The Neurological Examination in Adults with Autism Spectrum Conditions: A Pilot Study

A thesis presented in candidature for the degree of Master of Research - Chiropractic

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Candidate Statement

I certify that the work incorporated in this thesis has not been submitted for a higher degree to any other university or institution.

I certify that the work presented in this investigation is original work except where otherwise acknowledged and referenced within the text of this manuscript.

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Abstract

Background

Autism is a neurodevelopmental condition. However, the way neurological aspects of autism persist into adulthood and old age is not well understood. Neurological disorders are the second highest cause of mortality in adults with autism, the highest being suicide. A primary care clinician uses the neurological examination (neuroexam) as the first port of call to assess neurological function. The neurodevelopmental nature of autism begs the question of how useful the standard physical examination is in assessing neurological health or pathology in adults with autism.

Objectives

The study had two objectives: to assess the feasibility of the neuroexam protocol and the tolerability of the neuroexam to participants with autism, and to assess the results of the neuroexam for between group differences.

Methods

The present study recruited 17 participants, aged 18 – 30 years, to attend a neuroexam. Seven participants had a diagnosis of autism, whilst the other ten were typically developed participants as controls.

Results

The neuroexam was well tolerated by all participants. The protocol revealed some problems in the application of the graphaesthesia and timed motor coordination tests but otherwise ran smoothly. The neuroexam results displayed significant differences between groups in cranial nerves, and motor coordination and balance. Individual tests which were significant included: saccades, muscles of facial expression, finger-to-nose, and pronation/supination.

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Glossary of Terms

ADHD/ADD	Attention deficit hyperactivity disorder/Attention deficit disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
AD	Autistic disorder
ASC	Autism Spectrum Conditions
ASD	Autism Spectrum Disorder
AS	Asperger's syndrome
Aspect	Autism Spectrum Australia
B/L	Bilateral
CDC	Centre for Disease Control and Prevention
DALY	Disability-adjusted life year
DSM	Diagnostic and Statistical Manual of Mental Disorders
FEP	Fist-Edge-Palm (Luria's manual sequencing task)
FNF	Finger-to-nose-to-finger
ICD	International Classification of Diseases
ID	Intellectual disability
LL	Lower limb
MMSE	Mini Mental Status Examination
MRI	Magnetic resonance imaging
NSS	Neurological Soft Signs
NES	Neurological Evaluation Scale
PDD-NOS	Pervasive developmental disorder-not otherwise specified
PET	Positron emission tomography
RAM	Rapid alternating movements
SPECT	Single-photon emission computed tomography
SLUMS	Saint Louis University Mental Status
TD	Typically developed
UL	Upper limb

Chapter 1

1. Introduction

Autism is a neurodevelopmental condition that is characterized by social impairment, communication difficulties, and restricted, repetitive behaviours.(1) Currently, autism spectrum conditions (ASC) is an umbrella term used to discuss autism across different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the most recent being the DSM-5,(1) and revisions of the International Classification of Diseases (ICD-10).(1–3) This includes autism spectrum disorder (ASD), autistic disorder (AD), Asperger's Syndrome (AS), and pervasive developmental disorder-not otherwise specified (PDD-NOS). As the clinical understanding of autism increases more adults are being diagnosed, particularly women, who are being reclassified from an erroneous diagnosis of personality disorders or other psychiatric conditions.(4–9)

The Centre for Disease Control and Prevention (CDC) reports the prevalence of ASC in school-aged children at one in 68.(10) Whilst the 2010 global prevalence and burden of disease for ASC was estimated at one in 132 individuals: which translates into 52 million cases of ASC and 7.7 million disability-adjusted life years (DALYs) globally.(11) This makes ASC a commonly encountered condition and an important consideration in public health.

Research continues into the aetiology and neurology of autism. Imaging studies show that both children and adults with ASC display neural connectivity and architecture that differs from typically developed (TD) controls.(12) Recent research, performing fMRI studies of six-month-old infants with a high familial risk of autism, used machine learning techniques to learn patterns of functional connectivity. Of the 56 infants in the study,(13) an autism diagnosis was accurately predicted in nine of the 11 infants whom had a confirmed diagnosis at 24 months.

The persistence of ASC symptoms and neurological difference from childhood into adulthood and across the lifespan has not been well studied. A systematic review of longitudinal follow-up studies from childhood to adulthood performed by Magiati, Tay, and Howlin (2013)(14) found that IQ and autism diagnosis tended to remain stable; whilst adaptive functioning tended to improve between adolescence and early adulthood. Other work has demonstrated that the

same strengths and weaknesses of cognition in ASC remain throughout the lifespan.(15) This leads to considerations of how these manifestations continue to affect the same individuals as they reach adulthood and across the lifespan.

Primary care clinicians require pragmatic tools to support patients with ASC. All but the most severely impacted individuals with ASC 'age-out'(16) of autism specific assistance, which may have been available during childhood, and must seek support in a general health care setting. Adults with ASC report difficulty in accessing healthcare, even for common and treatable conditions, lower satisfaction with patient-provider communication, and more frequent emergency department visits.(17) On the other hand, clinicians report a lack of knowledge in treating adults with ASC.(18) A survey of primary care providers reported that 53% of physicians felt they required more training in treating adults with ASC.(19) In a survey performed by Pellicano, Dinsmore and Charman (2014)(20) adults with ASC, their family members, and clinicians all identified limited expert practitioner knowledge existed regarding co-occurring conditions. The same study also identified dissatisfaction in the diagnosis of autism, particularly for adult women.

Co-occurring conditions in ASC are a significant healthcare challenge. Many adults with ASC report that many symptoms are interpreted by their healthcare providers through the lens of being a symptom of their autism alone,(21) and an increasing body of work indicates that physical conditions, particularly in the field of neurology, frequently co-occur with ASC. Preliminary work with adults with ASC aged over 39-years has suggested that as adults with ASC age there is an increased prevalence of Parkinson's Disease compared to an age-matched TD population.(22)

In large, matched-case, cohort study of Swedish population registers the highest causes of mortality of individuals with ASC were diseases of the nervous system (OR=7.49) and suicide (OR=7.55).(23) Epilepsy, seizure disorders, and congenital neurological disorders were the most common causes of neurological associated deaths. Individuals with ASC with intellectual disability (ID) had a significantly higher odds ratio of mortality from nervous system disorders (OR=40.56) compared to those without an intellectual disability (OR=3.98). The confidence intervals in the ID calculations were very broad (26.82-61.33) indicating an imprecise estimate. Other causes of mortality were also increased in both ASC groups: for diseases of the digestive, endocrine, respiratory, and circulatory systems. Individuals with ASC have a 2.56 increased

odds of mortality compared to matched general population controls. The mean age at death was 53.87± 24.78 years (median = 55) compared to the control group's 70.20 ±24.16 years (median = 80).(23)

Thomas *et al* (2016)(24) reviewed studies of at least 100 participants with ASC and determined that the prevalence of epilepsy in the literature ranged between 4% to 38%. In other work,(25) prevalence of epilepsy in autism increases with age and intellectual disability. The diagnosis of seizure in autism can be difficult because the symptoms of complex partial and absence seizures: staring, nonresponsiveness, with or without repetitive motor behaviours, overlap with symptoms of autism.(26) Additionally, many kinds of seizure, such as a complex partial seizure, includes impaired awareness during the seizure and impaired memory of the event.(27)

It is clear that monitoring the neurological status of a patient with ASC is a necessity and basic duty of care to a patient. However, in a survey of neurologists treating adult patients who were diagnosed in childhood with neurodevelopmental conditions: 89% of the neurologists surveyed reported their comfort level in treating patients with autism as either 'not comfortable' (*n*=57, 58%) or 'impossible' (*n*=30, 31%).(28)

The first port of call, for a primary health care clinician in monitoring neurological status, is a neurological physical examination (neuroexam). Prior work indicates that adults with ASC may score differently to TD peers in neuroexam tests: giving results which are not indicative of a pathology but of their autism itself.(29–32) However, this work was performed with the objective of understanding the mechanisms of autism. To our knowledge no work has been performed in the diagnostic test accuracy of neuroexam tests to detect any specific pathology in an ASC population. Imaging studies such as: positron emission tomography (PET), Single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) are expensive, not always useful, and impractical in a standard routine of care. Unusual sensation is a normal part of the experience of autism and is part of the diagnostic criteria. It is also becoming increasingly clear that the experience of interoception for individuals with ASC is different than their typically developed peers.(33) These factors can make it difficult for an individual with ASC to interpret changes in neurological status from the 'background noise' of their autism. Diseases of the nervous system are a significant cause of mortality of individuals with ASC,(23) therefore the challenge lies in determining which neuroexam tests are more likely to give unusual results for an ASC individual, and which tests are most useful for

predicting pathology. The heterogeneity of ASC presentation may mean that a baseline neuroexam should be performed and regular checkup neuroexams performed to monitor for a change from the baseline.

