4 (1%)
Endocrine:	
Diabetes mellitus	11 (4%)
Hypothyroidism	8 (3%)
Polycystic ovarian syndrome	7 (3%)
Hyperthyroidism	3 (1%)
Dermatology:	
Eczema	13 (5%)
Psoriasis	2 (0.7%)
Raynaud’s disease	2 (0.7%)
Systemic lupus erythematosus	1 (0.3%)
Other Medical Conditions:	
Atopy	62 (22%)
Dyspraxia	22 (8%)
Obesity	8 (3%)
Accidental poisoning	4 (1%)
Sight loss	4 (1%)
Anaemia	2 (0.7%)
Malignant tumours	2 (0.7%)
Benign tumours	1 (0.3%)
Dyslexia	1 (0.3%)

Other medical ailments recorded as part of this study, given their relevance in available ASD literature, included sleep difficulties, appetite disturbance, use of medication and allergies. These findings are outlined in section 3.5.6.

As a number of physical diagnoses have been described as highly prevalent in autism spectrum disorder the demographic findings relating to these illnesses were examined in more detail. These included epilepsy, gastrointestinal disorders, dyspraxia and atopy. Twelve participants reported a previous diagnosis of epilepsy. These included 9 males (75%) and 3 females (25%) (p = 0.9). There was no statistically significant increase in either gender and all individuals were noted to be within the younger age bracket of 19 - 31 years (mean 24 years, SD 4.3 years). Age of seizure onset was not available. No particular ASD subtype was over-represented in this group. Of those with a diagnosis of autism spectrum disorder and epilepsy, 58% received a diagnosis of comorbid psychiatric illness; comorbid attention deficit hyperactivity disorder being the most common at 33%, followed by obsessive compulsive disorder (25%) and depression (17%). One individual was diagnosed with a comorbid psychotic disorder. As antipsychotics are known to lower the seizure threshold, the use of prescription medications was examined. Of those with autism spectrum disorder and epilepsy, 66% were on prescribed medication, 4 receiving an antiepileptic drug, 2 on antidepressants, 1 on benzodiazepines and 1 on antipsychotic treatment (Quetiapine 100mg nocte). Only 2 participants in the epilepsy group were in receipt of physical medication, namely treatment for gastrointestinal symptoms and acne.

Gastrointestinal disorders as reported by ASD participants included coeliac disease, constipation, haemorrhoids, hernias, history of appendicectomy, inflammatory bowel disease and irritable bowel disease. A total of 52 (18%) participants reported gastrointestinal symptoms. These included 42 (81%) males and 10 (19%) females aged 22 - 54 years (mean 37 years, SD 14.5 years). Gastrointestinal disorders were over-represented in those with Asperger's syndrome (62%) (p = 0.19) but not to statistical significance.

Dyspraxia was reported by 22 (8%) participants. These included 15 (68%) males and 7 (32%) females (p = 0.74), aged 18 - 50 years (mean 29 years, SD 11.4 years). Dyspraxia was noted for 10 (46%) individuals with Asperger's syndrome, 8 (36%) of those with atypical autism, 3 (14%) with childhood autism and 1 (4%) with PDD-nos.

Atopy, referring to eczema, allergic rhinitis and asthma, was reported by 62 (22%) participants. Although three individual ailments, this is the highest reported physical illness among the ASD group. Forty four (71%) males and 18 (29%) females ranging in age from 18 - 50 years (mean 30 years, SD 10.0 years) reported a prior diagnosis of eczema, allergic rhinitis or asthma. These conditions were reported most frequently by individuals with Asperger's syndrome (53%), followed by atypical autism (23%), childhood autism (16%) and PDD-nos (8%).

3.5.3 Results for Comorbid Physical Illness in Autism Spectrum Disorder - ASD Subtype

At initial analysis, a statistically higher risk for cardiac condition was noted among those with a diagnosis of PDD-nos compared to other subtypes of autism spectrum disorder. However, this statistical difference did not remain following correction for multiple testing as 36 tests reduced the Bonferroni critical value to $p<0.001$. Results relating to each comorbid physical condition recorded in adults with autism spectrum disorder, stratified by ASD subtype is outlined in Table 3.16.

Table 3.16

Comorbid Physical Illness in Adults with Autism Spectrum Disorder - ASD Subtype

Diagnosis	Asperger's Syndrome	Atypical Autism	Childhood Autism	PDD-nos	*p-value* BFC: n=36, p<0.001
Any comorbid medical condition	Yes 88.2% No 10.4%	Yes 76.6% No 22.1%	Yes 91.4% No 8.6%	Yes 75% No 18.8%	0.04
Neurological condition	Yes 32.6% No 66%	Yes 27.3 % No 71.4%	Yes 48.6% No 51.4%	Yes21.9 % No 68.8%	0.12
Respiratory condition	Yes 23.6% No 75%	Yes15.6 % No 83.1%	Yes 28.6% No 71.4%	Yes 15.6% No 75%	0.35
Orthopaedic condition	Yes 20.1% No 78.5%	Yes 14.3% No 84.4%	Yes 17.1% No 82.9%	Yes 25% No 65.6%	0.45
Gastrointestinal condition	Yes 22.2% No 76.4%	Yes 14.3% No 84.4%	Yes 8.6% No 91.4%	Yes 18.8% No 71.9%	0.19
ENT condition	Yes 18.8% No 79.9%	Yes 13% No 85.7%	Yes 11.4% No 88.6%	Yes 6.3% No 84.4%	0.29
Genitourinary condition	Yes 16.7% No 81.9%	Yes 10.4% No 89.6%	Yes 14.3% No 85.7%	Yes 9.4% No 81.3%	0.55
Cardiac condition	Yes 13.2% No 85.4%	Yes 3.9% No 94.8%	Yes 5.7% No 94.3%	Yes 18.8% No 71.9%	0.03
Dermatological condition	Yes 9% No 89.6%	Yes 3.9% No 94.8%	Yes 14.3% No 85.7%	Yes 3.1% No 87.5%	0.19
Endocrine condition	Yes 7.6% No 91%	Yes 11.7% No 87%	Yes 11.4% No 88.6%	Yes 9.4% No 84.4%	0.78

3.5.4 Results for Comorbid Physical Illness in Autism Spectrum Disorder - Age

Previous literature recommends two methods to assess the influence of age on the rates of physical illness in adults with autism spectrum disorder. Firstly, the group should be split at the median age (29 years) and again at age 30 years. Despite the proximity of the two splits, it was decided to proceed with analysis to remain in keeping with literature recommendations. There was no statistically significant difference in the rates of physical illness in younger versus older adults with autism spectrum disorder using either method.

Table 3.17

Comorbid Physical Illness in Adults with Autism Spectrum Disorder - Age

Diagnosis	**Age <29 years**	**Age >29 years**	***p-value***
Comorbid physical illness	Yes 116 No 26	Yes 126 No 15	0.10
Diagnosis	**Age <30 years**	**Age >30 years**	***p-value***
Comorbid physical illness	Yes 122 No 26	Yes 120 No 15	0.17

3.5.5 Results for Comorbid Physical Illness in Autism Spectrum Disorder - Gender

Females with autism spectrum disorder were statistically more likely to suffer from genitourinary conditions compared to males with the disorder. Cramer's V was reported at 0.3 showing a medium effect size for this variation. Likewise, endocrine conditions were statistically more likely in female participants with autism spectrum

disorder, this time with a small effect size. Comorbid physical illnesses seen in participants with autism spectrum disorder are outlined in Table 3.18.

Table 3.18

Comorbid Physical Illness in Adults with Autism Spectrum Disorder - Gender

Diagnosis	**Males**	**Females**	***p-value*** **BFC: n=9, p<0.006**
Any comorbid medical condition	Yes 83% No 17%	Yes 86.8% No 13.2%	0.48
Neurological condition	Yes 31.6% No 68.4%	Yes 32.9% No 67.1%	0.88
Respiratory condition	Yes 21.2% No 78.8%	Yes 21% No 79%	0.94
Orthopaedic condition	Yes 19.3% No 80.7%	Yes 17.1% No 82.9	0.64
Gastrointestinal condition	Yes 19.8% No 80.2%	Yes 13.2% No 86.8%	0.18
ENT condition	Yes 13.7% No 86.3%	Yes 18.4% No 81.6%	0.34
*Genitourinary condition	Yes 8% No 92%	Yes 30.3% No 69.7%	<0.001* (Cramer's V 0.3, medium effect size)
Cardiac condition	Yes 10.4% No 89.6%	Yes 10.5% No 89.5%	0.99
Dermatological condition	Yes 19.8% No 80.2%	Yes 13.2% No 86.8%	0.11
*Endocrine condition	Yes 6.1% No 93.9%	Yes 18.4% No 81.6%	0.002* (Cramer's V 0.19, small effect size)

* Statistically significant results after correction for multiple testing are marked with an asterisk

3.5.6 Results for other Physical Illnesses in ASD Group

Sleep Difficulties

Sleep difficulties were noted in a large proportion of those with autism spectrum disorder as 121 (42%) participants reported difficulties in this area. Initial insomnia was the most commonly recorded problem, followed by middle insomnia, reversal of sleep-wake cycle, early morning waking and hypersomnia.

Table 3.19

Sleep Difficulties in Adults with Autism Spectrum Disorder

Type of Sleep Difficulty	ASD Group n (%)
Any type of sleep difficulty	121 (42%)
Initial insomnia	74 (23%)
Middle insomnia	53 (17%)
Reversal of sleep-wake cycle	21 (7%)
Childhood insomnia	17 (5%)
Early morning waking	11 (4%)
Hypersomnia	6 (2%)

Eating Disturbance

Change in appetite or dietary intake was reported by one quarter of participants with autism spectrum disorder. Restricted dietary repertoire was the most common difficulty followed by reduced appetite and picky eating. The types of appetite disturbance seen in those with autism spectrum disorder as part of this study are outlined in Table 3.20.

Table 3.20 Eating Disturbance in Adults with Autism Spectrum Disorder	
Type of Eating Disturbance	**ASD Group n (%)**
Any type of eating disturbance	71 (25%)
Restricted dietary repertoire	20 (7%)
Reduced appetite	18 (6%)
Picky eater in childhood	11 (4%)
Eating a single meal per day	8 (3%)
Binge-eating	7 (2%)
Overeating	7 (2%)
Need reminding to eat	3 (1%)
Unhealthy dietary choices	2 (0.7%)
Only eats when alone	1 (0.3%)

Allergies

Allergies were reported by 123 (43%) participants with autism spectrum disorder. Penicillin was the most frequently occurring allergy followed by nuts, animal dander, pollen and shellfish. There were no statistically significant differences between the ASD and nonASD groups in terms of recorded allergy rates.

Table 3.21 Allergies in Adults with Autism Spectrum Disorder			
Type of Allergy	**ASD group n (%)**	**NonASD group n (%)**	***p-value***
NKDA	165 (57%)	68 (54%)	0.50
Penicillin	29 (10%)	8 (6%)	0.33
Nuts	3 (1%)	2 (2%)	0.56

Type of Allergy	ASD group n (%)	NonASD group n (%)	*p-value*
Animal dander	2 (0.7%)	0 (0%)	0.88
Shellfish	2 (0.7%)	0 (0%)	0.37
^Other	5 (2%)	3 (2%)	0.33

^Other allergies include strawberries, dairy, beestings, pollen and aspirin

Prescribed Medication Use

Just over two-thirds of the ASD group reported use of prescription medication, compared to just under half of the nonASD group. There was a non-significant trend for participants with autism spectrum disorder to receive more prescribed medication than the nonASD group (p = 0.10). These results could suggest that those with a diagnosis of autism spectrum disorder received more prescribed medications than neurotypical psychiatric patients despite both groups having comparable rates of comorbid psychiatric and physical illness. Analysis of a larger cohort may clarify this finding.

Though not of statistical significance, rates of sedative use in the ASD group were also notably high. Of the twenty two participants with autism spectrum disorder receiving a prescription for sedative medication (benzodiazepine and / or hypnotic), 16 (73%) had a diagnosis of anxiety spectrum disorder, 6 (27%) had depression and 12 (60%) described sleep difficulties. Use of medication to treat gastrointestinal disorders was also higher in the ASD group, this time statistically so. Gastrointestinal medication included proton pump inhibitors, antispasmodics, antiemetics and laxatives. A non-significant trend was also noted for participants with childhood autism to receive more prescribed psychotropic medication compared to other subtypes of autism spectrum disorder.

Results relating to medication use in those with autism spectrum disorder are outlined in Tables 3.21 and 3.22.

Table 3.22 Use of Prescribed Medication in Adults with Autism Spectrum Disorder			
Prescribed Medication	**ASD group** **n (%)**	**NonASD group** **n (%)**	***p-value***
Any prescribed medication	164 (67%)	59 (47%)	0.10
Psychotropic Medication:			
Antidepressant	86 (30%)	33 (26%)	0.77
Antipsychotic	25 (9%)	13 (10%)	0.76
Sedative	22 (8%)	5 (4%)	0.47
Mood stabiliser / AED	16 (6%)	3 (2%)	0.16
Physical Illness Medication:			**BFC: n=3, p<0.02**
Antihypertensives	21 (7%)	8 (6%)	0.78
Analgesia	20 (7%)	3 (2%)	0.07
*GI medications	17 (6%)	1 (0.8%)	0.02* (Cramer's V 0.12, small effect size)

* Statistically significant results after correction for multiple testing are marked with an asterisk

Table 3.23 Use of Prescribed Medication in Adults with Autism Spectrum Disorder - ASD Subtype					
Prescribed Medication	**Asperger's Syndrome**	**Atypical Autism**	**Childhood Autism**	**PDD-nos**	***p-value***
Any prescribed medication	Yes 33.3% No 65.3%	Yes 27.3% No 71.4%	Yes 14.3% No 85.7%	Yes 28.1% No 71.9%	0.19
Antidepressant	Yes 34.7% No 65.3%	Yes 28.6% No 71.45	Yes 14.3% No 85.7%	Yes 28.1% No 71.9%	0.39
Mood stabiliser / AED	Yes 4.2% No 95.8%	Yes 7.8% No 92.2%	Yes 8.6% No 91.4%	Yes 3.1% No 96.9%	0.53
Antipsychotic	Yes 7.6% No 92.4%	Yes 7.8% No 92.2%	Yes 8.6% No 91.4%	Yes 15.6% No 84.4%	0.50
Sedative	Yes 6.9% No 93.1%	Yes 7.8% No 92.2%	Yes 8.6% No 91.4%	Yes 9.4% No 90.6%	0.86

3.6 Summary of Results Chapter

This chapter describes the results of the demographic analysis of 413 adults. Initial analysis was undertaken on the study group as a whole. The group comprised mostly of males (72%), with a male-to-female ratio of 2.6:1, ranging in age from 18 - 70 years. The majority of participants were single and unemployed, referred by their community mental health team and noted to be suffering from a comorbid psychiatric illness.

Two hundred and eighty eight individuals within the group were diagnosed with autism spectrum disorder by the BGC consensus teams (the ASD group). This group consisted primarily of males (74%) with a male-to-female ratio of 2.8:1, ranging in age from 18 - 67 years. Again, a preponderance of individuals were single and unemployed. Asperger's syndrome was the most frequently diagnosed subtype of autism spectrum disorder. Demographic results for the remaining 125 participants, who did not fulfil

criteria for autism spectrum disorder (the nonASD group), revealed a largely male (70%) group with a male-to-female ratio of 2.3:1, ranging in age from 18 - 70 years.

A total of 324 participants in the overall study group were diagnosed with a comorbid psychiatric illness, 219 (76%) in the ASD group and 105 (84%) of the nonASD group. Although a lower proportion of the ASD group were diagnosed with a comorbid psychiatric illness, participants suffered relatively greater morbidity, receiving an average of 1.5 diagnoses each compared to 1.2 diagnoses among the nonASD group.

Anxiety was the most common comorbid psychiatric diagnosis in participants with autism spectrum disorder with almost half of the group receiving a diagnosis. Attention deficit hyperactivity disorder was the second most frequent comorbid diagnosis, followed by mood disorders, deliberate self-harm / self-injurious behaviour, psychotic illness, personality disorder, substance use disorder and eating disorder. Those with Asperger's syndrome were more likely to suffer from a comorbid psychiatric illness, most notably obsessive-compulsive disorder.

A total of 334 participants in the overall study group described a previous diagnosis of physical illness; 242 (84%) in the ASD group and 92 (74%) in the nonASD group. Neurological conditions were the most common comorbid physical diagnosis in participants with autism spectrum disorder, followed by respiratory, orthopaedic, gastrointestinal, ear nose and throat, genitourinary, cardiac, endocrine and dermatological conditions. Atopy was the most frequently occurring in those with autism spectrum disorder followed by head injury.

Sleep difficulties, appetite disturbance, allergies and use of prescribed medication are also reported in this chapter. Sleep difficulty was reported by 42% of ASD individuals in this study most frequently initial insomnia. Appetite disturbance was reported by a quarter of the ASD group most commonly restricted dietary repertoire. Penicillin allergy was the most commonly reported allergy among those with autism spectrum disorder and more of the group were in receipt of a prescription for medication to treat gastrointestinal disorders than observed in the nonASD group.

Chapter 4: General Discussion Chapter

4.1 Overview

This chapter includes the thesis summary, summary of findings and discussion of study findings. It outlines implications for aetiology of comorbid illness in autism spectrum disorder and provides a critique of study design, methodology and sample selection. This chapter also addresses some possible implications for clinical practice and future research and finishes with the thesis conclusions.

4.2 Thesis Summary

Autism spectrum disorder is a pervasive illness characterised by deficits in social skills, impaired communication style and characteristic repetitive and ritualised behaviours. It belongs within the family of conditions known as the neurodevelopmental disorders, which also include attention deficit hyperactivity disorder and intellectual disability. Autism spectrum disorder has been operationalised by both the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders allowing categorisation of symptoms. Diagnosis requires clinical assessment, collateral information, screening questionnaires and gold standard diagnostic tools. When diagnosed early by skilled clinicians patients are more likely to access treatment, reducing the likelihood of a poor long term outcome.

Challenges remain in the diagnosis and treatment of autism spectrum disorder, namely the small number of assessment centres and the shortage of trained assessors. Despite increased awareness and interest among general adult psychiatrists, there is an acute lack of specialised diagnostic services for adults with a normal range intelligence quotient in the Republic of Ireland. Further research in the area of comorbidity in normal IQ adults with autism spectrum disorder could assist in providing a strong research base from which to acquire increased diagnostic and treatment services. In turn, this could allow research in Irish adults with normal IQ autism spectrum disorder.

Rates of autism spectrum disorder, psychiatric comorbidity, physical comorbidity and social morbidity have not previously been examined in a large cohort of normal IQ adult

patients with autism spectrum disorder. This study availed of information relating to 413 adults patients assessed at a specialised tertiary referral clinic in the United Kingdom, 288 of whom were diagnosed with autism spectrum disorder. The principal aims of this study were to determine the frequency of Axis I and Axis II comorbid psychiatric disorder in adults with normal IQ autism spectrum disorder, the frequency of reported physical conditions in adults with normal IQ autism spectrum disorder, the frequency of psychiatric and physical illness by specific ASD subgroup, the frequency of psychiatric and physical illness by gender and to draw comparison between the rates of psychiatric and physical illness among the ASD population and reported rates among the general population.

This study tested the hypothesis that a sample of adults with normal IQ suffering from autism spectrum disorder would report higher rates of comorbid psychiatric and physical illness compared to the general population. The findings of this study are examined in relation to this hypothesis.

4.3 Summary of Study Findings

Previous literature to examine rates of psychiatric and physical illness in adults with normal range IQ and a diagnosis of autism spectrum disorder amounts to ten articles, relating to populations from six countries between 2005 and 2014. The research study outlined in this thesis is the first to examine rates beyond mainland Europe and the United States of America.

Demographic Data

The main findings for demographic data relating to normal IQ adults with autism spectrum disorder show:

1. Autism spectrum disorder was diagnosed in 70% of participants in this study.

2. A male-to-female ratio of 2.8:1 was noted for autism spectrum disorder in normal IQ adults.

3. Milder forms of autism spectrum disorder, namely Asperger's syndrome, atypical autism and PDD-nos were recorded for 88% of participants with autism spectrum disorder.

4. A trend towards diagnosis in later life was noted for participants with milder forms of autism spectrum disorder.

5. Sixty seven percent of participants with autism spectrum disorder were not in a stable relationship.

6. Participants with autism spectrum disorder were more likely to be unemployed. Participants with lower functioning forms of autism spectrum disorder were especially at risk for unemployment.

7. Participants with autism spectrum disorder were less likely to live independently.

8. Participants with autism spectrum disorder were statistically more likely to have been victims of school-yard bullying in national and / or secondary school.

Psychiatric Illness

The main findings for psychiatric illness among normal IQ adults with autism spectrum disorder show:

1. A total of 76% of participants with autism spectrum disorder suffered from a comorbid Axis I psychiatric illness.

2. Within the group of participants with autism spectrum disorder, 2% also suffered from a comorbid Axis II condition.

3. Anxiety spectrum disorders were the most common comorbid psychiatric illness diagnosed in participants with autism spectrum disorder.

4. Attention deficit hyperactivity disorder was the second most frequently diagnosed comorbid psychiatric illness in participants with autism spectrum disorder.

5. Mood disorders and deliberate self-harm occurred at equal rates in participants with autism spectrum disorder and were the third highest ranking comorbid condition.

6. Depression occurred at significantly higher rates than bipolar affective disorder in participants with autism spectrum disorder. Unlike comorbidity in adolescent cohorts it was not the most common psychiatric condition.

7. Comorbid psychosis rates were lower than expected in participants with autism spectrum disorder.

8. Rates of personality disorder were relatively low compared to other psychiatric illnesses in participants with autism spectrum disorder.

9. Alcohol addiction is the most frequently occurring substance use disorder in participants with autism spectrum disorder. Recorded rates were lower than expected.

10. Use of illicit drugs was statistically less likely in participants with autism spectrum disorder compared to participants without autism spectrum disorder.

11. Eating disorder was rarely diagnosed in participants with autism spectrum disorder.

12. Tic disorder including Tourette's syndrome was diagnosed at a lower than expected rate in participants with autism spectrum disorder.

13. Catatonia was not noted for a single participant with autism spectrum disorder.

14. Participants with Asperger's syndrome were statistically more likely to be diagnosed with a comorbid psychiatric illness compared to participants with other forms of autism spectrum disorder.

15. Obsessive compulsive disorder occurred at a statistically higher frequency among participants with Asperger's syndrome compared to participants with other forms of autism spectrum disorder.

16. Older participants with autism spectrum disorder were statistically more likely to be diagnosed with depression and generalised anxiety disorder than younger participants.

17. Female participants with autism spectrum disorder were more likely to suffer from bipolar affective disorder than male participants with autism spectrum disorder. However, this finding lost statistical significance on correction for multiple testing.

Physical Illness

The main findings for physical illness among normal IQ adults with autism spectrum disorder show:

1. A total of 84% of participants with autism spectrum disorder had a history of physical ill health.

2. A total of 16% of participants with autism spectrum disorder described good physical health.

3. Neurological conditions were the most prevalent systems illness among participants with autism spectrum disorder, at a rate of 32%. Epilepsy rates were lower than expected at 3%, the third most frequently occurring neurological condition in participants with autism spectrum disorder.

4. Atopy was the most prevalent disease among participants with autism spectrum disorder, at a rate of 22%.

5. Allergies were documented for 43% of participants with autism spectrum disorder.

6. Sleep difficulties were notably high at 42% among participants with autism spectrum disorder.

7. Eating disturbance was noted in 25% of participants with autism spectrum disorder.

8. Dyspraxia rates were recorded at 8% in participants with autism spectrum disorder.

9. Dyslexia was rarely recorded for participants with autism spectrum disorder (0.3%).

10. Smoking was less likely in participants with autism spectrum disorder than in neurotypical participants.

11. Participants with autism spectrum disorder were statistically more likely to take medication prescribed for gastrointestinal illness than participants who did not suffer from autism spectrum disorder.

12. A notably high prescription rate was seen for sedative medication among participants with autism spectrum disorder compared to participants without autism spectrum disorder. This difference did not reach statistical significance.

13. No differences were noted in rates of physical illness in participants with autism spectrum disorder when examined according to age.

4.4 Discussion of Study Findings

4.4.1 Demographic Findings in Normal IQ Adults with Autism Spectrum Disorder

Prevalence Rate of Autism Spectrum Disorder in Normal IQ Adults

It is generally agreed that the prevalence rate for autism spectrum disorder in children of the general population is between 0.6% and 1%. These figures, published in 2006 and 2008, are significantly higher than the prevalence rate of 0.04% recorded in 1966. A number of possible factors have been proposed to explain this gradual increase in ASD prevalence over time. Two main theories exist; increased awareness among the general public, physicians and psychiatrists which has allowed increased recognition of previously undiagnosed and newly arising cases (Miles 2011, Nylander 2013) and improved diagnostic criteria reducing diagnostic overshadowing (Kim 2011, Vannucchi 2014a). Other possible reasons for the gradual increase in prevalence rates were identified by the author in this study. These include varying research methodologies such as differing sample sizes, differing assessment or diagnostic methods and instruments, differing study participants, original research versus use of national data, poor participation rates, wide interpretation of diagnostic criteria, the mixing of age and IQ within a single cohort, the development of specialist diagnostic services for children and in some regions for adults across Europe and the United States of America which allowed increased recording of caseness for research purposes and the recognition that autism spectrum disorder can co-exist with intellectual disability, normal IQ and psychiatric morbidity which has allowed revision of diagnoses in the form of diagnostic substitution and recording of both true cases and those of mixed morbidity. Other factors identified by the author include population growth which is a naturally occurring phenomenon leading to increased prevalence in all illnesses and changes in political and healthcare policy which impact prevalence data, as services are planned in accordance with illness rates. Factors previously considered causal, but currently known to be incidental in the prevalence trends for autism spectrum disorder include age of the cohort under investigation, cluster alarms, cultural variability, geographical variation, immigration, social class and a rise in the true rate of the disorder.

A prevalence rate for autism spectrum disorder in adults with an IQ in the normal range has not previously been published. White et al (2011) described a rate of 1.9% in a university population in the United States of America. This is the closest figure available for a community prevalence rate in the literature to date. It is however notably higher than the rate seen in child cohort community studies. This is interesting as autism spectrum disorder is a neurodevelopmental condition, present from birth. As one cannot develop the condition in adulthood, two options remain to explain the higher rates noted by White et al (2011). Firstly, community paediatric studies may have underestimated the rate of autism spectrum disorder in their samples. An alternative explanation is that individuals with high-functioning autism spectrum disorder show greater academic attainment and are more likely to attend university, thus increasing the rates identified by White et al.