1.1. Objectives

The study had two objectives: the primary objective was to determine the feasibility of neuroexam study in an ASC population, the secondary objective was to analyse the neuroexam data gathered to determine any differences between the control and ASC groups. This study was a pilot study as defined by Eldridge *et al* (2016)(34) in which a pilot study as a subset of a feasibility study, where a feasibility study "asks if something can be done,[…] and if so how", and a pilot study adds specific design feature or part thereof as intended for use in a future, larger study. In this case, the design feature being tested is the neuroexam protocol. Pilot studies are recommended not to focus on hypothesis testing(35) but instead to focus on determining the essential parameters of the work such as recruitment and the experimental protocol, as well as potentially using the results to generate power calculations for a main study.

The primary objective included the development of a neuroexam protocol which uses quantified scoring and is validated against the current literature. The feasibility characteristics gathered in this study can be broken into two broad categories: the participant characteristics, and the neuroexam characteristics.

The secondary objective was to analyse the data gathered during the neuroexam. It is recommended that pilot studies with any recorded clinical outcomes be interpreted with caution due to a lack of statistical power.(35) Hobart *et al* (2012)(36) in an analysis of sample sizes required to determine reliability and validity of rating scales used in neurology suggested a rule of thumb of a minimum of 20 participants for reliability, and 80 participants for validity. For these reasons, the data gathered in the neuroexam in this study can be considered indicative only and as a precursor to larger studies.

Chapter 2

2. Background

2.1. The Neuroexam

The neuroexam is a physical examination comprised of tests across a full range of neurological function. Neurological function testing includes mental status (attention and orientation, memory, language, praxis, neglect and constructions, sequencing tasks, frontal release signs, and logic and abstraction), cranial nerves (smell, sight, hearing and vestibular function, facial expression and sensation, muscles of mastication, articulation, tongue movement, and swallowing) coordination and gait (gait, single leg standing, balance), motor (strength and tone), sensory examination (light and sharp touch, two-point discrimination, stereognosis, and graphesthesia), and reflexes (deep tendon reflexes and frontal release signs).(37)

The neuroexam has a long history, the current categorisation of regions of examination: mental status, cranial nerves, motor, sensory, and reflexes with their associated subtests were developed from a long process of observation, hypothesis, and trial and error. Jean-Martin Charcot (1825-1893) is considered to be one of the founders of the neuroexam.(38) He documented patients' clinical signs and symptoms and correlated them with findings on autopsy. In this way, he was able to distinguish between diseases such as multiple sclerosis and Parkinson's disease. From this foundation neurology advanced to start associating specific diseases with specific pathology found on autopsy: the neuroexam evolved to be able to localise a focal lesion to a specific region of the brain. Georg Monrad-Krohn, in 1921, published the *Clinical Examination of the Nervous System*,(39) which was a fundamental stepping-stone to the current application of a clinical neuroexam. In 1919, the English translation of August Wimmer's *Psychiatric-Neurologic Examination Methods, With Special Reference to the Significance of Signs and Symptoms*(40) was published. Even at this early time there existed dichotomy between a neurological examination for neuropsychiatric purposes as compared to testing for pathology. As examinations evolved, the neuroexam, as used by GPs or specialists such as neurologists, has been refined as a bedside tool to assist in diagnosing specific neurological diseases, and to localise focal defects, as might occur in stroke. Within the field of

neuropsychology, the neurological examination diverged into investigation of functional areas: especially as related to cognition.(41) In this way, specialised tests and batteries were developed to investigate realms of thought such as: attention, executive function, memory, motor speed, language and perception.(42) The evolution of neuropsychology means that some of the testing systems, such as tests of intellectual function, like the Wechsler Adult Intelligence Scale-IV (WAIS-IV),(43) have little in common with a clinical neuroexam. Whereas others, such as the Luria-Nebraska Battery (LNB)(44–46) have a significant overlap.

Into this diverse landscape of neurological testing then came the conceptualisation of 'hard' and 'soft' neurological signs. Hard signs are usually classed as those which can be localised to a specific region of the brain or nervous system. Examples are: the deep tendon reflexes, muscle strength and tone, or motor disorders such as the dyskinesias.(47) Whereas neurological soft signs (NSS) are not localised to a specific region and are associated with functional networks such as: motor coordination, and sensory integration.(48) Neurological soft sign inventories and scales were originally developed for the investigation of neurological correlates of schizophrenia:(49) where it had been observed that difficulties in motor coordination often occurred. These NSS inventories tested for both soft signs and a selection of hard signs, and whilst classed as neuropsychological tests, they are substantively similar to a scaled-down clinical neuroexam. For a useful comparison of different inventories and scales see Bombin, Arango and Buchanan (2003).(50) Hard neurological signs are often considered to be an indicator of pathology, therefore their inclusion into a NSS inventory may be puzzling: however studies have shown that they are present in schizophrenic patients and their first degree relatives.(51–53) An example of hard signs often included in NSS inventories are the primitive reflexes: otherwise known as the frontal release signs.(37) These reflexes are brainstem-mediated autonomic responses present in early infancy and consist of, amongst others: glabellar, grasping, rooting, sucking, and snouting reflexes. These reflexes become cortically inhibited by the frontal lobes by approximately 12-months of age.(54) Disinhibition is usually considered to be a sign of frontal lobe problems.

Neurological soft sign inventories are relevant to this study as data on the performance of clinical neuroexam testing of adults with ASC is limited. What research does exist lies exclusively within the realm of the NSS inventories. Research into autism using other neuropsychological measures, such as the Wisconsin card sorting test,(55) the Trail Making Test,(56) or the Grooved Pegboard is extensive, but does not provide a framework to compare a clinical neuroexam results for individuals with ASC. The NSS inventories do provide limited baseline data in some of the frequently used neuroexam tests in adults with ASC.

2.1.1. Neurological Soft Sign Research in ASC

Neurological soft sign inventories have been used to determine putative endophenotypes of schizophrenia and correlation with soft signs to MRI region of interest (ROI) analysis.(57,58) The validation of NSS inventories lies largely in the capability of the inventory to detect a target condition, usually schizophrenia, from controls.(57) In the field of autism research, a study by Jansiewicz *et al* (2005)(59) used an NSS inventory designed and validated for children, the Physical and Neurological Exam for Subtle Signs (PANESS),(60) to discriminate between boys with ASC and controls. The PANESS includes tests of gait (ordinary gait, tandem, plantarflexion, dorsiflexion, forced), tandem-stance Romberg's test, pronator drift, finger-tap, foot-tap, heel-toe alternating tap, hand pronation/supination, and sequential finger apposition. Studies incorporating the PANESS comprises the most substantial body of work of NSS inventories in autism. The PANESS, however is validated against child and adolescent populations,(61–63) hence this body of work is in regard to children.

The studies utilizing the PANESS to investigate autism is part of an ongoing debate regarding sensorimotor integration impairment marking an endophenotype of autism. Clumsiness and poor postural stability were included in the earliest descriptions of autism by Kanner.(64) Additionally, the inclusion of motor clumsiness was suggested as part of the diagnostic criteria by various authors (65,66) in the development of the ICD-10 description. Whilst motor clumsiness was not included in the diagnostic criteria, motor coordination and sequencing of skilled actions, have remained a consistent theme within autism research. This investigation into motor skills has led to the concept of developmental dyspraxia, defined by Steinman, Mostofsky, and Denckla (2010)(67) as an impaired performance of skilled gestures out of proportion with any underlying sensorimotor deficits, as a condition strongly associated with autism.(68–75) The acquisition of skilled movements is a process of developmental maturation:

hence age-matched comparators are required to make a diagnosis. If the performance of skilled movements is more consistent with a younger age-bracket, then it is considered as a developmental delay, rather than developmental dyspraxia. Developmental dyspraxia requires unique patterns of problems in skilled movement that are different to patterns associated with developmental maturation.(67) Additionally, the terms apraxia and dyspraxia are often, but not always, used interchangeably. This adds a level of linguistic confusion to an already difficult field.

The work using the PANESS to investigate neurological correlates in children with ASC is useful but cannot be compared to an adult population. Motor skills improve with developmental maturation and the presence of poor coordination in childhood does not guarantee an adult will display the same deficits. Of work concerning the study of adults with ASC using NSS inventories, a literature search found only four papers: as listed in Table 1.

Table 1: Adult ASC research using NSS inventories

Author	Title	NSS Scale
Hirjak *et al* (2014)(29)	Neurological abnormalities in recent-onset schizophrenia and Asperger-syndrome	Heidelberg(76)
Hirjak *et al* (2016)(30)	Neuroanatomical Markers of Neurological Soft Signs in Recent-Onset Schizophrenia and Asperger-Syndrome.	Heidelberg
Manouilenko *et al* (2013)(31)	Autistic traits, ADHD symptoms, neurological soft signs and regional cerebral blood flow in adults with autism spectrum disorders	Neurological Evaluation Scale (NES)(77)
Tani *et al* (2006)(32)	Clinical neurological abnormalities in young adults with Asperger's syndrome	Rossi (78)

The NSS scales often divide their inventories into subscales. These subscales are usually intended to highlight neurological functional networks. Commonly used subscales are: motor coordination, complex motor tasks and motor sequencing, and sensory integration.(47,50) Disinhibition and hard signs are also included in some inventories. Unfortunately, there is little consistency across different NSS inventories in the way tests are grouped into subscales. Therefore, whilst many NSS inventories may contain identical neurological tests, they are often reported in the literature by the subscale, and cross inventory subscales are not comparable. Table 2 gives a comparison of the subscales used in the inventories which have been used to

investigate adult ASC: the Heidelberg scale,(76) the neurological evaluation scale (NES),(77) and the Rossi scale.(78) The Rossi scale does not define subscales and so the tests included in this scale are simply marked with an asterisk. Even the execution of specific neuroexam tests can exhibit significant variation between inventories. For example, the Heidelberg scale instruction on pronation/supination, also known as rapid alternating movements (RAM), is to perform the action as fast as possible with eyes closed, then eyes opened. The NES instruction for the same test is to perform 20 timed iterations of the movement with the eyes opened. The Rossi scale labels this same action as dysdiadochokinesia.

Of the research using NSS inventories to investigate adults with ASC two studies used the Heidelberg scale in which Asperger's Syndrome participants were compared to schizophrenic participants and controls.(29,30) Within the field of NSS research the use of schizophrenia as a comparator with autism is logical, as NSS has been studied in schizophrenia for over thirty years and can be considered a relatively known quantity.(57) The Heidelberg Scale, used by Hirjak *et al* (2014, 2016) in two studies, divided the tests into the following subscales: motor skills and coordination (Ozeretski's test, diadochokinesia, pronation/supination, finger-to-thumb opposition, speech articulation), complex motor tasks (finger-to-nose test, fist-edge-palm test), integrative function (station and gait, tandem walking, two-point discrimination), right/left and spatial orientation (right/left orientation, graphesthesia, face-hand test, stereognosis), and hard signs (arm holding test, mirror movements). Both Hirjak *et al* studies demonstrated a statistically significant difference between participants with ASC and controls for the total NSS score and within each subscale barring right/left and spatial orientation subscale in the study published in 2016. The motor skills and coordination subscale displayed the greatest significance in both studies. The capability of the scale to differentiate between AS and schizophrenia was significant only on the motor skills and coordination subscale, with the schizophrenic group scoring higher, as in greater impairment, than AS.(29,30)

Manouilenka *et al* (2013)(31) performed a study using the neurological evaluation scale (NES) and attempted to correlate ASC and attention deficit hyperactivity disorder (ADHD) traits with MRI imaging. Due to the method of analysis it is not possible to directly compare Manouilenka *et als* study results with the NES subscale data with the Heidelberg scale data derived from the Hirjak *et al* studies Overall, the Manouilenka *et al* study indicates that a statistically significant difference exists between participants with ASC and controls in the motor coordination and sensory integration subscales as correlated with a sensory-motor factor loading. The motor sequencing subscale was significantly correlated with intelligence/motor sequencing factor loading.

Tani *et al* (2006)(32) used the Rossi scale to compare AS young adults with controls in conjunction with MRI imaging to rule out pathological causes of difference. The Asperger's syndrome participants demonstrated statistically significant difference in complex motor acts and whole-body clumsiness (as measured by gait and balance).

Table 2: Comparison of NSS inventories and subscales

Test Items	Heidelberg	NES	Rossi
Ozeretski	MOCO	COMT	
Diadochokinesia (screw in light bulb)	MOCO		
Praxis (demonstrate tool use in imaginary acts)			*
Complex motor acts (tie up a shoelace)			*
Pronation/supination	MOCO	MOCO	*
Finger-to-thumb	MOCO	MOCO	
Speech articulation	MOCO		
Station and gait	IF		
Tandem walk	IF	MOCO	
Two-point discrimination	IF		
Sharp vs blunt discrimination			*
Audio-visual integration		IF	
Finger-to-nose	COMT	MOCO	
FEP	COMT	COMT	
Fist-ring test		COMT	
Rhythm tapping test B (produce taps as instructed)		COMT	*
R/L orientation	RLSO	IF	
Graphaesthesia	RLSO	IF	*
Face-hand (extinction)	RLSO	IF	*
Stereognosis	RLSO	IF	*
Arm holding test (pronator drift)	HS	HS (adventitious overflow)	
Mirror movements	HS	HS	*
Romberg		HS	
Rhythm tapping test A (closed eyes while examiner taps, then reproduce series of taps)		HS	
Convergence		HS	*
Nystagmus			*
Synkinesis (head movement on tracking pen to horizontal gaze)		HS	
Gaze impersistence		HS	*
Primitive reflexes		HS	*
Short-term memory		HS	

MOCO: Motor coordination, IF: integrative function (listed as Sensory Integration in NES), COMT: complex motor (listed as Sequencing of Complex Motor Acts in NES), RLSO: right/left and spatial orientation, HS: hard signs (listed as Others in NES)

Chapter 3

3. Methods

The study aimed to recruit 10 TD participants as controls and 10 participants with ASC to attend a neuroexam appointment at Macquarie University, Sydney. This recruitment target was derived from three separate factors. The first was a power calculation based around the primary objective of testing the feasibility of the neuroexam protocol with participants with ASC. This calculation was based on the fact that it was possible for individuals to start but not complete the neuroexam. The second was based on recommendations in the literature. The third was pragmatic decision: the Masters of Research program is ten-months in duration, hence there was limited time for recruitment and conduction of neuroexams.

The first was based on primary research goal of determining the tolerability of the neuroexam protocol to individuals with autism. We assumed that individuals with ASC might start a neuroexam, but not complete it, due to discomfort associated with the stimulus. A typically developed individual might possibly start the but not complete the neuroexam for pecuniary reasons, a gift voucher was given before the start of the exam, or impatience with the duration of the examination. As no data was available on the likelihood of either group starting but not completing a neuroexam we performed a power calculation based on a one sample proportion with a 95% CI and z=1.96 as demonstrated below.

$$ME = \sqrt{\frac{p(1-p)}{n}} \qquad 5 = \sqrt{\frac{95(5)}{n}}$$

Solving for n returns a value of 19. The number was increased to twenty so that we could aim of recruiting an equal number of ten participants in each group.

The second factor in the recruitment decision for ten participants in each group as based on the recommendations of Hobart *et al* (2012)(36) suggesting that a rule of thumb of a minimum of 20 participants to provide for a level of reliability was required when testing rating scales used in neurology.

The feasibility data concerned the participant characteristics and the neuroexam protocol characteristics. The participant characteristics included the response rates to the online screening questionnaire, participant demographics, neuroexam attendance, and tolerability of the protocol for participants with ASC. The tolerability of the neuroexam was particularly important for participants with ASC and was measured by the number of scheduled or unscheduled breaks taken, adverse events, and a post-examination question. The neuroexam characteristics included any issues discovered with the neuroexam protocol including unclear instructions, and difficulties or errors in the conduction of the neuroexam tests.