Autism spectrum disorder was diagnosed in 70% of participants in this study. As the sample does not represent a community population, the rate cannot be generalised or interpreted as a prevalence rate for autism spectrum disorder in the general population. It could however provide an indication as to the high prevalence rate of autism spectrum disorder within the psychiatric population. More specifically the high rate of autism spectrum disorder in difficult to diagnose, difficult to treat complex cases.

Gender Ratio in Normal IQ Adults with Autism Spectrum Disorder

This study identified a male-to-female ratio of 2.8:1. This ratio is equivalent to that reported previously in the literature relating to mixed age and mixed IQ populations, where 2:1 - 3:1 is considered a reasonable estimate of gender ratio in autism spectrum disorder. It is however higher than rates reported by White et al (2011), who reported a ratio of 1.5:1 in normal IQ college students and lower than Brugha et al (2011) who reported a ratio of 9:1 in mixed IQ adults.

The male-to-female ratio in autism spectrum disorder has remained relatively stable over time. The most likely explanation is that males more frequently suffer from autism spectrum disorder. However, another possible reason could be that the current concept of autism spectrum disorder focuses primarily on the male presentation. If diagnosticians are overly focused on the mode of male presentation, they are likely to miss the more subtle phenotype in females. In fact, it has been shown that although

expressing the same levels of ASD symptoms, girls are less likely to receive a diagnosis than boys (Constantino, 2015). Hans Asperger originally thought the condition was unique to males but later modified his view to say it was 'much more common in boys than girls' (Wing, 1981). Lorna Wing (1981) points out that girls tend to be more superficially sociable than boys and Maria Råstam (2008) suggests closer consideration of the female phenotype, 'in the same way as anorexia nervosa criteria are designed to pick up females, if the criteria of ASD were to be broadened to include behaviours and attitudes more appropriate to females maybe more girls would be considered for ASD'.

Relationship Status in Normal IQ Adults with Autism Spectrum Disorder

This study showed that 67% of participants with autism spectrum disorder were not in a stable relationship. This rate is consistent with previous literature showing the majority of high-functioning adults with autism spectrum disorder are single. Joshi et al (2013) noted 84% of their sample of normal IQ adults with autism spectrum disorder to be single. Rydén and Bejerot (2008a), Hofvander et al (2009) and Roy et al (2015) also note low relationship rates among participants, ranging from 16% to 28%. Information relating to the status of parental relationships is virtually unreported in autism spectrum disorder. The only reference identified as part of this literature review was by Kanner (1943) who noted three sets of parents (27%) were separated. This study recorded parental marital status for 71% of participants with autism spectrum disorder. Most frequently, participants' parents were reported to be married or widowed (37%) followed by divorced or separated (34%).

Employment Status in Normal IQ Adults with Autism Spectrum Disorder

This study showed that adults with normal IQ autism spectrum disorder were more likely to be unemployed compared to neurotypical participants. Those with lower functioning forms of autism spectrum disorder were especially at risk for unemployment. Global functioning is generally more impaired in adults with autism spectrum disorder compared to their neurodevelopmentally typical counterparts (Joshi, 2013). Although two thirds have graduated from secondary school and one quarter have completed a college or university qualification, showing equal educational

attainment to the general population and the potential to work, few are in regular employment (Barnhill 2007, Rydén 2008a, Hofvander 2009). Employment rates range from 9% - 34% but inevitably individuals with autism spectrum disorder experience lower social and occupational functioning (Barnhill 2007, Rydén 2008a, Hofvander 2009, Howlin 2012). Mark Romoser (2000) coined the term *malemployment* to describe the working lives of many with Asperger's syndrome, finding themselves working in a job below their skillset to which they are essentially unsuited.

Accommodation Status in Normal IQ Adults with Autism Spectrum Disorder

Study participants with autism spectrum disorder were noted to be less likely to live independently. Only 19% of participants were living alone while the majority (56%) continued to live with family members. A surprisingly high percentage (8%) also resided in supported accommodation or were effectively homeless. Balfe and Tantam (2010) have previously shown that the majority of adults with autism spectrum disorder continue to live with their parents. This is supported by Hofvander et al (2009), Bruder et al (2012) and Roy et al (2015) who also showed that less than half of their study participants lived independently.

Bullying in Normal IQ Adults with Autism Spectrum Disorder

Bullying, or peer victimisation, refers to direct or indirect, verbal or physical, repeated intimidation, aggression and harassment of an individual by another person driven by a desire for power or social dominance (Plenty, 2014). Rates in neurotypical children typically peak in the preteen years and reduce thereafter (Bejerot, 2013). It is a global issue affecting 5% - 45% of school-age children in the general population (Idsoe 2012, Plenty 2014, Takizawa 2014). In the general population, boys are almost three times more likely to fall victim to school-yard bullying, however girls are shown to experience a greater negative psychological impact as a result of bullying (Idsoe, 2012). Females display higher rates of internalising behaviours including post-traumatic stress disorder and males more externalising behaviours, with those of higher functional ability falling victim most frequently (Hoover, 2015). Risk factors for being bullied include being male, unassertive, withdrawn or of inhibited temperament, easily upset, of low emotional intelligence, socially vulnerable, gullible, highly credulous, perceived as

unusual, deficient in social skills, overweight, of an ethnic minority, have below average motor skills or to have an illness or disability (Gladstone 2006, Sofronoff 2011, Plenty 2014, Wolke 2015). A number of these characteristics are seen in individuals with autism spectrum disorder, most notably male preponderance, low social intelligence, socially vulnerable, gullible and credulous, poor social skills, reduced motor skills and being 'perceived as unusual'. It is estimated that 44% - 77% of children with autism spectrum disorder have been bullied over the last month and as many as 94% over the past year (Hoover, 2015).

Studies in neurotypical children who have experienced bullying show increased rates of all mental illnesses compared to children who have not been bullied (Lereya, 2015). These included increased rates of depression, anxiety and suicidality in children, post-traumatic stress disorder among female children (Idsoe, 2012) and increased anxiety, agoraphobia, generalised anxiety disorder, panic disorder and suicidality among young adults aged 19 - 26 years (Copeland 2013, Hoover 2015). Though less frequently researched in adults, anxiety spectrum disorders are again clinically considered to be significantly associated with a childhood experience of bullying. Takizawa et al (2014) examined adult health outcomes of childhood bullying in 7,771 adults in a British birth cohort. They showed increased frequency of depression, anxiety spectrum disorders and poorer cognitive function among the study sample compared to nonbullied counterparts. Similarly, research looking at psychiatric outcomes in children with autism spectrum disorder with a history of being bullied showed increased rates of anger, loneliness, symptoms of depression, panic disorder and generalised anxiety disorder, self-injury and suicidality (Hoover, 2015). Research in young adults with autism spectrum disorder shows increased anxiety, suicidal ideation and suicide attempts (Hoover, 2015). This is concerning given the findings of Takizawa et al (2014) and Lereya et al (2015) showing childhood bullying to result in more severe longterm adverse mental health outcomes than physical or emotional maltreatment, sexual abuse or neglect and similar mental health sequelae to individuals who had lived in institutional care.

Literature quotes a rate of 44% - 95% for school-yard bullying among normal IQ individuals with autism spectrum disorder (Hofvander 2009, Balfe 2010, Hoover 2015). A rate of 40% is suggested for sexual or financial exploitation among the same population (Balfe, 2010). Findings from this study are consistent with previous literature

showing that 61% of participants with autism spectrum disorder were bullied in school and that this population are statistically more likely to be victims of bullying compared to their neurotypical counterparts.

Ratio of High-Functioning to Low-Functioning Autism Spectrum Disorder in Normal IQ Adults

As people differ in their skill level of social interaction, use of non-verbal skills and behavioural habits, the triad of impairments clinically characteristic of autism spectrum disorder may be found to varying degrees in many individuals among the general population (Wing, 1981). Similarly, the severity of impairment in each domain among those with a diagnosis of autism spectrum disorder can vary from mild to severe. Individuals on the more severe end of the autism spectrum, especially those with language delay, typically receive a diagnosis of childhood autism. Those with less severe impairments, tend to receive diagnoses of Asperger's syndrome, atypical autism and pervasive developmental disorder, not otherwise specified (Cederlund 2008, Lungegård 2012). The term 'high-functioning' is widely used to refer to this group with milder impairment who generally use language in a superficially normal way and can display normal or sometimes above average intelligence (White 2011, Van Elst 2013). Approximately 10% - 30% of individuals with autism spectrum disorder fall into the high-functioning category with a preponderance of males in this category (Ghaziuddin 2002a, Goldstein 2002, Williams E 2008).

While Kanner was unsure as to the level of intellectual functioning of individuals with early infantile autism, Asperger reported normal intelligence levels for all subjects with autistic psychopathy (Rutter 1978, Wing 1981, Wing 2002a). Currently, it is agreed that IQ in autism spectrum disorder is on a spectrum from profound intellectual disability to superior intellectual functioning as seen in the general population (White, 2011). As approximately 70% of ASD individuals have an intellectual disability (Newschaffer 2003, Kannabiran 2009), the remaining 30% fall within the normal or superior IQ range. Despite registering IQ levels in the normal to superior range, it has been suggested that individuals with average or superior IQ and autism spectrum disorder demonstrate subnormality in specific areas of intelligence. The most commonly described subnormal skill is that of executive function, shown to be less than expected for the

individual's IQ ability. Executive dysfunction with associated cognitive rigidity could impair problem solving ability leading to poorer coping and greater comorbidity rates. It has been shown that the rate of comorbid intellectual disability in autism spectrum disorder is falling. Judith Miles (2011) noted a progressive reduction in the prevalence of intellectual disability among those with autism spectrum disorder from 70% to 50% and more recently to 30%. Her research reflects the hereto poor detection rates of autism spectrum disorder in high-functioning individuals. As detection rates among the normal IQ population improve, the relative prevalence of intellectual disability declines.

A small number of researchers have focused on IQ in autism spectrum disorder and show outcomes to be more positive and problems less pervasive in individuals with a higher IQ and poorer for those with an IQ below 50 (Howlin, 2000 and 2004). However, adults with autism spectrum disorder are shown to receive better support when their diagnosis is associated with a lower IQ (Brugha, 2011). Overall, IQ at either extreme, at the time of original diagnosis has for some time been considered a reasonable predictor of outcome (Rutter 1978, Newschaffer 2003, Billstedt 2005a, White 2011).

Looking solely at high-functioning individuals with autism spectrum disorder, ratios of childhood autism to Asperger's syndrome appear to consistently suggest childhood autism is the more prevalent of the two. A current ratio of 5:1 is accepted (Fombonne, 2005). This study did not correlate with previous literature as milder forms of autism spectrum disorder more frequently presented to the assessment clinic. It is likely that diagnoses of milder forms of autism spectrum disorder are more complex to finalise leading to higher rates of referral for tertiary assessment. Alternatively, it may suggest that individuals with more impaired subtypes of autism spectrum disorder are diverted away from the community psychiatric services, perhaps to disability services or other community supports.

Diagnosis in Childhood versus Adulthood in Normal IQ Adults with Autism Spectrum Disorder

The diagnosis of autism spectrum disorder is most frequently made in childhood (Cath 2008, White 2011) as parents, caregivers or teachers note difficulties in the child's social skills and means of communication or behaviours, most commonly before the age of five years. Parents become concerned if a child or adolescent is failing to make

friends, behaves inappropriately in public or appears indifferent to the opinions of others (Lainhart, 1999). The child is initially assessed by a general practitioner followed by referral to their local child and adolescent psychiatric service. Child and adolescent psychiatrists, paediatricians and child psychologists are skilled in the diagnosis and detection of childhood-onset disorders including autism spectrum disorder. Once diagnosed, a child can access increased academic and social supports and parents are provided with a foundation of knowledge on which to better engage their child. Interventions at this age are shown to improve the child's cognitive, linguistic, social and self-help skills (Howlin, 1999). Approximately 80% of cases are detected in this way with childhood autism repeatedly shown to be detected at an earlier age than Asperger's syndrome.

When language, cognitive and social impairments are subtle, diagnosis can be missed in childhood (Cath, 2008) and autism spectrum disorder without intellectual disability in particular is often diagnosed later in life (Strunz, 2014). In fact, nearly 50% of those with Asperger's syndrome remain undiagnosed until adulthood (Roy, 2015). This leads to two main unfortunate outcomes for young adults with undiagnosed autism spectrum disorder. Firstly, they typically have completed education before receiving a diagnosis, thus possibly leading to poorer academic attainment than might have been possible (White, 2011). Secondly, adult psychiatrists are generally less aware of the autism spectrum disorder phenotype than their child and adolescent psychiatry colleagues and the condition can remain undiagnosed despite general practitioner and subsequent consultant psychiatrist assessment (Anholt, 2010).

This study showed a non-statistically significant trend towards older age at diagnosis for participants with PDD-nos. This suggests that individuals with PDD-nos were more likely than individuals with other forms of autism spectrum disorder to receive their diagnosis as adults. This finding is in keeping with literature indicating those with less impairment are diagnosed later in life.