The neuroexam data was gathered to compare the ASC and control groups for significant differences between groups.

3.1. Ethics

Ethics approval was obtained from the Macquarie University Human Research Ethics Committee (HREC Medical Sciences) (reference number 5201700410).

3.2. Recruitment

Advertising, in the form of a flyer about the study, was placed around Macquarie University campus and at two psychology clinics in the Sydney region. The clinics, Diverse Minds Psychology Clinic (Erskineville), and Jeroen Decates Psychology (Hornsby), specialise in helping a clientele with ASC. Online advertising was conducted with Autism Spectrum Australia (Aspect) and limited social media with blogger Tip of the Asperg. The electronic advertising was identical to the physical flyers.

The advertising directed interested individuals to an online questionnaire that performed basic screening for inclusion and exclusion criteria. The criteria included consent to be contacted, willingness and ability to travel to Macquarie University for a neurological examination and being within the age range of 18-30 years old.

3.3. Inclusion and Exclusion Criteria

Executive function has been extensively studied in ASC. A meta-analysis of studies into executive function demonstrated that children and adolescents with ASC exhibit significant differences in executive function compared to controls.(79) The same study determined that adults with ASC still display significant difference in executive function compared to controls, albeit that the differences are smaller than in the younger age groups. It has been hypothesized that the reduction in the differences in executive function may be due to either adults with ASC reaching developmental maturity, or that as individuals with ASC age, they develop adaptive or compensatory strategies to the challenges presented by autism The 18-30 years old age range was chosen for this study as individuals were adults, but had limited time in which to develop adaptive responses to the challenges presented by autism. To ensure participants recruited were in the correct age-bracket the screening questionnaire confirmed respondents were in the 18-30 years old age bracket.

The questionnaire excluded smokers, those who were pregnant, those who were not fluent in spoken English, those with any professional medical experience or training in the conduction of the neuroexam including students, those with an intellectual disability, and those with a language impairment. Individuals with any medical training were excluded to avoid any anticipation effects during the conduction of the neuroexam. Individuals with an intellectual disability were excluded due to the complex instructions contained within the neuroexam. It would be difficult to differentiate between whether instructions were not understood or if the participant was unable to perform the action. Similarly, individuals with a language impairment were excluded as the neuroexam tests the cranial nerves including the ones controlling speech and hearing. The neuroexam protocol was standardised with scoring of individual test items based on literature reviews, and the instructions and interactions were scripted to ensure limited variation between examinations. This standardisation made it untenable for the study to include individuals who potentially would not understand the instructions such as those not fluent in spoken English, and those who had a language impairment.

3.3.1. Autism Diagnosis

The study relied on self-reporting of an autism diagnosis and limited participants with ASC to those with a DSM-4 diagnosis of Autistic Disorder or Asperger's Disorder, or a DSM-5 diagnosis of Autism Spectrum Disorder – Level 1 (Social Communication), Level 1 (Restricted Repetitive Behaviour). This level of diagnosis was specified for this study because the limited prior work into NSS examination was performed largely on AS participants. As this is a pilot study, an initial consistent population is required before the protocol can be expanded across a more diverse population.

3.3.2. Co-Occurring Conditions

The questionnaire also asked if the participant had experienced depression or anxiety never, longer than six months ago, or currently. We excluded controls with current anxiety or depression but included those with a history of greater than six-months ago. The reasoning for excluding controls with current anxiety or depression was to minimise any factors that could influence the outcome of the neuroexam. Participants with ASC were not excluded based on current depression and/or anxiety as these two conditions are reported so frequently in individuals with autism(15,80,81) that it was not viable to exclude them. For similar reasons, the questionnaire asked if the participant had ever been diagnosed with attention deficit hyperactivity disorder/attention deficit disorder ADHD/ADD (82–85) but did not exclude either individuals with ASC or controls from the study if the answer was positive. They were, however excluded if they were currently taking psychostimulants prescribed for ADHD/ADD.

3.3.3. Medications

A medication naive ASC population was anticipated to be difficult to obtain. The atypical antipsychotic, risperidone, is prescribed in paediatric ASC populations to reduce severe behavioural problems,(86) however this is the only medication which is specifically prescribed for autism. The prescription of psychotropic medications are highly prevalent in ASC populations with the most commonly prescribed medications being antidepressants, antipsychotics and stimulants.(87,88) A list was compiled of medications commonly prescribed in Australia for depression, anxiety, ADHD/ADD, and epilepsy or seizures. This list covered the classes of antidepressants, anxiolytics, antipsychotics (typical and atypical), psychostimulants, antiepileptics, and dopamine agonists. We consulted a pharmacist for advice on compilation of this list and for advice on which medications were least likely to have effects that would affect

the results of the neuroexam. Table 3 lists the medications that were permitted in the study and the medications that were excluded.

Table 3: Medications

Class	**Active Ingredients**
Not Permissible Medications	
Antipsychotics (typical)	Chlorpromazine, Droperidol, Flupentixol, Fluphenazine, Haloperidol, Periciazine, Trifluoperazine, Zuclopenthixol
Antipsychotics (atypical)	Amisulpride, Aripiprazole, Asenapine, Clozapine, Olanzapine, Paliperidone, Quetiapine, Remoxipride, Reserpine, Risperidone, Ziprasidone
Psychostimulants	Dexamphetamine, Methylphenidate, Atomoxetine
Antiepileptics	Carbamazepine, Ethosuximide, Gabapentin, lacosamide, Lamotragine, levetiracetam, oxcarbazepine, pregabalin, Tiagabine, topiramate, valproate, zonisamide
Antidepressants (MOAIs)	Phenelzine, Tranylcypromine
Dopamine Agonsists	metoclopramide, domperidone
Permissible Medications	
Antidepressants (SSRI)	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
Antidepressants (SNRI)	Desvenlafaxine, Duloxetine, Venlafaxine
Antidepressants (Tricyclics)	Amitriptyline, Clomipramine, Dosulepin (dothiepin), Doxepin, Imipramine, Nortriptyline
Antidepressants (Other)	Agomelatine, Mianserin, Mirtazapine, Moclobemide, Reboxetine, Vortioxetine

3.4. Participant Protocol

A protocol was developed for all participant interactions, from the questionnaire material, to emails, and to the interactions at the neuroexam itself. This protocol was developed in-line with the recommendations of the Cooperative Research Centre for Living with Autism (Autism CRC) inclusive research practice guides checklists for autism research (89) and the recommendations for accommodating physical examinations for adults with ASC.(90) Participants who met the inclusion criteria in the screening questionnaire were emailed an invitation to participate in a neuroexam. The invitation to the neuroexam included three document attachments: one *About the Neuroexam*, the second *How to get to Macquarie (MQ)*, and the third document was *Participant Information and Consent Form* (PICF). The PICF was provided at this stage so that participants had the opportunity to review it without any pressure prior to arriving at the appointment. The *About the Neuroexam* document provided information about the neuroexam including images of some of the tests, how to request a break, who would be there, and what to wear. This information allowed individuals to decide if the neuroexam would be tolerable stimulus. This introduced an unavoidable element of non-response bias into the study however ethical considerations precede the limitation of bias.

Figure 1: Images from *About the Neuroexam*

The information provided in *How to Get to Macquarie (MQ)* included images of the entry points to the clinic as well as a map and written information.

Susan Abel (SA) performed the questionnaire screening and scheduling of appointments. The neuroexam appointments were scheduled outside of normal clinic hours to ensure a quiet environment for participants. At the appointment, SA greeted the participant and walked the

participant through the examination protocol, as well as gaining consent for the examination. After the consent was signed participants received their incentive payment: a twenty-dollar gift voucher. All participants were taken through the same introduction protocol irrespective of autism status. The protocol advised participants they were free to leave at any time without repercussions. The participants were also advised that there were two optional five-minute breaks during which time the examiner would leave the room. Participants were requested to ask for a halt to the examination if they experienced an intensity of discomfort greater than five out of ten. They were also provided with a red-card, to be used if the participant was unable to verbally request a stop. In this case, the examiner left the room for five-minutes and then checked on the participant to determine their requirements: if they needed a longer break, to stop the examination, to see a psychologist or their emergency contact, or to continue with the neuroexam.