Misdiagnosis in Normal IQ Adults with Autism Spectrum Disorder

Although referral rates of adults with suspected autism spectrum disorder to tertiary assessment centres is rising (Ketelaars, 2008), Nylander et al (2013) suggests the autism spectrum disorder diagnosis can be frequently overshadowed by comorbid

illness. Often, it is when a patient fails to recover from an original diagnosis, for example a depressive episode, that the clinician begins to consider the possibility of an underlying neurodevelopmental disorder. Perhaps adult psychiatrists are not accustomed to taking a long-term developmental perspective on their patient's presenting complaint (Nylander, 2013). Occasionally, even in the absence of a comorbid condition, neurodevelopmental disorders can be missed (Roy, 2013) or are not the first consideration among adult psychiatrists. Due to atypical presentations or less severe symptoms, many patients with high-functioning autism spectrum disorder are misdiagnosed as suffering from depression, bipolar affective disorder, anxiety spectrum disorders, schizophrenia, obsessive compulsive disorder, borderline personality disorder or other forms of personality disorder (Wing 2002a, Van Elst 2013, Vannucchi 2014a). Van Elst et al (2013) hypothesised that very few adult patients in Germany are recognised as suffering from autism spectrum disorder and instead many patients receive a diagnosis of 'atypical depression', 'atypical psychosis', 'atypical OCD' or 'combined personality disorder'.

This study showed that 30% of participants were suspected of having autism spectrum disorder by the community mental health team but later found to be neurotypical. The majority of these participants were found to be suffering from another psychiatric illness, most commonly personality disorder followed by psychotic disorder. This finding suggests a tendency towards misidentification of personality disorder and psychotic symptoms as autism spectrum disorder symptoms by general practitioners and general adult psychiatrists.

4.4.2 Psychiatric Illness in Normal IQ Adults with Autism Spectrum Disorder

Increasingly autism spectrum disorder is associated with a higher prevalence of psychiatric illness than seen in the general population (Stewart 2006, Nylander 2008, Raja 2008). Roy et al (2015) noted a lifetime prevalence of one of more comorbid psychiatric illness in 70% of normal IQ adults with autism spectrum disorder.

As part of this study, the author reviewed all available literature to compile a table comparing prevalence rates for sixteen psychiatric illnesses in the general population to rates among adults with normal IQ autism spectrum disorder in previous literature and in this study. Comparisons are outlined in Table 4.1.

Table 4.1

Prevalence Rates for Psychiatric Illness in Adults

Diagnosis	Rates in the General Population	Rates for Adults with Normal IQ Autism Spectrum Disorder in Previous Literature	Rates for Adults with Normal IQ Autism Spectrum Disorder in this Study
Anxiety spectrum disorders	1% - 28%	50%	49%
Obsessive compulsive disorder	1.5% - 3%	7% - 50%	23%
Generalised anxiety disorder	2% - 5%	15% - 29%	20%
Social phobia	8% - 12%	13% - 50%	19%
Agoraphobia	2%	15% - 24%	13%
Specific phobia	7% - 9%	6% - 18%	1%
Post-Traumatic stress disorder	Unreported	5%	1%
Attention deficit hyperactivity disorder	5%	37% - 43%	27%
Depression	6%	30%	23%
Bipolar affective disorder	0.4% - 0.8%	6% - 9%	2%
Suicidal behaviour	Suicidal Ideation 9% Suicide Attempt 3%	Suicidal Ideation 66% Suicide Attempt 17% - 35%	Deliberate self-harm 25% Self-injurious behaviour 16%

Diagnosis	Rates in the General Population	Rates for Adults with Normal IQ Autism Spectrum Disorder in Previous Literature	Rates for Adults with Normal IQ Autism Spectrum Disorder in this Study
Schizophrenia	0.3% - 1%	0%	4%
Alcohol addiction	1% - 3%	6%	1%
Eating disorder	0.3% - 4%	5%	0.3%
Tic disorder / Tourette's syndrome	0.1%	5% - 20%	1%
Catatonia	Unreported	Unreported	0%

Of the sixteen illnesses assessed in this study, eleven were noted to be more prevalent in normal IQ adults with autism spectrum disorder compared to the general population. These were anxiety spectrum disorders, obsessive compulsive disorder, generalised anxiety disorder, social phobia, agoraphobia, attention deficit hyperactivity disorder, depression, bipolar affective disorder, suicidal behaviour, schizophrenia and tic disorder. Increased rates varied from a factor of two to a factor of ten. Examples include social phobia occurring at a rate of 8% in the general population but 19% in the normal IQ ASD population and generalised anxiety disorder occurring at a rate of 2% in the general population but 20% in the normal IQ ASD population. Rates reported in this study, though higher than those seen in the general population, were more conservative than those reported in previous literature.

Three illnesses previously reported as more prevalent in normal IQ adults with autism spectrum disorder compared to the general population were noted to occur at comparable rates in this study. These included specific phobia (occurring at 7% - 9% in the general population and 1% in participants with autism spectrum disorder), alcohol addiction (occurring at 1% - 3% in the general population and 1% in participants with autism spectrum disorder) and eating disorder (occurring at 0.3% - 4% in the general population and 0.3% in participants with autism spectrum disorder).

This study found a lower prevalence of post-traumatic stress disorder in adults with normal IQ autism spectrum disorder compared to previous literature (previously reported at 5% and found at a rate of 1% in this study). To the best of my knowledge, this study is the first to report a prevalence rate for catatonia in a normal IQ ASD population. This finding, however, should be noted cautiously as the study design did not include a specific assessment tool for catatonia.

Anxiety Spectrum Disorders in Normal IQ Adults with Autism Spectrum Disorder

Rates of anxiety spectrum disorders are reported to be higher in the ASD population compared to the general population. Davis et al (2011) found rates of anxiety increased from toddlerhood, peaked in childhood and rose again in young adulthood though not reaching childhood levels. Lugnegård et al (2011) noted a rate of approximately 50% in 54 normal IQ Swedish adults, while Joshi et al (2013) found anxiety spectrum disorders to be the third most common comorbid psychiatric illness in a group of 63 normal IQ American adults. Previous literature has identified social phobia as the most common anxiety spectrum disorder, followed by generalised anxiety disorder, specific phobia, obsessive compulsive disorder and post-traumatic stress disorder (Joshi, 2013).

In line with previous literature, rates of anxiety spectrum disorders were found to be extremely high in participants with autism spectrum disorder in this study. In fact, they were noted to be the most common comorbid psychiatric illness occurring at a rate of 49%. Contrary to previous literature, obsessive compulsive disorder was the most commonly occurring of the anxiety spectrum disorders, followed by generalised anxiety disorder, social phobia and agoraphobia. Prevalence rates for obsessive compulsive disorder in individuals with autism spectrum disorder, as reported by five previous studies, ranged from 7% - 50% (Russell 2005, Cath 2008, Ketelaars 2008, Hofvander 2009, Joshi 2013). This study identified a prevalence rate of 30% in keeping with past research. Prevalence rates for generalised anxiety disorder in those suffering from autism spectrum disorder was previously reported to range from 15% - 29% (Hofvander 2009, Lugnegård 2011, Joshi 2013). A rate of 27%, as found in this study, is at the higher end of this range. Prevalence rates for comorbid social phobia have been reported to range from 13% - 50% (Cath 2008, Ketelaars 2008, Hofvander 2009,

Joshi 2013, Stunz 2014). The rate of 21% reported in this study is again in keeping with previous literature. Finally, prevalence rates for agoraphobia range from 15% - 24% (Lugnegård 2011, Joshi 2013), a rate of 13% as noted in this study is lower than previous research.

Autism spectrum disorder, especially high-functioning autism spectrum disorder, shares a number of features in common with the anxiety spectrum disorders including profound social interaction deficits and communication skills deficits (Cath 2008, Tyson 2012). It is hypothesised that anxiety spectrum disorders, similar to depression, could be a result of the individual's struggle to comprehend complex social interactions and their awareness of being inherently different to others (Balfe, 2010). Prevalence of anxiety spectrum disorders may also be increased by an over-representation of bullying and victimisation in this population (Balfe, 2010).

Both disorders could also share common aetiological factors. Similar genetic liability, family history of psychiatric illness and behavioural deficits could be lead to the emergence and maintenance of both disorders (Tyson, 2012). Although it is not known if the disorders share a common neural basis (Russell, 2005), it has been suggested that autism spectrum disorder, attention deficit hyperactivity disorder and obsessive compulsive disorder could constitute a group of developmental basal ganglia disorders (Anholt, 2010). Further research in the area is required to clarify this question.

Attention Deficit Hyperactivity Disorder in Normal IQ Adults with Autism Spectrum Disorder

Roy et al (2013) suggest that there are several overlapping symptom profiles between attention deficit hyperactivity disorder and high-functioning autism such as attentional impairments, deficits in social interaction, interpersonal struggles, sensory hypersensitivity, motor clumsiness and hyper-focussed special interests. Autism spectrum disorder and attention deficit hyperactivity disorder also have age and developmental stage of onset in common (Taurines, 2010). Theories as to common aetiology lie in similar increases in gray matter volume in both conditions and structural abnormalities in the prefrontal cortex and inferior parietal lobe (Roy, 2013). The conditions are also noted to stem from partly similar genetic origins with overlapping loci at chromosome 5p13 and 16p13 (Taurines, 2010). Vannucchi et al (2014b)

suggest that autism spectrum disorder and attention deficit hyperactivity disorder could share up to 50% - 72% of their genetic aetiology.

In this study, 27% of participants received a diagnosis of attention deficit hyperactivity disorder making it the second most frequently diagnosed comorbid psychiatric illness in participants with autism spectrum disorder. This rate is conservative compared to previous literature which quoted a rate of 37% (Rydén, 2008a). The most likely reason for this discrepancy lies in the differences in recruitment between the two studies. Ryden et al (2008a) recruited participants from an inpatient neurodevelopmental service specialising in the treatment of autism spectrum disorder and attention deficit hyperactivity disorder. It is likely that this increased the rate of attention deficit hyperactivity disorder referred to and diagnosed by their study group compared to the participants assessed in this study.

Mood Disorders in Normal IQ Adults with Autism Spectrum Disorder

Research investigating rates of mood disorder in adults with normal IQ autism spectrum disorder frequently fail to specify the subtype of mood disorder, namely depression, bipolar or mania being assessed. Reports generally focus on overall rates for mood disorders and range from 24% - 53% (Ketelaars 2008, Hofvander 2009, Stunz 2014). Research in adult patients with normal IQ autism spectrum disorder reports lifetime prevalence of major depressive disorder as 70% - 77%, recurrent depression as 50%, current depressive episode as 30% and dysthymia as 8% (Cath 2008, Lugnegård 2011, Joshi 2013). Although rates reported in this study are significantly lower than those seen in previous research relating to individuals with autism spectrum disorder, they remain greater than rates reported for the general population, namely 6% (Olsen, 2004). Comparison of rates is outlined in Table 4.2.

Table 4.2 Comparison of Rates of Depressive Illnesses between Current Study and Previous Literature		
Depressive Illness	**Previous Literature**	**Current Study**
Major depressive disorder	30%	11%
Recurrent depressive disorder	50%	8%
Dysthymia	8%	4%

While some previous authors have described depression as the most prevalent comorbid psychiatric condition in adults with normal IQ autism spectrum disorder (Ketelaars 2008, Hofvander 2009, Lugnegård 2011, Strunz 2014), this study found depression to be less frequently occurring. Cath et al (2008) also noted depression to no more common than obsessive compulsive disorder or social phobia in 12 adults in the Netherlands. Likewise, Joshi et al (2013) noted depression to be the second most frequently occurring illness following social phobia in 63 adults in the United States of America.

Lifetime bipolar II disorder has a reported prevalence of 25%, current bipolar II disorder of 9% and current bipolar I as 6% in the normal IQ adult ASD population (Lugnegård 2011, Joshi 2013). Rates of bipolar illness reported in this study were lower at 2%. As comparable lifetime prevalence rates in the general population are bipolar I disorder 0.35% - 0.6% and bipolar II disorder 0.8% (Merikangas 2007, Perälä 2007), rates of illness in this study sample remain at least two fold higher than the general population.

Self-injurious and Suicidal Behaviour in Normal IQ Adults with Autism Spectrum Disorder

As research in deliberate self-harm in adults with normal IQ autism spectrum disorder is rare, rates are often extrapolated from mixed IQ and mixed age samples. One study on mixed IQ adults with autism spectrum disorder identified 14.4% of patients with a history of self-harm (Kobayashi, 1998). A mixed age study of individuals with normal IQ autism spectrum disorder noted suicidal ideation in 40% of their study group while 15% reported a previous suicide attempt (Balfe, 2010). Similarly, a study of adults with mixed IQ autism spectrum disorder identified suicidal ideation in 31% of respondents but lower rates of previous suicide attempt at 4%, deliberate self-harm in 4% and completed suicide in almost 8% (Raja, 2011). Studies in normal IQ autism spectrum disorder include Cassidy et al (2014) who reported suicidal ideation in 66% of 374 adults with Asperger's syndrome, Ryden et al (2008a) reported a 17% prevalence of suicide attempt in 130 normal IQ adults with autism spectrum disorder in Sweden, while Paquette-Smith et al (2014) reported a prevalence rate of 35% for attempted suicide in 50 adults with Asperger's syndrome in Ontario. Rates of completed suicide in adults with normal IQ autism spectrum disorder have not been reported (Richa, 2014).

This study identified a prevalence rate of 25% for deliberate self-harm and a rate of 16% for self-injurious behaviour in participants with autism spectrum disorder. It is difficult to compare these rates to previous literature given the wide array of nomenclature used in the area of self-induced injury. It would however appear to be broadly in line with previous estimates of 17% - 35% and again remains significantly higher than the 3% rate reported for the general population.

Personality Disorders in Normal IQ Adults with Autism Spectrum Disorder

Cluster A personality disorders, namely schizoid, schizotypal and paranoid personality disorders and Cluster C, obsessive-compulsive, anxious-avoidant and dependent personality disorders are more common in adults with normal IQ autism spectrum disorder than the general population (Anckarsäter, 2006). Rydén et al (2008b) studied a group of 41 difficult-to-treat adult female patients with normal IQ emotionally unstable personality disorder in Stockholm, to determine the rate of comorbid autism spectrum disorder in this population. They identified a comorbidity rate of 15% in their EUPD

patients which they described as ‘high’ and ‘substantial’. Of interest, all patient with emotionally unstable personality disorder fell into the milder ASD subtypes of Asperger’s syndrome or PDD-nos.

Sixty two percent of participants with normal IQ autism spectrum disorder in a 2009 study by Hofvander et al were found to have a comorbid personality disorder. Obsessive-compulsive personality disorder was the most frequently diagnosed at 32%, followed by avoidant (25%), schizoid (21%), paranoid (19%), schizotypal (13%), borderline (9%), dependent (5%) and antisocial and narcissistic (3%) personality disorders. No patient received a diagnosis of histrionic personality disorder. Strunz et al (2015) also noted a high prevalence of personality disorder in 59 normal IQ adults with autism spectrum disorder in Berlin, Germany. They reported a prevalence rate of 45%.

This study found only 2% of participants with autism spectrum disorder to have a comorbid personality disorder. This rate is significantly lower than that reported in previous literature, ranging from 45% - 62% (Hofvander 2009, Strunz 2015). The inconsistency most likely lies in the different assessment methods used between studies. Hofvander et al (2009) utilised the SCID-II to assess for personality disorders as part of clinical assessment while Strunz et al (2015) used two self-report questionnaires to identify personality disorders in their study sample. It is likely that a 2% prevalence of personality disorder in adults with normal IQ autism spectrum disorder, as seen in this study, is an underestimation of the true prevalence rate.

Psychotic Disorders in Normal IQ Adults with Autism Spectrum Disorder

Schizophrenia has a lifetime prevalence of 0.30% - 0.87% in the general population (Perälä 2007, Van Os 2009). Rates among those with autism spectrum disorder are less clearly defined. As early as the 1940s, Asperger noted that only one of his 200 case studies developed schizophrenia (Wing, 1981). Volkmar and Cohen (1991) restarted the debate on comorbidity between autism spectrum disorder and schizophrenia by examining 163 individuals aged 15 - 41 years with mixed IQ autism spectrum disorder in 1991. They identified a single subject with schizophrenia, one male with mild intellectual disability from 163 cases assessed. Volkmar and Cohen (1991) showed schizophrenia to be rare in individuals with autism spectrum disorder,

‘no more commonly observed together than would be expected by chance’. Unfortunately, research on the prevalence of comorbid psychotic disorders in adults with autism spectrum disorder over the subsequent decades has been scarce (Nylander, 2008). Skokauskas et al (2010) conducted a systematic literature search of all available studies and did not identify a single such study in the intervening two decades. They report a prevalence rate of zero percent to 6% by combining results from 11 studies of child and adult subjects with mixed IQ. Following on from Skokasukas et al (2010), this study identified four papers addressing the prevalence rates of psychotic illness in normal IQ adults with autism spectrum disorder, Hofvander et al (2009), Lugnegård et al (2011), Joshi et al (2013) and Selten et al (2015). Both Hofvander et al (2009) and Joshi et al (2013) provided prevalence rates for the global term ‘psychotic disorders’, ranging from 8% - 12%. Lugnegård et al (2011) identified the conditions by subtype; reporting a 2% prevalence rate for brief psychotic disorder, 2% prevalence of psychotic syndrome-nos, 13% prevalence of ‘recurrent hallucinations’ and zero percent for schizophrenia, schizoaffective disorder and substance-induced psychotic disorder. Selten et al (2015) took a broader approach, incorporating six psychotic illnesses under the term nonaffective psychotic disorder (NAPD). By examining the occurance of NAPD in 9,062 young adults of mixed IQ they demonstrated a prevalence rates of 0.6% in cases compared to 0.1% of controls. Distinguishing between those with and without an intellectual disability, they showed NAPD to occur at a rate of 0.4% in normal IQ young adults with autism spectrum disorder, representing a four-fold increased risk of NAPD. Unspecificed nonorganic psychotic disorder was the most commonly occurring form of NAPD at 45.6%. Schizophrenia was diagnosed in 9 cases representing a prevalence rate of 0.99%, comparable to the rate among controls. The high detection rate for unspecified psychotic disorder may account for the higher odds ratio noted by Selten et al (2015) compared to other researchers.

Researchers interested in schizophrenia have also looked at rates of autism spectrum disorder in their study samples. One such study identified far higher comorbidity rates between schizophrenia and autism spectrum disorder than noted above. Hallerbäck et al (2012) examined 46 young adults aged 23 - 33 years with schizophrenia or schizoaffective disorder for the presence of autism spectrum disorder using the SCID, DISCO-11 and AQ. A significantly higher prevalence rate for autism spectrum disorder was recorded at 52%, mostly among the subgroup with paranoid schizophrenia. The

authors acknowledge their rates are ‘clearly at odds with the widespread clinical view that there is little or no overlap between autism and schizophrenia’ which they attribute to limitations in their study design such as small sample size, preponderance of males and use of the DISCO-11 instead of gold standard tools such as the ADI-R and ADOS-G.

This study showed a 4% prevalence rate of schizophrenia in normal IQ adults with autism spectrum disorder. It also identified schizophrenia as the only psychotic disorder diagnosed in participants with autism spectrum disorder. This rate is in keeping with previous literature and midway between previously reported rates of zero percent to 8%.

Substance Use Disorders in Normal IQ Adults with Autism Spectrum Disorder

Research is at odds regarding the use of substances by individuals with autism spectrum disorder. Authors have suggested that individuals with autism spectrum disorder may turn to drugs and alcohol in an attempt to alleviate social awkwardness, thereby increasing their risk for substance use disorder (Sizoo, 2009). However, Miles and McCarthy (2012) proposed that individuals with autism spectrum disorder would have lower rates of substance use disorder owing to their lack of peer relationships and lack of social interactions in which alcohol / drugs would be a feature.

Ketelaars et al (2008) and Hofvader et al (2009) reported substance use disorder of 16% - 20% in adults with normal IQ autism spectrum disorder in Northern Europe. In 2009, Sizoo et al examined 75 normal IQ adult patients with autism spectrum disorder and comorbid addictive alcohol and drug use identifying a prevalence rate of 18% for comorbid substance use disorder in the Netherlands. In 2010, when examining a further 70 normal IQ adults with autism spectrum disorder, the group noted a prevalence rate of 30% for alcohol, drug and gambling addiction (Sizoo, 2010). Joshi et al (2013) reported current alcohol and drug addiction rates of 6% and 3% consecutively in a group of 63 normal IQ adults with autism spectrum disorder in the United States of America.

Although rates vary widely and research in the area is severely limited, it does appear substance use disorder in normal IQ adults with autism spectrum disorder ranges from 3% - 30%. This is lower or in line with rates of addiction in both the general population

and the psychiatric population (Sizoo 2010, Miles 2012) indicating substance use disorder is no more prevalent in the ASD population than in other populations. Early identification and diagnosis of those with substance use disorder remains an important issue to ensure those with the comorbidity receive early and appropriate treatment (Singh 2012, Kronenberg 2014). A targeted approach to individuals with comorbid substance use disorder and autism spectrum disorder, differing to the approach applied to treatment of addiction in the general or other psychiatric populations, can be used to good effect (Kronenberg, 2014). This includes creating and maintaining structure in the lives of those with autism spectrum disorder and addiction as well as working to strengthen their self-management skills (Kronenberg, 2014).

This study identified a 2% prevalence for substance use disorder in normal IQ adults with autism spectrum disorder. Alcohol addiction was found to be the most frequently occurring substance use disorder. This rate is significantly lower than that quoted in previous literature. However, individuals with autism spectrum disorder were statistically less likely to use illicit drugs than individuals with other psychiatric illnesses assessed in this study, which is in line with previous literature.

Eating Disorders in Normal IQ Adults with Autism Spectrum Disorder

Eating disorders include anorexia nervosa, bulimia nervosa and binge-eating disorder (American Psychiatric Association, 2013). Lifetime prevalence estimates among women in the general population are: anorexia nervosa 0.9%, bulimia nervosa 1.5% and binge-eating disorder 3.5% (Hudson, 2007). Rates among men in the general population are slightly lower at: anorexia nervosa 0.3%, bulimia nervosa 0.5% and binge-eating disorder 2% (Hudson, 2007).

While research on eating disorder in normal IQ adults with autism spectrum disorder is scarce, it is agreed that autism spectrum disorder is over-represented in the anorexia nervosa population (Oldershaw, 2011). A single study was identified from the literature quoting a prevalence rate for eating disorder among adults with normal IQ autism spectrum disorder, Hofvander et al (2009) who found 5% of their study sample suffered from an eating disorder. The rate seen in this study is similarly low at 2%.

Tic Disorder, including Tourette's syndrome in Normal IQ Adults with Autism Spectrum Disorder

While considerable comorbidity between tic disorder and autism spectrum disorder is noted in child cohorts (Bejerot, 2007), the prevalence of adult Tourette's syndrome and tic disorder in the ASD population has been reported only three times. Hofvander et al (2009) reported a 20% prevalence rate of tic disorder, Lugnegård et al (2011) identified a 5% prevalence rate for Tourette's syndrome and Joshi et al (2013) reported a lower rate of 2%. This study showed a prevalence rate of 1%, which is a further reduction in rates. It is interesting that the rate of comorbid Tourette's syndrome is so low considering the neurodevelopmental origins of both disorders. This may be due to difficulty distinguishing between tics and stereotyped repetitive behaviours (Lainhart, 1999). Without targeted research it is not possible to determine whether the low rate is due to expert clinical skill leading to clearer diagnostic identification of tic disorder in those with normal IQ autism spectrum disorder or poor diagnostic ability leading to misdiagnosis and under-reporting.

Catatonia in Normal IQ Adults with Autism Spectrum Disorder

To the best of my knowledge a prevalence rate for catatonia in adults with normal IQ autism spectrum disorder has not been published. This study is the first to refer to catatonia in this population and reports a prevalence rate of zero percent. This is unexpected given a reported prevalence of 6% - 18% in child and intellectual disability populations and the high rate of other illnesses, with which catatonia is associated, in this population. In this study, it may relate to the lack of a screening questionnaire for catatonia as part of the assessment process, it may be due to the low occurrence of the more commonly catatonia-associated physical and psychiatric illnesses in the study sample or catatonia may in fact be an extremely rare condition among adults with normal IQ autism spectrum disorder.

Psychiatric Illness in Asperger's Syndrome Compared to Other Forms of Autism Spectrum Disorder

Research findings in the area of outcome and comorbidity by ASD subtype is sparse. Ghaziuddin et al (2002) noted a lack of research on conditions co-occurring with milder forms of autism spectrum disorder, such as Asperger's syndrome and PDD-nos, compared to childhood autism. This was reinforced in 2008 by Ketelaars et al who noted an ongoing deficit in research. In 2005, Billstedt et al reported a tendency towards poorer outcome in individuals with 'classic' autism compared to those with milder forms of the condition. However, this study is not entirely representative as 95% of their study sample had a comorbid intellectual disability.

This study showed that individuals with Asperger's syndrome were statistically more likely to be diagnosed with a comorbid psychiatric illness compared to individuals with other forms of autism spectrum disorder. It also showed that obsessive compulsive disorder occurred at a statistically higher frequency among participants with Asperger's syndrome compared to participants with other forms of autism spectrum disorder. Although Asperger's syndrome was previously considered to have a substantially better social outcome than childhood autism - such as higher psychosocial adjustment, higher rates of independent living, greater educational attainment and more frequently in a relationship (Cederlund 2008, Henninger 2012, Lehnhardt 2012), no comparable research is available in relation to rates of comorbid psychiatric illness. It is possible that individuals with Asperger's syndrome could show greater social attainment while still suffering from higher rates of comorbid psychiatric illness.

Gender Differences in Rates of Psychiatric Illness in Normal IQ Adults with Autism Spectrum Disorder

Although studies from the 1990s showed that females with autism spectrum disorder tended to do worse than males (Billstedt, 2005b), research in the 2000s showed males fare worse than females (Cederlund, 2008). To complicate the picture further, more recent research would imply that the differences between outcomes in males and females are very few (Hofvander, 2009) or non-existent (Lugnegård, 2011). Vannucchi et al (2014a) have suggested that women display greater improvements in compensatory socio-communication ability into adulthood suggesting outcomes can

vary if older females are assessed. Kočovská et al (2012) agree that age of assessment impacts on findings in female cohorts, but argue in the opposite direction, saying more female cases of autism spectrum disorder are missed if assessed at a younger age. Although statistical significance was lost on correction for multiple testing, this study initially showed that adult females with autism spectrum disorder are more likely to suffer from bipolar affective disorder than males. As bipolar affective disorder was relatively rarely diagnosed among the study sample, examination of a larger cohort could possibly clarify this finding.

Discrepancies remain as to the impact of gender on epidemiology, symptom expression and outcomes in autism spectrum disorder. This area would benefit from further research given the significant rates of morbidity and social suffering associated with undiagnosed bipolar affective disorder and mania.