A randomly generated four-digit number was allocated to each participant as a unique identifier, which was used for the neuroexam to maintain the blinding of the examiner to personal information about the participants. The examiner (AS), a chiropractor of over 25 years' experience and clinic supervisor at Macquarie University Chiropractic Clinic, performed the neuroexam. The examiner has experience as a primary care clinician in performing neurological screening of patients but no specific expertise within the field of autism, and only a passing familiarity with the diagnostic definitions of ASC. He also was unaware of the prior research into the neurology of autism, and which, if any, neuroexam tests may give different results in an ASC population compared to controls. The reasoning behind this was twofold: one was to maintain examiner blinding, the other was a test of how a primary care clinician with limited expertise in autism would interpret neuroexam results.

After the completion of the neuroexam SA asked the participants : "Did you learn anything about yourself during the examination?", and "Did you experience any difficulty in the examination? (emotional, sensory, specific parts of exam)".

The examiner, AS, was asked "Do you believe that the individual examined has an autism spectrum condition? Y/N". In the case of the affirmative a further question was asked "What makes you think that?".

An adverse event was considered to be one in which the neuroexam was terminated early and the participant required the assistance of their emergency contact or a psychologist.

3.5. Limitations

The geographic location of the clinical examination at Macquarie University, in Sydney, was a geographic limitation to the recruitment of participants to the study. The advertising flyer made the location of the study clear. To alleviate anxiety about travel to novel locations participants were emailed *How to Get to Macquarie (MQ)* which had a map of the path from the train station to the clinic, a picture of the sign labelling the building, a picture of the entrance to the building, and a picture of the buttons to press for entry to the car park as well as written instructions on where to turn and what participants would see at decision points for making turns on the path.

Other limitations to recruitment included the paper flyers being located at three physical locations: Macquarie University, and two psychology clinics. This limited the number of individuals who were likely to see the physical flyers, though the provision of advertising in the psychology clinics were targeted advertising to individuals utilising services specifically aimed at individuals with ASC. The online advertising was a limitation as only individuals comfortable with using social media or other online avenues were likely to see the recruitment material. The demographic being recruited for this study meant that it was likely that this group would be relatively comfortable with computers and the internet.

The specific online recruitment avenues: Aspect, and Tip of the Asperg limited the recruitment of participants to only those individuals familiar with these particular forums.

3.6. Neuroexam Protocol

The neuroexam is widely used and recognised in primary health care, but there is no one single definitive version. The tests comprising the neuroexam in this protocol were derived from neurology text books as well as a review of the literature for validated test protocol instructions and scoring systems. Blumenfeld's *Neuroanatomy Through Clinical Cases, 2nd Edition* (37) was the primary neuroanatomy text used as it provided online videos demonstrating the conduction of examination techniques, ensuring consistency in the training of the conduction of the protocol. The protocol scoring applied the most commonly used scales, as listed in Table 4, to ensure that data obtained was easily comparable to other research in the field.

Table 4: Standard scales with abbreviations

Scales Used	Abbreviation	Measures
Mini Mental Status Examination (91)	MMSE	Mental status
Saint Louis University Mental Status (92)	SLUMS	Mental status
Neurological Evaluation Scale (77)	NES	Various
Walker Reflex Scale (93)	WRS	Deep tendon reflexes
American Spinal Injury Association (2000) (94)	ASIA	Light touch and pinprick
Medical Research Council (95)	MRC	Tone and clonus
Modified Ashworth Scale (96)	MAsh	Muscle strength

Table 5 provides detailed information on the component parts of the neuroexam protocol including the list of tests, the origin of the text describing the conduction of the test, and the origin of the scoring of the test. The NES was used as a basis for many tests as it is one of the most widely used NSS inventories in the literature and has clear scoring criteria and significant work has been performed in interrater reliability and other aspects of the scale.(97–99) The terminology 'scripted' indicates that the test was scripted for the protocol and not specifically based upon any individual paper or book. The terminology 'after' indicates that the test protocol was based upon elements listed as the source, but there are minor variations in the execution. The neuroexam protocol is listed in the supplementary material. The scoring was made such that a decreasing score indicated decreased function. If any of the standard ordinal scales from the literature used an increasing score to denote greater dysfunction the score was reversed to make the overall scoring system consistent.

The protocol was designed as a typical example of the neuroexam as used primary care clinician. It purposefully did not include any of the testing that might be used by specialists in the field, such as neurologists or psychologists. The verbal instructions and interactions during the examination were scripted to limit variation in directions and comprehension of the instructions. If the participant did not understand the instruction as it was scripted and asked for clarification the examiner expanded beyond the script as appropriate, then returned to scripted interaction as soon as feasible.

AS was trained in the neuroexam protocol, in conjunction with refinements being made to the protocol scripting and scoring, in five trial-neuroexams. The final trial-neuroexam was with an ASC community advocate who could provide feedback on the experience from the perspective of an individual on the spectrum.

3.6.1. Statistical Methodology

The analysis of the neuroexam data was performed using qualitative statistics and limited use of nonparametric tests in-line with recommendations that undue weight is not placed on hypothesis testing pilot studies with clinical data.(34)

The large range of differing scales used as standards in the neuroexam meant that when grouping results the scales had to be converted to a consistent numbering so that individual tests did not receive undue weighting due to scale variations. All raw data was normalised to unity prior to performing the statistical analysis.

Within neuroexam analysis, a normal distribution can only be expected in timed motor coordination and sequencing tests. Most other tests, even in cases of specific pathology, will not have a normal distribution, hence nonparametric statistical analysis is the standard in studies of neuroexam test accuracy and predictive values. In our case, due to our small sample size, an independent 2-group Mann-Whitney U test with a 5% confidence interval was used for testing significant differences between TD and ASC populations. This confidence interval was chosen as our sample sizes were small. The effect sizes were calculated based on a significance threshold of .05 also based on the Mann-Whitney U test. Analysis of grouped sections of the neuroexam was performed by summing the scores.

Future work would use Kolmogorov-Smirnov test to assess for normality and use Mann-Whitney U test for the nonparametric data. For the data that met normality criteria analysis of covariance (ANCOVA) to assess the data with respect to neurological scores and demographic data.

Table 5: Neuroexam Protocol

Neuroexam Tests	**Instruction**	**Scoring**
Attention and orientation, Short-term memory, repeat a sentence	MMSE	MMSE
Long-term memory, logic and abstraction	SLUMS	SLUMS
Calculations, language (naming, comprehension), write a sentence, finger agnosia, Otoscope examination, two-point discrimination	Scripted	Scripted
Right-left confusion, Ozeretski test, Sensory neglect/extinction (face-hand test), UL Rapid alternating movements (pronation/supination) (B/L x 10), Stereognosis, Graphaesthesia, Fist-Edge-Palm (FEP)	NES	NES
Romberg (30s)	Blumenfeld (2010)	After NES
Praxis	Scripted	After NES and Bartolo *et al* (2008)(100)
Visual extinction, sensorimotor (line-bisection) Visual fields, conjugate movement, convergence, smooth pursuits, saccades, pupillary light constriction/consensual response, Muscles of facial expression, facial sensation, Muscles of mastication, jaw jerk reflex, voice and cough, dysphagia, Poke out tongue/tongue in cheek,	Blumenfeld (2010)	Scripted
Colour blindness	Ishihara (2010) (101)	Ishihara (2010)
Dysarthria	After Miller *et al* (2014)(69)	Scripted
Dix-Hallpike test	After Zainun *et al* (2013)(102)	Scripted
Finger-nose-finger (B/L x 10)	After Amer *et al* (2012)(103)	After NES
Fukuda Step Test	After Fukuda (1959)(104)	Scripted
Deep Tendon Reflexes (Biceps, brachioradialis, triceps, patella, achilles)	Blumenfeld (2010)	WRS
Gait (ordinary gait, tandem, plantarflexion, dorsiflexion, forced)	After Sullivan *et al* (2012)	After NES
Joint position sense 1	After Chu (2017)	Scripted
Joint position sense 2 Vibration sense	After Gilman (2002)(105)	Scripted
Finger-nose (B/L)	After Sullivan *et al* (2012)(106)	After Notermans *et al* (1994)(107)
Pronator drift	After Sullivan *et al* (2012)	Scripted
Forearm rolling test	After Amer *et a*l (2012)	Sawyer *et al* (1993)(108)
Finger rolling test	After Anderson *et al* (2005)	After Sawyer *et al* (1993)
Tone and clonus (UL tone, fast elbow test, UL clonus, LL tone, LL clonus)	Blumenfeld (2010)	MAsh
Muscle strength	ASIA	MRC

3.6.2. Excluded from Neuroexam

The protocol was required to walk the fine line between a comprehensive examination and placing as little stress on participants as possible. For this reason, some tests were excluded from the protocol. The omitted tests were olfactory nerve testing, ophthalmoscope examination, visual acuity (Snellen eye chart), Rinne and Weber's tuning fork tests, and primitive reflexes.

The olfactory nerve examination was excluded for two reasons: a potential hyper-responsiveness to scent for participants with ASC, and the difficulty in quantifying scent response. There have long been anecdotal reports from individuals with ASC that smells can be overwhelming.(109) Testing of the sense of smell, olfaction, is conducted via two primary classes of tests: odour threshold and odour discrimination. Tests of odour threshold evaluates the lowest concentration of a stimulus that can be detected.(110) Odour discrimination tests evaluates the ability to differentiate between different smells. Odour discrimination requires higher order processing than the odour threshold testing as odour discrimination not only requires a smell to be detected, but also for that information to be integrated against memories of prior smells and with semantic memory to put a verbal description to that smell.(111) The experimental procedures used in the literature to evaluate odour threshold and odour discrimination are lengthier are require more specialised equipment than is used in a standard neuroexam and it was felt that this work was better left to studies exclusively researching olfaction rather than to attempt a poor execution with a potentially unpleasant stimulus to participants within this study.

The opthalmoscopic examination was excluded as the purpose of this examination is to look for pathology of the retina and optic cup with associated vasculature. As the population recruited was not pathological it was deemed that the shining of a bright light and close physical proximity of the examiner during an ophthalmic examination did not provide significant additional information to the study to warrant the potential discomfort to participants.

The visual acuity tests were excluded as a comprehensive examination of visual acuity was not possible and as we did not screen to exclude those with glasses or astigmatism, the visual acuity test would have not added value to the examination.

The prevalence of hearing loss in ASC is controversial, with prevalence rates of peripheral hearing loss ranging from 3.5%, (112) a figure ten times higher than the general population, to prevalence levels similar to the general population.(113) Hyperacusis, a reduced tolerance for loud sounds, has been displayed in children with ASC who exhibited discomfort in pure-tone sounds at significantly lower loudness than TD peers.(114) Even with the use of sophisticated techniques such as audiometry and MRI the processes of hearing and central auditory processing remain unclear in autism.(115–117) Rinne and Webers tests aim to distinguish between sensorineural and conductive hearing loss, however, given the complexity of hearing in autism and the potential for the tuning forks to present an unpleasant stimulus it was deemed that the information gained from performing these tests was limited and therefore these tests were foregone.

Primitive reflexes are usually included in NSS inventories,(50) however the significance of primitive reflexes in any population remains controversial.(118,119) A Canadian study of 2,914 subjects aged 65 and over found in healthy subjects a prevalence of palmomental, snout, and glabellar reflexes of 7.8% , 7.1%, and 5.6% respectively compared to subjects with dementia who had a prevalence of the same reflexes at 25.8%, 35% and 36.8% respectively.(120) In a younger healthy population (<50 y) the prevalence is reported palmomental 0-30%, snout 0-10%, glabellar 0-50%.(121,122) The rooting and grasping reflexes are generally not found in a healthy younger populations.(122) Interpretation of a positive response in primitive reflexes requires more than detecting a response to stimulation. Interpretation of the response needs to include the intensity of the response and the degree of habituation as well as a sound understanding of which reflexes occur with some frequency in a healthy population.(122) The lack of clarity around primitive reflexes in terms grading the strength of a reflex response, and which reflexes or combinations thereof constituted an abnormal response, made the inclusion of the primitive reflexes in this study untenable.

Chapter 4

4. Results

4.1. Participant Characteristics

A total of 17 participants were recruited to the study with neuroexam testing taking place between March to early July 2018. Of the 17 participants, 10 were controls and seven were participants with ASC. The overall male:female ratio was 1:1.8, with controls having a ratio of 1:4 and ASC participant ratio of 4:3. All neuroexam participants identified themselves as right-handed and none identified themselves as having a diagnosis of ADHD/ADD. The participant characteristics are shown in Table 6.

Table 6: Participant Characteristics

	Questionnaire		**Neuroexam**	
	ASC (*n* =17)	Control (*n*=50)	ASC (*n*=7)	Control (*n*=10)
Gender (m:f:other)	8:8:1	11:39	4:3	2:8
Handedness (right:left)	-	-	7:0	10:0
Diagnosis (AS only, ASD only, both)	5,3,8 (17)	-	3,1,3 (7)	-
History of depression (currently, longer than 6 months ago)	5,3 (8)	4,12 (16)	3,1 (4)	0
History of anxiety (currently, longer than 6 months ago)	9,2 (11)	8,12 (20)	3,1 (4)	0
ADHD/ADD	5	2	0	0
Number of participants history of both depression and anxiety	6	14	3	0
Antidepressant medications (n)	3 SSRI, 2 SNRI (5)	3 SSRI	2 SSRI, 1 SNRI (3)	0
Psychostimulants	2	1	0	0
Other medications (n)	4	6	2	0
Vitamins and supplements	6	8	2 B group vitamins, 1 vitamin D and 1 iron (4)	1

NB: The Questionnaire Control *n*=50 is the number of participants who were not automatically excluded, but before a manual exclusion processing had occurred.

A history of depression, anxiety, or both was prevalent in the ASC population, with 65% (*n*=11) of questionnaire respondents with ASC and 71% (*n*=5) of neuroexam participants with ASC reporting a history of those conditions. The control questionnaire population reported a 40% (*n*=20) history of depression, anxiety or both. One or more vitamins were reported to be used in 57% of the ASC neuroexam attendees compared to 10% in the control group. Vitamins, particularly the D and B groups have been contested in the literature. The prevalence of nutritional deficiency (123–125) due to restricted diets can make research on effects of vitamin regulation in autism difficult.(126) Vitamin D deficiency is linked to bone weakening, as extreme examples of this are diseases such as rickets. Bone weakening in autism has been studied with some authors (127,128) suggesting that low serum levels of vitamin D has led to individuals with ASC having increased likelihood of reduced bone density. More significantly, vitamin D has been linked to neural differentiation in foetal development and neuroprotective effects in adulthood,(129) with several authors suggesting vitamin D research in autism as a priority.(130,131) The B group vitamins are also important in foetal development and maintenance of the adult nervous system. Vitamin B group deficiencies can lead peripheral neuropathies and disorders of cognition and depression.(132–134) A post-mortem study (135) found brain levels of vitamin B12 (methylcobalamin and adenosylcobalamin) significantly reduced compared to age-matched controls.

Antidepressants were less utilised than vitamins, with 43% (*n*=3) of neuroexam attendees with ASC, and 29% of questionnaire respondents with ASC, reporting antidepressant use. Only 6% (*n*=3) of the control questionnaire group reported antidepressant use. Of the questionnaire respondents with ASC, 29% (*n*=5) reported having a diagnosis of ADHD/ADD compared to 4% (*n*=2) of the control questionnaire respondents.

4.2. Feasibility Results

Overall, there was a 55% attendance of neuroexam to participants invited. There was a 16% difference between controls and participants with ASC in the rate of attendance to invitation, with the participants with ASC having a 47% rate of attendance to invitation. There was a significant gender disparity in the response to the online questionnaire, strongly biased towards females, however this disparity followed through neuroexam participants only in the control group: the participants with ASC being relatively equally represented between male and female participants. The optional scheduled-breaks during the neuroexam were exclusively utilised by the participants with ASC, with 43% (*n*=3) of participants taking a break. The results are shown in Table 7.

A timeslot of 90 minutes was allocated to each neuroexam, with the estimation of 15-minutes for the introduction and informed consent, and one hour for the neuroexam inclusive of the two optional five-minute breaks and an additional allotment of 15-minutes for any unscheduled breaks. The full time allocated was generally not used.