4.4.3 Physical Illness in Normal IQ Adults with Autism Spectrum Disorder

Early researchers believed individuals with autism spectrum disorder lacked the ability to perceive pain, to communicate their distress and in fact lacked 'the social inclination' to do so (Lainhart, 1999). More recently authors have hypothesised that individuals with autism spectrum disorder have difficulty reporting physical complaints and instead express pain and physical distress as agitation and / or behavioural disturbance (Russell, 2005). There is an urgent need to accurately assess the patterns and rates of physical comorbidity in adults with autism spectrum disorder. At planning and policy level, it is also important to understand the physical health needs of adults with autism spectrum disorder, if clinicians are to ensure the delivery of effective treatment services (Mouridsen, 2012).

Medical conditions are seen in approximately 10% - 20% of the intellectual disability population suffering from autism spectrum disorder (Oliveira, 2007). A number of conditions in particular are thought to occur more commonly, including epilepsy, tuberous sclerosis and retinopathy (Gillberg, 2000). However, previous literature on comorbidity in normal IQ adults with autism spectrum disorder is sparse. Only anecdotal accounts exist in relation to adults with normal range IQ, many of which hypothesise that rates of physical ill-health are increased compared to the general population (Howlin, 2012). This study could not identify a comparable paper of physical

illness rates in normal IQ adults with autism spectrum disorder. The closest matching research was a study by Kelbrick et al (2015), which looked at physical illness in 16 adult males with mixed IQ levels. Kelbrick and colleagues identified a prevalence rate of 50% for at least one comorbid physical illness across a range of body systems. The most commonly reported ailment was cardiometabolic illness including hyperlipidaemia, excess weight, low activity levels and hypertension.

This study identified a prevalence rate of 84% for at least one physical health condition among normal IQ adults with autism spectrum disorder, noting atopy, asthma and head-injury to be the most commonly reported physical ailments. Findings would suggest physical ill-health to be more common among adults with normal IQ autism spectrum disorder compared to a mixed IQ sample. This is unexpected as the proven increased rates of physical illness among adults with intellectual disability compared to the general population (Emerson, 2016) would suggest that physical illness in normal IQ autism spectrum disorder surpasses both.

Neurological Conditions in Normal IQ Adults with Autism Spectrum Disorder

The prevalence of epilepsy within the neurotypical population is reported as 2% - 3% for children and 0.63% for adults (Canitano 2007, Bolton 2011). To my knowledge, only a single study has reported the prevalence rate of epilepsy among normal IQ adults with autism spectrum disorder. Mouridsen et al (2011) reported epilepsy rates among 118 adults who had received a diagnosis of autism spectrum disorder as children. Their study group was of mixed IQ but as they report results for each of three distinct IQ categories, the prevalence rate for epilepsy in adults with autism spectrum disorder and an IQ greater than 69 was noted to be 8.8% (Mouridsen, 2011).

Epilepsy rates in this study were lower than expected at 3%, the third most frequently occurring neurological condition in participants with autism spectrum disorder. As there is only one previous study for comparison, it is difficult to know why the rates in this current study are lower than previously seen. One possible reason could be Mouridsen et al's restriction of their sample to individuals with childhood autism only. Comparably, childhood autism only comprised 25% of this study's cohort of individuals with epilepsy. As childhood autism is considered to be lower functioning than the three other subtypes of autism spectrum disorder and epilepsy occurs at higher rates in low-functioning

individuals, such as those with an intellectual disability compared to the general population, it is possible that the prevalence of epilepsy is higher in individuals with childhood autism compared to those with Asperger's syndrome, PDD-nos and atypical autism. This may indicate an over-representation of the prevalence of comorbid epilepsy in Mouridsen et al's sample. Further research is required to expand the literature on this subject.

Atopy in Normal IQ Adults with Autism Spectrum Disorder

Atopy was the most prevalent disease among participants with autism spectrum disorder recorded at a rate of 22%. This group consisted primarily of individuals suffering from asthma (16%). Rates for allergic rhinitis and eczema were 6% and 5% respectively.

It is difficult to compare rates of asthma in those with normal IQ autism spectrum disorder to the general population given the significant geographical variation in asthma prevalence and the scarcity of literature relating to asthma in individuals with autism spectrum disorder. The illness is thought to occur at an average rate of 4.3% worldwide (To, 2012). However it appears at the significantly higher rate of 18% in the United Kingdom, where this study sample resided (To, 2012).

Two studies reporting rates of asthma in autism spectrum disorder were identified as part of the literature review for this study. Lyall et al (2015) recorded a prevalence rate of 16% in a child cohort in the USA. Kobayashi et al (1998) reported a significantly lower rate of 7% in adults with intellectual disability in Japan. Comparatively, the general population prevalence rates for asthma in the United States and Japan are lower at 7.8% and 6.5% respectively (Nishima 2009, Moorman 2011). A prevalence rate for asthma in normal IQ adults with autism spectrum disorder could not be identified as part of the literature search for this study. Overall however, it would appear that the rate of 16% identified in this study is comparable to the rate seen in the general population in the same region.

Allergies in Normal IQ Adults with Autism Spectrum Disorder

This study reported a prevalence rate of 43% for allergies in adults with autism spectrum disorder. Lyall et al (2015) reported a slightly higher rate of allergy in those with autism spectrum disorder compared to neurotypical controls in a sample of 951 children in the United States, occurring in 42% and 40% respectively. Dairy was the most frequently occurring food allergy and penicillin was the most frequently occurring medication allergy. This study showed comparable rates of overall allergy to those seen in Lyall et al's normal IQ paediatric cohort.

Food allergies are estimated to affect 5% of the general adult population (Sicherer, 2014) and were suspected to be higher in individuals with autism spectrum disorder (Råstam, 2008). This study identified food allergies among 2% of the ASD sample. Despite Råstam et al's prediction, rates of food allergy appear to be lower than that seen in the general population. Rates of medication allergy in the general population are approximately 7% (Demoly, 2014). This study reported a medication allergy rate of 10%, slightly higher than that seen in the general population. A comparable prevalence rate for allergies, to food or medication, in adults with normal range IQ and autism spectrum disorder could not be identified as part of the literature review for this study.

Sleep Difficulties in Normal IQ Adults with Autism Spectrum Disorder

Sleep appears to be a relatively well-researched topic in autism spectrum disorder. In fact, it has been referred to as the second most researched area of ASD comorbidity, only surpassed by epilepsy (Mannion, 2014b). This literature review supports this finding sourcing a large number of studies relating to normal IQ individuals of all ages with autism spectrum disorder. A possible reason for the greater interest in sleep disorders may be the established link between sleep disturbance, age and intellectual functioning in autism spectrum disorder.

Sleep studies in normal IQ infants with autism spectrum disorder have shown that 90% of sleep difficulties start at an early age including difficulty falling asleep, more frequent night waking and early morning waking (Øyane, 2005). Studies of school-age children with autism spectrum disorder have noted difficulties with bedtime resistance, increased sleep latency, poor sleep maintenance, early morning waking, reduced

sleep time and quality, increased night waking and irregular sleep patterns in 50% - 80% of subjects (Øyane 2005, Limoges 2005, Canitano 2007, Reynolds 2011). Insomnia rates of 36% have been reported in the child population, most commonly middle insomnia, followed by initial insomnia (Mattila, 2010). Adolescent and young adult studies also identify a high prevalence of sleep disorders (80%) including low sleep efficiency, short total sleep time, long sleep latency, more frequent shifts into REM sleep from waking and increased REM sleep disruption (Ghaziuddin 2002a, Øyane 2005).

Studies in adults with normal IQ autism spectrum disorder have identified a less stable circadian rhythm relating to sleep, weaker links to environmental synchronisers, difficulty initiating and maintaining sleep, increased early morning waking, increased REM sleep disruption and fragmentation, reduced sleep quality, quantity and efficiency, reduced periods in NREM and slow wave sleep, reduced rapid eye movements during REM sleep, reduced sleep spindles with increased θ power and reduced Δ power on EEG and higher rates of periodic limb movements of sleep (Godbout 1999, Tani 2003, Tani 2004, Limoges 2005, Hare 2006a). However, as yet the prevalence rate for sleep disturbance and sleep disorders among adults with normal IQ autism spectrum disorder have not been reported (Deliens, 2015).

In this study, 42% of participants with autism spectrum disorder reported sleep difficulties. Initial insomnia was the most frequently occurring sleep difficulty followed by middle insomnia, reversal of sleep-wake cycle, childhood insomnia and early morning waking. Hypersomnia was rarely reported. To my knowledge, this is the first recorded prevalence rate of sleep difficulties in adults with normal IQ autism spectrum disorder. It is comparable to rates seen in school-age children but lower than rates reported in adolescents. This suggests that while sleep difficulties vary with age in individuals with autism spectrum disorder, rates remain extremely high at each developmental stage.

The aetiology of sleep disturbance in individuals with autism spectrum disorder remains to be clarified. A number of theories have been proposed over the decades, although none have proven sufficient to explain each impairment of sleep function. Some theories are outlined below, the variety of which suggests the aetiology of sleep difficulties in autism spectrum disorder is most likely multifactorial.

- Psychiatric illnesses such as depression and demographic factors such as gender could influence sleep quality and quantity, however this has not been shown by objective assessment (Tani 2004, Hare 2006a).

- A previous suggestion by Tani et al (2004) that increased baseline anxiety worsening sleep quality and quantity was explored by Limoges et al in 2005. Limoges and colleagues measured both anxiety and cortisol levels in normal IQ adults with autism spectrum disorder with and without sleep disturbance. They showed both anxiety scores, rated on the State-Trait Anxiety Inventory and saliva cortisol levels to be equal in both groups concluding 'this prevents further association' between anxiety spectrum disorders, autism spectrum disorder and sleep disturbance (Limoges, 2005).
- Physical comorbidities commonly seen in those with autism spectrum disorder such as epilepsy, obstructive sleep apnoea, constipation, eczema and asthma could account for a proportion of sleep difficulties (Richdale 2009, Reynolds 2011).

- Strict nocturnal routines, as part of the insistence on sameness, seen in autism spectrum disorder have been suggested as a cause for poor sleep patterns in ASD individuals. Theorists suggest a rigid and unusual night-time routine can lead to difficulty settling to sleep (Richdale, 1999) and could explain difficulties with sleep latency.

- Social and communication deficits have been suggested as resulting in the ASD individual missing environmental cues that act for others as indicators of bedtime (Richdale, 2009).

- Hypersensitivity to external noise has been proposed as a cause for initial insomnia in those with autism spectrum disorder (Tani, 2003).

- Neurochemical and neuropharmacological studies have noted deficits in plasma 5-HT in individuals with normal IQ autism spectrum disorder. This could be associated with sleep disturbance as melatonin, a major element in the modulation of the circadian rhythm relating to the human sleep-wake cycle, is

synthesised from serotonin (Hare 2006a, Reynolds 2011). Abnormal levels of melatonin and elevated levels of catecholamines have also been implicated in paediatric studies (Venkat, 2012).

- In my opinion, increased use of hypnotics and benzodiazepines in the adult ASD population could also account for the differences in sleep patterns. However, studies to date have not examined this possible link.

It is important to determine the presence of sleep difficulties in individuals with autism spectrum disorder as such difficulties are highly debilitating yet highly amenable to treatment. Treatment options for sleep difficulties in individuals with autism spectrum disorder include behavioural therapy, chronotherapy, light therapy, massage therapy and use of immediate-release melatonin to reduce sleep latency or controlled-release melatonin to increase total sleep time (Richdale 1999, Øyane, 2005, Canitano 2007, Galli-Carminati 2009, Guénolé 2011, Deliens 2015).

Eating Disturbance in Normal IQ Adults with Autism Spectrum Disorder

Although historically considered almost diagnostic for autism spectrum disorder, eating disturbance is now known to be associated with only 12% - 40% of child and / or intellectually disabled individuals with autism spectrum disorder (Gillberg 2000, Whiteley 2000, Råstam 2008, Kuschner 2015). As part of the literature review for this study, the author was unable to find a published prevalence rate for eating disturbance in normal IQ adults with autism spectrum disorder. Kuschner et al (2015) also noted an absence of published literature relating to abnormal eating habits in adults with autism spectrum disorder without an intellectual disability.

Six of Kanner's original case studies displayed feeding difficulties in infancy while two of Asperger's cases had a below average body weight (Kanner 1943, Råstam, 2008). Kanner (1943) proposed that the rejection of food by infants with autism spectrum disorder was their way of expressing an anxiety to 'keep the outside world away' and an effort to not be interfered with. Through the 1980s and 1990s, a link was made between excess CNS opioid, derived from gluten and casein foods, and challenging behaviour in children with autism spectrum disorder (Whiteley, 1999). A Cochrane

review in 2008 showed evidence for this theory to be poor (Millward, 2008) and it has since largely fallen from favour (Lange, 2015). More recently, Kuschner et al (2015) reported a preference for familiar foods, dislike of textured foods such as apple sauce, cottage pie and chunky peanut butter and strong flavours such as spices among 65 adolescents and young adults with normal IQ autism spectrum disorder. This suggests a link between eating disturbance and sensory processing difficulties in the normal IQ ASD population.

Eating disturbance was noted in 25% of participants with autism spectrum disorder in this study. Restricted dietary repertoire was the most commonly reported eating disturbance. Further difficulties included reduced appetite, picky eating, eating only a single meal per day, only eating when alone, unhealthy dietary choices, binge-eating, overeating and unhealthy dietary choices. Though rates are comparable to those seen in child and intellectual disability ASD populations, true comparison is not possible due to the likely differences in clinical significance, social impact of such difficulties and available healthcare / treatment services to children and individuals with intellectual disability such as dietetics, occupational therapy and speech and language therapy, not currently available for normal IQ adults with autism spectrum disorder. It is unfortunate that the findings of this study cannot be compared to rates in the general population or the normal IQ ASD population, given the significant number of participants outlining such difficulties.

Motor Skills in Normal IQ Adults with Autism Spectrum Disorder

Asperger described awkwardness as typical in autistic psychopathy (Wing 2002a, Barnhill 2007, Raja 2009) while Kanner (1943) noted that several children under his care were somewhat clumsy in gait with gross motor deficits but all were skilled in fine motor movements. Although not included in the DSM-5 diagnostic criteria, clumsiness is commented upon in the ICD-10's description of Asperger's syndrome (World Health Organisation, 1992). Wing (1981) observed poorly co-ordinated movements, odd posture and abnormal gait while more recently Vannucchi et al (2014b) described clumsiness and illegible handwriting as atypical features of Asperger's syndrome and Van Wijngaarden-Cremers et al (2014) noted clumsiness in the case of a 14 year old girl with Asperger's syndrome and comorbid drug addiction.

In general, it is acknowledged that motor skill deficits are frequently observed in patients with autism spectrum disorder with a prevalence of 21% - 100% (Gowen, 2012). This study reports dyspraxia rates of 8% in adults with normal IQ autism spectrum disorder. This rate is lower than that previously reported. This may be due to the lack of a screening questionnaire for motor skill deficits as part of the clinical assessment or the lack of occupational therapy input as part of the multidisciplinary assessment.

Smoking in Normal IQ Adults with Autism Spectrum Disorder

Available research on smoking rates in those with autism spectrum disorder is sparse (Mattila, 2010). As part of this literature review, only two papers were found in relation to this research question, Bejerot and Nylander (2003) and Joshi et al (2013). Bejerot and Nylander (2003) reported a current smoking rate of 15.8% in 95 community dwelling normal IQ adults with autism spectrum disorder in Stockholm, Sweden. 'Current' smoking was defined as the consumption of at least one nicotine containing product (cigarette or snuff) per day for the preceding six months. Joshi et al (2013) reported a current smoking rate of zero percent in 63 adults with normal IQ autism spectrum disorder attending an adult neurodevelopmental clinic in Massachusetts, USA. Smoking prevalence among the general public is 10.7% in Sweden and 13.7% in North America (OECD, 2013). Both papers suggest a lower rate of smoking in patients with autism spectrum disorder compared to the psychiatric population but comparable rates to the general public.

This study identified a similarly low rate of smoking in adults with normal IQ autism spectrum disorder compared to the general population. In 2014, 19% of adults in the United Kingdom were smokers (Ash, 2016). As only 12.5% of ASD participants in this study were recorded as current smokers, the rate is comparably lower. In fact, smoking was statistically less likely in those with autism spectrum disorder compared to neurotypical study participants. Suggestions as to the reason for lower smoking rates in those with autism spectrum disorder compared to those with other psychiatric illnesses include reduced social outlets, rigid routines and lower reward dependence (Bejerot, 2003).

Gastrointestinal Disease in Normal IQ Adults with Autism Spectrum Disorder

Available research in relation to gastrointestinal disease in autism spectrum disorder is varied and controversial. Less again is available in relation to the prescription of gastrointestinal medications in individuals with autism spectrum disorder. However, both the literature review and identified rates of gastrointestinal disease among ASD participants in this study would suggest that previously reported higher rates of gastrointestinal disease in individuals with autism spectrum disorder were greatly exaggerated. In this light, the finding that participants with autism spectrum disorder were statistically more likely to take medication for gastrointestinal illness, was unexpected. Literature could not be found which may explain this discrepancy. However, this finding may suggest a lingering perception among physicians that individuals with autism spectrum disorder are at higher risk of gastrointestinal disease, leading to potential diagnostic overshadowing when assessing patients with ambiguous physical symptoms. Further research among primary care physicians would be helpful in determining which treatment options they consider in adults with normal IQ autism spectrum disorder and vague physical symptoms.

Dyslexia

Previous literature identifies a prevalence rate of 14% for dyslexia in normal IQ adults with autism spectrum disorder (Hofvander, 2009). Dyslexia was infrequently recorded in the BGC medical reports reviewed for this study. It would appear that a greater number of participants received a diagnosis of dyslexia from their community mental health team (dyslexia 8.5%) than at the Behavioural Genetics Clinic (dyslexia 0.3%). It is most likely that dyslexia was under-reported in this study as the diagnosis requires specialist testing by a psychologist, testing which was not undertaken as part of the assessment.

4.5 Possible Aetiology of Comorbid Psychiatric Illness in Autism Spectrum Disorder

There have been many studies that explore the factors placing individuals with autism spectrum disorder at increased risk of psychiatric illness but the results of each study

and opinion of each researcher varies significantly (Howlin, 2012). While Van Elst (2013) promotes a causal relationship between autism spectrum disorder and psychiatric illness, specifying that autism spectrum disorder symptoms result in chronic conflicts and failure in relationships which in turn lead to depression, anxiety spectrum disorders and sometimes psychosis-like stress reactions, other researchers have not been so direct. A broad range of risk and causal factors have been suggested including age, degree of social deprivation, interplay of environmental factors, poor self-confidence, severity of ASD symptomatology particularly communication deficits, experience of major life transitions and life events such as loss, inadequate support, loneliness and social isolation often associated with rejection by peers (Kannabiran 2009, Howlin 2012).

Stress Response

Stress is a physical reaction of the body to happy or unhappy life events, which place the individual under pressure to maintain the homoeostasis of equilibrium (Hirvikoski, 2014). It is a subjective experience when an individual feels the perceived social demands outweigh their available resources and skill-set (Hare, 2014). Exactly what type of experience or demand is considered stressful differs from individual to individual as does the individual's subjective opinion of their ability to withstand such pressures (Hirvikoski, 2014). Should the individual repeatedly endure such stressors, psychological sequelae can result including psychiatric illness (Groden, 2001). Individuals with autism spectrum disorder report significantly higher stress levels and a poorer ability to cope compared to neurotypical individuals (Hirvikoski, 2014). This could account for a higher rate of psychiatric illness in this population.

Hirvikoski et al (2014) examined self-perceived stress levels in 25 adults with autism spectrum disorder in Stockholm, Sweden. In this study, intellectually able adults with autism spectrum disorder reported high levels of subjective stress and a perception of low coping ability regarding stressors in everyday life. High levels of self-perceived stress were statistically associated with higher perceived distress and lower perceived coping ability, akin to the levels previously shown for individuals with attention deficit hyperactivity disorder. Hirvikoski and colleagues suggest a link between executive dysfunction, sensory processing difficulties and impaired adaptive behaviour in autism

spectrum disorder and the inability to select an appropriate coping skill. Despite average intellectual capacity, individuals with autism spectrum disorder struggle in many everyday situations (Hirvikoski, 2014). Without the required coping skills to adequately manage such stresses they are at increased risk for anxiety spectrum disorders and depressive illness (Gillott 2007, Hare 2014).

Many of life's greatest challenges are endured during adolescence. It is the time of greatest change, of self-awareness and self-development, a time of individuation from the primary care giver and of starting one's journey into adulthood. This transition to adulthood is particularly challenging for individuals with autism spectrum disorder. The increased requirement for proficient interpersonal skills to develop social relationships and a supportive social network is notably absent for young adults with autism spectrum disorder (Barnhill 2007, Hare 2014).

As early as 1998, Ghaziuddin et al hypothesised that if depression is proven to be more common in individuals with autism spectrum disorder 'it may be linked to difficulty in coping and the resulting social stigma experienced by patients during adolescence'. In 1999, Lainhart suggested that 'difficulties in coping with situations result in dysfunctional behaviours and distressful emotions such as anxiety and depression'. More recently, significant similarity has been shown between an ASD individual's response to stress, namely through high levels of self-focus and rumination, and the cognitive models of generalised anxiety disorder (Hare, 2014).

Increased insight into the causes of stress, distress and perceived inability to cope with social demands in individuals with autism spectrum disorder would be a valuable step in understanding the pathway to psychiatric illness in this population. Early diagnosis and appropriate support and treatment opportunities would be invaluable in this setting.

Interpersonal Difficulties and Social Isolation

Features of autism spectrum disorder can negatively affect social functioning. Predisposing factors include a compromised capacity for mentalising the feelings and self-states of others, poor social perception and social incompetence (Rydén 2008b, Van Elst 2013). Since the early 1980s, it has been suggested that the ASD individual's subjective awareness of reduced social functioning can lead to negative self-image, feelings of distress, high anxiety states particularly social anxiety, interpersonal

difficulties, over-sensitivity to criticism, vulnerability to bullying and victimisation, self-isolation and loneliness (Wing 1981, Barnhill 2007, Rydén 2008b, White 2011). More recently, Van Elst et al (2013) argue that many cases of comorbid psychiatric illness including depression, anxiety spectrum disorders and some psychosis-like stress reactions, are a direct result of influential ASD symptoms which result in interpersonal misunderstandings and failure in personal and work relationships.

Autism Symptomatology

An association has been shown between severity of ASD symptomatology and rates of psychiatric illness. Symptoms such as insistence on sameness, an extensive repertoire of fixed behaviours and routines, hyper- and hypo- reactivity to sensory input and a fear of change have a relationship with clinically detectable psychiatric illness (Gillott, 2007). The inability to accurately predict another's intent, actions or emotions can lead to fear, severe panic and anxiety (Lainhart, 1999). Reduced fine motor co-ordination can lead to avoidance or compulsive behaviours (Lainhart, 1999). Sometimes, cognitive compensatory strategies such as keeping eye contact and ensuring accurate turn taking in conversation could lead to exhaustion in adulthood (Van Elst, 2013). Depression and anxiety spectrum disorders in particular are felt to result from increased severity of ASD symptomatology (Van Elst 2013, Hare 2014).

4.6 Critique of Study Design, Methodology and Sample Selection

Strengths of the Study

- This study is the first to examine rates of psychiatric and physical comorbidity in adults with normal IQ autism spectrum disorder outside of mainland Europe and the United States of America. Previous literature from the United Kingdom has referred to mixed IQ adult samples or child cohorts. No previous literature referring to adults with normal IQ autism spectrum disorder could be sourced on an Irish population.

- This study examines the largest cohort of normal IQ adults to date. Previous studies have ranged in number from 12 to 130 adults, this study includes over double that number at 288. This study includes adults across a broader age range than previous studies. Previous studies looked at adults up to age 60 years, this study includes adults up to age 70 years. This study includes a sizeable proportion of female participants and participants aged over 50 years, two demographics which have been significantly under-represented in previous studies. Researchers propose that time and financial constraints have previously prevented such a cohort being examined.

- This study was based in a national tertiary referral centre specialising in the assessment of adults with normal range IQ for autism spectrum disorder. Consultant, NCHD and psychology staff are highly skilled in the diagnosis of autism spectrum disorder and other psychiatric illnesses. Assessments were lengthy and thorough as clinicians used clinical interview, collateral information, referral letters, school reports, previous clinical reports, expert clinical opinion and multidisciplinary consensus meetings to reach clear diagnoses supported by gold standard diagnostic tools. All findings were presented in clear standardised reports. These methods exceed previous research for rigour and completeness.

- All diagnoses of psychiatric comorbidity and autism spectrum disorder were in line with the ICD-10, removing an obstacle encountered by previous researchers when diagnostic criteria changed mid-study. All consultants provided patients with comorbid diagnoses where appropriate, despite hierarchal systems endorsed by ICD-10.

Limitations of the Study

- The single largest limitation to this study is the lack of a definitive IQ measurement for each participant. There is a possibility that participants with an IQ outside of the normal range were included as IQ was not directly

measured during each assessment. However, dedicated autism spectrum disorder clinics assess very low proportions of patients with genetic syndromes or autism spectrum disorder related to a known medical condition and these children and adults are typically seen in medical genetics clinics (Miles, 2011). Furthermore, significant care was taken to identify and exclude any participant with a documented or suspected low range IQ or intellectual disability at the data gathering stage of this study.

- The use of a clinical sample of individuals referred by community psychiatric services is a limitation of this study and a community based, targeted recruitment would have been preferable. However, this approach is widely cited as time-consuming, resource-consuming and expensive due to the nature of the diagnostic assessment required. This reduced the feasibility of recruiting a population-based cohort. The present design may thus be the only feasible option. Alternatively, use of a psychiatrically-referred population could be considered a strength in a clinical sense, as the sample under investigation could more closely represent those patients seen by psychiatry colleagues on a daily basis allowing greater generalisability.

- Although all attempts were made to extensively include all potential comorbid psychiatric and physical illnesses in a normal IQ autism spectrum disorder adult population, no comprehensive list of such disorders has been previously compiled. This study focuses on well-known Axis I and II psychiatric conditions and major physical illnesses.

- Certain parameters were recorded through patient report only. This could lead to bias relating to poor recall - examples include history of bullying, childhood eating or sleeping difficulties and medical history. Formal assessment such as a questionnaire relating to childhood bullying, parental collateral on childhood disorders or medical records from the participant's general practitioner could have strengthened the reliability of these data.

- Although it would have been preferable to record both prevalence and incidence of all psychiatric and physical illnesses, the use of a cross-sectional sample does not definitively allow measurement of illness by age of onset, only by binary presence or absence at a particular age.

- The Behavioural Genetics Clinic does not routinely accept referrals for patients who currently use illicit substances. Consequently, this could reduce this study's ability to pick up a truly reflective prevalence of drug use in participants with autism spectrum disorder.