All participants who attended the neuroexam appointment completed the neuroexam, there were no no-shows to appointments, nor were there any adverse events. Participants were offered two scheduled 5-minute breaks as well as the potential for an unscheduled break if discomfort levels became greater than five out of ten. There were no unscheduled breaks. The breaks were statistically significant (*p*=.028, r=-.535).

Table 7: Neuroexam Feasibility

	Total (*N*)	**ASC (*n*)**	**Control (*n*)**
Questionnaire attempted (male:female:other)	88 (23:64:1)	-	-
Questionnaire exclusion (age, not fluent in spoken English, smoking, training in neuroexam)	21 (3,1,4,13)	-	-
Manual Exclusion	19	2	17
Neuroexam Attended/Invited	17/31 (54.8%)	7/15 (46.7%)	10/16 (62.5%)
Neuroexam cancellations	5	2	3
Participants utilising scheduled breaks (n)	3/17 (17.6%)	3/7 (42.8%)	0/10 (0%)
Total number of breaks	4	4	0

4.2.1. Post-Neuroexam questioning of participants and the examiner

Participants were asked to comment on their experience by answering two questions: (1) Did you learn anything about yourself during the examination? and (2) Did you experience any difficulty during the examination? The results are shown in Table 8 and 9.

Table 8: Participant Post-Examination Question 1: *Did you learn anything about yourself during the examination?*

	Comments
Control (50% response rate)	That my knees are weirdly not responsive. I have a history of lots of injuries from ice hockey
	My knowledge of names of fingers wasn't good and spelling backwards took me longer than I thought it would, and I couldn't remember the suburb of where we are
	Surprised by knees reflexes. I have a history of right surgery knee arthroscopy
	I feel like memory [was poor] with a few objects
	that I am colour blind
ASC (29% response rate)	I'm not as coordinated as I thought I was
	Yes. [re Fukuda step test] what I thought I was doing isn't what happens

Table 9: Participant Post-Examination Question 2: *Did you experience any difficulty during the examination?*

	Comments
Control (30% response rate)	sprained my ankle yesterday and so hopping was difficult
	Sometimes difficult to differentiate between left and right sides
	Couldn't tell what shape one of the figures was [graphaesthesia], but other than that I think not.
ASC (57% response rate)	Staring was unnerving for 20 seconds [Dix-Hallpike]
	I had problems with the fist-palm one [FEP]
	During the pressure sensation I couldn't tell if he was pressing down differently or I was feeling it differently between sides
	Not really. Sometimes I had to take a bit time to relax my muscles – they wouldn't do it [tone and clonus]

The controls responded with comments to the first post-examination question one at a 50% (*n*=5) response rate compared to the ASC 29% (*n*=2). The second post-examination question regarding difficulty elicited a higher response rate in the participants with ASC, 57% (*n*=4) than the controls 30% (*n*=3). Overall both questions tended to elicit responses about specific parts of the neuroexam.

The examiner, AS, wrote qualitative comments on the neuroexams if he felt that any results required clarification. Additionally, at the conclusion of each neuroexam the examiner was asked if he believed the participant he had just examined had autism. This was a test of examiner blinding. The examiner was incorrect in his assessment of the participants' autism status in three instances: two participants he thought had autism when they did not, and one participant he did not have autism when they did. Overall, the examiner blinding was poor. The comments derived from the examiner covered three different issues: movement on coordination and/or motor sequencing tests tended to be slow and deliberate; the participant demonstrated a startle response on being touched when he/she couldn't see where he/she was being touched (several tests of sensation require the participant to have closed eyes); and a literal interpretation of any instruction. The distribution of the comments is listed in Table 10.

Table 10: Examiner Comments

Comment	**ASC (*n*)**	**Control (*n*)**
Slow and deliberate on motor coordination tests	71% (5)	20% (2)
Startled on testing when I was outside the field of view (mainly dermatome testing, lower limb tone and clonus)	57% (4)	10% (1)
Very literal in interpretation of instructions	42% (3)	10% (1)

4.3. Neuroexam Results

The analysis was performed both on individual neuroexam tests and on the grouped sections of the neuroexam testing for a null hypothesis that no difference existed between the ASC and control groups. An independent 2-group Mann Whitney test with a 5% confidence interval was used for generating the *p*-value. Table 11 lists the grouped sections of the neuroexam, and the overall *p*-value between ASC and control groups. Items marked as no difference (ND) indicate that all participants in the study obtained identical scores for that section. This occurred in sections where no abnormal results were recorded, such as the muscle strength testing, where no individual exhibited muscular weakness.

The neuroexam has a multitude of rating scales used as standards in various individual tests. In the calculations of the means of groups of tests, as displayed in Table 11, the scores were normalised to unity to prevent any individual test having undue weighting in the group means due to scaling differences.

Table 11: Neuroexam section results

Neuroexam Test Sections	Control ($\bar{x}$)	ASC ($\bar{x}$)	Effect Size (r)	*p*-value
Mental Status (A0x3, memory, naming, comprehension, repeat a sentence, LR confusion, finger agnosia, write a sentence, calculations, logic and abstraction, praxis)	.923	.949	.118	.080
Motor Sequencing (FEP, Ozeretski test)	.75	.75	.004	. 984
Extinction (line bisection, face-hand test, visual extinction)	1	1	ND	ND
Cranial Nerves (visual fields, saccades, conjugate movement, smooth pursuits, convergence, pupillary response, consensual response, muscles of facial expression, facial sensation, muscles of mastication, jaw-jerk reflex, voice and cough, dysphagia, dysarthria, poke out tongue, tongue in cheek, otoscope examination, Dix-Hallpike)	**.978**	**.904**	**.207**	**.001**
Coordination and balance (pronation/supination, finger-nose-finger, Romberg, Fukuda)	**.942**	**.845**	**.187**	**.054**
Deep tendon reflexes	.985	.962	.125	.103
Gait (Ordinary gait, tandem, dorsiflexion, plantarflexion, forced gait)	.980	.943	.142	.191
Sensory Exam (Stereognosis, graphaesthesia, two-point discrimination)	.917	.937	.046	.702
Proprioception (joint position sense (identifying direction of DIP joint movement index finger), joint position sense 2 (passively moving limbs with closed eyes and asking participant to reposition in same pose), finger-nose)	.958	.917	.154	.120
Sensory Exam - dermatomes (light touch and pinprick in dermatomes: C3-C8, T1, L2-L5, S1), vibration sense	1	1	ND	ND
Sensory Exam – right/left sensation (Does left and right feel the same: light touch and pinprick in dermatomes: C3-C8, T1, L2-L5, S1)	.967	.946	.206	.229
Motor Functional Exam (Pronator drift, forearm rolling test, finger rolling test)	1	1	ND	ND
Tone and Clonus (UL tone, fast elbow test, UL clonus, LL tone, LL clonus)	.962	.969	.111	.146
Muscle Strength (myotomes C1-C8, T1, L1-L5, S1,S2)	1	1	ND	ND

LL: lower limb, UL: upper limb, ND: no differences between scores

Overall, there was no difference in the mental status examination between the two groups. The mental status examination was notable as the participants with ASC recorded no errors in the tests of attention and orientation, whereas the control group had 50% of participants making an error on these tasks. The ASC group recorded no errors in short-term memory, whilst the control group recorded two participants with errors. This was interesting from the perspective of the debates on executive function and memory. For reviews of executive function see Demetriou *et al* (2018),(79) for reviews of memory in autism see Boucher, Mayes, and Bigham (2012)(136) and Kercood *et al* (2014)(137). The left/right confusion task demonstrated 40% of the control group compared to 29% of the ASC group making errors. Of those who had difficulty two participants from each group scored zero: meaning two or more errors of the eight tasks distinguishing between right and left sides on self and others. The logic and abstraction task had five participants scoring poorly. Three of the controls scored zero out of three, while one participant with ASC scored zero, and another scored one out of three.

The cranial nerves examination had the following tests where no participant exhibited an unusual response: visual fields, extinction, pupillary light response, muscles of mastication, voice and cough, dysphagia, tongue in cheek, and Dix-Hallpike. One participant displayed errors in conjugate movement, but this was due to a notable strabismus in one eye. The statistical significance between groups originated in the tests of saccades, smooth pursuits, muscles of facial expression, facial sensation, jaw jerk, dysarthria, and poke out tongue.