- Sourcing literature on autism spectrum disorder was difficult. Many articles focused on a particular subtype of autism spectrum disorder such as childhood autism or Asperger's syndrome, while others favoured a particular subset of participants such as children, adolescents, adults or the intellectually disabled population. Unfortunately, the majority of authors mixed their study populations, often combining children with adults or intellectually disabled participants with those of normal intellectual functioning. Some authors also failed to differentiate between mixed population studies when citing previous research; misrepresenting rates of illness among adults by quoting mixed age studies, rates in normal IQ populations by quoting mixed IQ research and aetiology in humans by quoting primate studies. Care had to be taken to prevent similar errors in this study. While an abundance of literature focusing on children and intellectually disabled populations was available, literature pertaining to normal IQ adults with autism spectrum disorder was scarce.

- Despite the limitations of this study, it highlights high rates of psychiatric and physical comorbidity in an under-researched population and is the largest study sample ever to report on this research topic.

4.7 Implications for Clinical Practice

Diagnosis of autism spectrum disorder in normal IQ adults is difficult but crucial (Spencer, 2011). Individuals with normal IQ autism spectrum disorder suffer higher rates of physical and psychiatric morbidity, display a poorer ability to engage with treatment and have a lower chance of recovery. Suspecting and accurately diagnosing autism spectrum disorder is important in both understanding the patient's psychopathology and in directing treatment.

Considering the genetic heritability, neurocognitive deficits, complex psychiatric comorbidity, significant physical health needs and the nature of the treatments proposed, it is reasonable that psychiatry, based within a multidisciplinary team, is the best placed discipline to take responsibility for the assessment, diagnosis and treatment of patients with autism spectrum disorder.

As children previously diagnosed with autism spectrum disorder by child and adolescent psychiatrists are growing into adults, they require ongoing medical and psychiatric input for complex healthcare needs. As adults, they expect the same degree of expertise and knowledge available to them when they were children (Nylander, 2008). At present, the health services are not adequately resourced or trained to fulfil this requirement. The diagnosis and treatment of physical and psychiatric morbidity and comorbidity in normal IQ adults with autism spectrum disorder is a significant unmet need.

Adults with normal IQ autism spectrum disorder have particular and highly specific needs. Community mental health teams, general practitioners, hospital medical staff and liaison psychiatrists may not be well equipped to diagnose or treat this population. Clinicians, at all stages of training and in all disciplines, should be educated to consider autism spectrum disorder more frequently in their patients and to adjust not only their treatment models but their clinical approach to a large cohort of patients with significant social and communication difficulties.

The clinical recommendations from this study are:

- Improved knowledge of childhood disorders (autism spectrum disorder, attention deficit hyperactivity disorder and Tourette's syndrome) by adult physicians and psychiatrists as well as increased knowledge of adult disorders (personality disorders) by child psychiatrists and paediatricians is needed to better serve patients.

- Increased awareness of complex symptom presentations and diagnostic overshadowing is required to prevent inappropriate and / or ineffective treatments as inappropriate and / or ineffective treatments lead to poorer engagement with treatment, leading to poorer health and social outcomes.

- Strong consideration should be given to creating specialist multidisciplinary diagnostic teams for assessment and treatment of autism spectrum disorder in adults with normal range IQ in the Republic of Ireland.

- Multidisciplinary assessment teams should consist of psychiatry, psychology, occupational therapy and speech and language therapy specialists to ensure not only accurate diagnosis of a neurodevelopmental disorder if present, but accurate detection of each comorbid condition associated with the disorder.

- Increased awareness of autism spectrum disorder, increased availability of assessment, creation of targeted treatments programmes and ongoing research in the area of adult autism spectrum disorder is vital.

4.8 Implications for Future Research

The area of autism spectrum disorder and comorbidity is grossly under-researched, underdiagnosed and undertreated. The problem to date underlying all research has been the human and financial resources and the considerable cost involved (Wing, 2002a). A need for increased research into the neural basis of anxiety spectrum

disorders in autism spectrum disorder, the prevalence rate of epilepsy in normal IQ adult autism spectrum disorder, the impact of gender on comorbidity and the causes of stress and varying coping styles that result in higher rates of comorbidity, were identified as under-researched areas of the literature. This study is an initial step towards meeting that need, hopefully improving understanding of psychiatric and physical illness in adults with autism spectrum disorder.

Further research should consider the impact timing of a comorbid condition has on autism spectrum disorder. Research on the temporal relationship of comorbidity in autism spectrum disorder would provide clinicians with a better understanding of the effects of comorbidity at different life stages for a patient with autism spectrum disorder, allowing more efficient research into treatment options.

Further research is required into the link between experience of childhood bullying and increased rates of anxiety spectrum disorders in adults with autism spectrum disorders. Post-traumatic stress disorder in particular is a rarely examined form of anxiety spectrum disorder in those with autism spectrum disorder (Morrow Kerns, 2015). Studies in neurotypical populations show rates of post-traumatic stress disorder among bullied children to range from 28% - 41% and among adolescents to range form 44% - 76% (Idsoe, 2012). Hoover (2015) suggests a combination of self- and parental-report is sufficient to accurately detect bullying rates in future research. Few valid rating scales measuring incidence of bullying could be identified as part of the literature review for this study, however future research may consider use of instruments such as the Social Vulnerability Scale (Sofronoff, 2011) or the Bullying Screener (Wolke 2015) to lend strength to the research design.

Bullying is shown to result in lower educational attainment, increased unemployment, reduced tendency to marry or form longterm relationships, reduced social support and poorer quality of life in neurotypical adults who were bullied as children (Takizawa, 2014). Expansion of this area of research to include the social and economic impact of bullying for normal IQ adults with autism spectrum disorder would be beneficial. Such research would assist previous researchers in calling for educator-based interventions for children with autism spectrum disorder who are bullied in mainstream school to reduce rates or perhaps prevent the negative social, economic and mental health consequences of undetected school-yard bullying on this vulnerable population.

Diagnosis of comorbid psychiatric illness in individuals with autism spectrum disorder is complex with high rates of misdiagnosis and diagnostic overshadowing noted in previous literature (Hannon, 2013). An emerging area of research, the Experience Sampling Method, could assist clinicians in better understanding the often unique presentation of psychiatric illness in normal IQ adults with autism spectrum disorder. Devised in 1975, the Experience Sampling Method is a valid means of capturing the subjective experiences of individuals in their natural environment (Csikszentmihalyi, 2014). The method uses a bleeper or programmed watch to randomly alert the research participant to record desired information using questionnaires or free text. The Experience Sampling Method has a number of advantages over other research designs. It reduces recall bias by using immediate self-report of thoughts, feelings or experiences as they occur, is less intrusive and labour intensive than objective assessment, is more ethical (Weisner, 2001) and more reflective of an individual's subjective experience than semi-structured or structured interview. It has proven high correlation (0.93) with diary entry as a research method (Weisner, 2001).

The Experience Sampling Method could address questions such as the timing, context, nature, severity and impact of psychiatric symptoms in the daily lives of normal IQ adults with autism spectrum disorder. It has been used in neurotypical adult patients to distinguish 'social anhedonia' from social anxiety in schizophrenia and provided clearer descriptions of the subjective experience of agoraphobia (Myin-Germeys, 2009). In 1994, Hurlburt et al used the Experience Sampling Method to examine the inner experiences of three high-functioning adults with Asperger's syndrome. The group demonstrated a greater capacity to describe inner emotional experiences, especially in visual form than previously appreciated. More recently, Hintzen et al (2010) disproved the generally-held belief that a lack of peer relationships on the part of ASD individuals was due to social anhedonia. They showed that normal IQ adults with high-functioning autism spectrum disorder did not prefer to be alone, did not spend more time alone and derived equal pleasure from the company of others as neurotypical controls (Hintzen, 2010). Future researchers should utilise the Experience Sampling Method to enrich clinical information available to diagnosticians thereby improving not only diagnostic methods and diagnostic accuracy but the range and effectiveness of treatment options available to normal IQ adults with autism spectrum disorder.

Research into the ability of normal IQ adults with autism spectrum disorder to access healthcare services and identification of the most appropriate treatment pathways for this vulnerable group is urgently required. Research performed jointly by child and adolescent psychiatrists and adult psychiatrists could be an initial step in this direction. A better understanding of the number of children, adolescents and adults with normal intellectual ability and autism spectrum disorder within the Irish population is not currently available. Data relating to diagnostic rates within the CAMHs service, discharge rates and numbers graduating to general adult mental health services is acutely lacking.

Research questions could include:

- The number of suspected cases of normal IQ autism spectrum disorder referred to the CAMHs service on a yearly basis
- The prevalence of diagnosed normal IQ autism spectrum disorder within the CAMHs service
- An indication of the services provided by CAMHs to children and adolescents with normal IQ autism spectrum disorder
- Discharge rates for children and adolescents with normal IQ autism spectrum disorder from the CAMHs service on a yearly basis
- The frequency of discharge when a patient is considered fit and well compared to the numbers discharged due to unavailability of follow-on care

- The number of suspected cases of normal IQ autism spectrum disorder referred to the general adult psychiatry services on a yearly basis
- The prevalence of diagnosed normal IQ autism spectrum disorder within the general adult psychiatry services

- An indication of the expertise available within general adult psychiatry services to assess and diagnose autism spectrum disorder in adults with normal intellectual ability
- An indication of the resources available to general adult psychiatry services to co-ordinate treatment for normal IQ adults with autism spectrum disorder
- An indication of resource utilisation by individuals with normal IQ autism spectrum disorder compared to other patients attending general adult psychiatry

services, for example those with transient illness, chronic and enduring mental illness, those with personality disorder and individuals with complex care needs

- The number of suspected cases of normal IQ autism spectrum disorder on General Practitioner caseloads
- An indication of the reasoning for such unreferred cases on General Practitioner caseloads

- Very little is known of what happens to individuals with autism spectrum disorder as they age as almost all adult studies focus on participants aged 20 - 40 years. Increased research in older adults; assessing the impact of aging on mental and physical health and the diagnostic, treatment and social care health needs of this patient group is required.

Valuable information could be gained through the above research questions to determine the potential value of creating and implementing a National Care Programme in Adult Autism Spectrum Disorder.

Studies examining ASD individuals of mixed intellectual ability from age 10 to 52 years have shown that caring for an individual with autism spectrum disorder is associated with greater caregiver burden than caring for a person with an intellectual disability, Fragile X syndrome, Down syndrome or attention deficit hyperactivity disorder and comparable to levels of strain seen in those caring for individuals with a brain injury (Kring 2010, Cadman 2012). Cadman et al (2012) hypothesised that low diagnostic rates among adults with high-functioning autism spectrum disorder result in a significant lack of health and social care service involvement with the burden of care falling to family members. Research focusing on individuals with normal IQ autism spectrum disorder is required to determine who provides support and care to these individuals, which risk factors lend to increased burden and which moderate risk, the impact of receiving a diagnosis of autism spectrum disorder and the impact of comorbid psychiatric and physical illness on carer burden.

Researchers could extend the assessment of burden beyond maternal strain and the family unit as higher proportions of high-functioning individuals with autism spectrum disorder may be in school, employment and relationships compared to child and ID

samples. Studies could utilise distress measurement instruments such as the Brief Family Distress Scale (Weiss, 2010) to quantify carer burden allowing comparison with prevalence rates of different forms of physical and psychiatric illness. Studies should examine the most effective means of supporting family, partners and carers of individuals with normal IQ autism spectrum disorder and the cost to society of undiagnosed cases.

It is striking that only ten studies examining psychiatric comorbidity in normal IQ adults with autism spectrum disorder were identified as part of the literature review for this study. These studies spanned a significant period of research activity, ten years. Future research should continue to investigate the overlap between autism spectrum disorder, psychiatric illness and physical illness. Addition to this body of knowledge is crucial.

4.9 Conclusions

Autism spectrum disorder is a pervasive illness characterised by deficits in social skills, impaired communication style and characteristic repetitive and ritualised behaviours. It is a lifelong condition associated with significant social suffering, physical morbidity, psychiatric morbidity and overall increased mortality. As previously undiagnosed and misdiagnosed cases of autism spectrum disorder are identified, the numbers will grow worldwide. As the population ages, those diagnosed with autism spectrum disorder will reach young, middle and older adulthood. As a consequence, an improved understanding of their healthcare needs will be urgently required.

Adults, just as frequently as children, suffer from autism spectrum disorder and a substantial number remain undiagnosed into adulthood. A first diagnosis rate of 82%, as seen in this study, highlights the under-recognition of autism spectrum disorder in the normal IQ population and by extension in general practice surgeries and community mental health clinics. To improve outcomes for adults with autism spectrum disorder it is imperative to increase awareness of the condition and ensure diagnoses are provided early. However, diagnosis alone without adequate identification of comorbid psychiatric and physical illness would be an injustice.

This study has shown that 76% of normal IQ adults with autism spectrum disorder suffer from a psychiatric illness and 84% suffer from physical ill-health. The presence of co-occurring psychiatric and physical illness indicates a potential for increased use of psychiatric and medical services by adults with autism spectrum disorder. Although there is no known medical treatment, well-structured behavioural interventions have been beneficial and high levels of compensatory learning can occur. In this light, all clinicians require access to training on appropriate engagement, effective assessment and accurate diagnosis of this patient group. Only consistent diagnosis of the primary disorder and associated comorbidity will allow appropriate intervention strategies resulting in effective treatments for individuals affected by autism spectrum disorder. It is important to understand the comorbid needs of our ASD patients if we are to adequately support and treat them.

Chapter 5: References

5.1 Reference List

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