Table 12 lists the individual tests which displayed a statistically significant difference between the ASC and control groups.

Table 12: Significant individual neuroexam tests

Individual Tests	***p*-value**	**Effect Size (r)**
Finger-to-nose (over both hands)	**.008**	**.457**
Finger-to-nose (dominant hand)	**.028**	**.535**
Pronation/supination (over both hands)	**.033**	**.366**
Saccades	**.008**	**.643**
Muscles of facial expression	**.027**	**.537**

All participants who demonstrated an atypical response in the saccade task were in the ASC group, and of these, it was consistently the vertical saccade task. No participant demonstrated an atypical response in the horizontal saccade task.

The muscles of facial expression task gave verbal instructions as well as the examiner demonstrating the task. It is difficult to determine if the imitation aspect of the test caused difficulty for participants with ASC.

The neuroexam test sections demonstrated a significant difference between the ASC and control groups in the domains of motor coordination and balance, and cranial nerve function. When the tests were grouped according to the NES subscales as in Table 13, the motor coordination subscale showed a significant difference between the ASC and control groups (*p*=.004. r=.311), with the ASC group scoring lower, (less function) than the controls. The study protocol excluded one item from the NES motor coordination subscale of finger-thumb opposition. When the tests were grouped according to the NES subscale of sensory integration (graphaesthesia, stereognosis, face-hand test, right/left confusion) result was not significant (*p*=.345, r=.115). The study protocol excluded one item from the NES sensory integration subscale of audio-visual integration. As the stereognosis and face-hand test recorded no atypical responses from any participants the *p*-value is effectively derived from the graphaesthesia and right/left confusion tests.

Table 133: NES Subscale analysis

NES subscale	***p*-value**	**Effect Size (r)**
Motor Coordination (tandem walk, pronation/supination, finger-to-nose)	**.004**	**.311**
Sensory Integration (graphaesthesia, stereognosis, face-hand, left/right differentiation)	.345	.115
Complex Motor Acts (FEP, Ozeretski) *equivalent to motor sequencing section*	.984	.004

Chapter 5

5. Discussion

5.1. Feasibility: Participant Protocol

The neuroexam appeared to be generally well tolerated. There were no adverse events or unscheduled breaks. The post-examination questions revealed attitudes towards specific tests in the neuroexam, but no participants reported overwhelming sensory stimulation. The neuroexam participants with ASC were quite evenly matched in gender, which was valuable result given the significant gender bias towards males (8,138,139) historically in autism research. The participant protocol displayed strengths in the level of information provided to potential participants prior to confirming a neuroexam, to allow participants to understand the process as well as deciding if the neuroexam was appropriate for them. The scheduled breaks were utilised at a statistically significant rate (p=.028, r=.535), demonstrating the value in their inclusion in the protocol. A rule of thumb for effect size interpretation is that a value above r≥.5 is considered to be large.(140)

Based on previous research key elements of the participant protocol in providing a tolerable environment for participants with ASC included: the provision of information before the appointment detailing what would occur at the appointment, conducting the neuroexam at quiet times, ensuring that the examination provided sufficient time for the participant to respond at their own pace and manner, and provision of breaks during the protocol.(17,21,89,141) Even with all the above provisions, in routine clinical care many individuals with ASC find the sensory components of physical examination techniques overwhelming.(21,142) . Some individuals are always going to find physical examination techniques extremely challenging. Nicolaidis, Kripke and Raymaker (2014)(90) provide a valuable set of recommendations accommodating the needs of adults with ASC during a physical examination. This set of recommendations helped define the participant protocol and aided its success.

The work of Nicolaidis, Kripke, and Raymaker (2014) laid the groundwork for the creation of the Autism Healthcare Accommodations Tool (AHAT).(17) Individuals with ASC fill out their own sensitivities and requirements in an online tool, then a report is generated to be sent to a nominated healthcare provider. Unfortunately, this online tool could not be used for this study as it had not been deployed in Australia. Future work would benefit from the incorporation of AHAT.

The post-examination participant answers also revealed that some of the areas that could be anticipated as difficult or uncomfortable for an individual with ASC, such as looking into the eyes of the examiner for 20 seconds in the Dix-Hallpike test. This difficulty catered for in the protocol design in various tests of gaze by requesting participants keep a steady gaze at the examiner's nose, rather than his eyes. The examiner was also provided with sticky dots to place on the wall behind him, to provide a fixed point of gaze, if this was preferable to the participant. The Dix-Hallpike test was the only test which required direct gaze into the examiner's eyes. This test could potentially be removed from a future protocol, unless tests of vestibular function seemed clinically indicated.

Making a neuroexam protocol that is as comfortable as possible for participants with ASC is an important issue as research into the primary barriers to healthcare amongst spectrum adults include: fear or anxiety (35%), can't process information fast enough (32%), and facilities cause sensory issues (30%).(143) A non-response bias is inherent in the work, as individuals with ASC who were uncomfortable with medical physical examinations were unlikely to complete the screening questionnaire. Participants with ASC who felt they could not tolerate the stimulus of the neuroexam after reading *About the Neuroexam*, did not go on to make appointments.

The intended recruitment of ten participants with ASC was not achieved. Delays in approvals for the advertising material significantly impacted the period that advertising occurred to around the University campus, at the psychology clinics and via social media, limiting the period to approximately five months. As an autistic person, I found the social engineering aspects of making contacts to request permission for advertising one of the most challenging aspects of the recruitment process.

Of those who identified themselves as having an AS only diagnosis, 60% of questionnaire respondents attended a neuroexam even though an AS only diagnosis comprised only 29% of the questionnaire respondents with ASC. This may indicate that the social media advertising with blogger, Tip of the Asperg, was particularly useful for recruitment. However, as there is no data on the advertising source which attracted respondents or the response rates of any of the media used, no specific conclusions can be drawn. Half of the participants with ASC identified themselves as having a diagnosis of both ASD and AS, which is potentially indicative of the DSM-5 changes in eliminating AS as a diagnostic entity.(144–148)

A gender disparity was apparent in questionnaire responses, and particularly in the recruitment of control participants into the neuroexam, with a male:female ratio of 1:4. Of the questionnaire control group after automatic exclusions the ratio was 1:3.5, whereas the male:female ratio for the ASC group was 1:1, with one individual whom identified as other. A demographic bias has emerged since the advent of easy internet access to large proportions of the population that females are more likely to respond to online research questionnaires;(149,150) however this effect was only apparent in the control group. It is possible that the higher representation of males with an ASC diagnosis levelled the questionnaire gender effects in the ASC group.(151)

Examiner blinding was poor, as the examiner correctly stated the ASC status 82% of the time. This was potentially influenced by the knowledge that he was testing participants with ASC and so interpreted any unusual participant characteristics, either in affect or neuroexam tests, as being autism based. This effect is a problem in healthcare as clinicians tend to interpret information in the clinical encounter as a symptom of autism and nothing else.(21,152)

A more proactive advertising strategy, particularly one which made greater use of social media avenues, would potentially give a better overall response in future work. It would have been useful to time the duration of the neuroexam appointments, as it became apparent that even if a participant took no scheduled breaks the conduction of the neuroexam it generally took longer for participants with ASC than controls.

5.2. Feasibility: Neuroexam Protocol

The neuroexam protocol had nearly 100 tests, which needed to have some form of quantitative grading consistently applied. Of these tests, very few gave problems in the execution or the grading of the test. The five trial-neuroexams conducted prior to the start of recruitment eliminated most confusion about the conduction of tests or application of the scoring criteria. The tests which demonstrated problems were graphaesthesia, which was only evident in the analysis of the results, and the timed components motor sequencing and motor coordination.

The scripted interactions throughout the protocol were also being tested for their clarity in explaining the process to participants. This language was written to be as direct about requirements as possible and to limit idiomatic or figurative language. The language used was informal in tone to make the process less intimidating to participants. The examiner had a degree of freedom to explain if the participant did not understand the scripting but was directed to return to the script as soon as possible. There was little difficulty in the scripted text, with no feedback on any one piece of text being unclear in the running of the neuroexam.

The application of the testing of graphesthesia was potentially not indicative of the neurological status of the participants, as 10 of the 17 participants recorded at least one error in reporting the correct sequence of EN4. The statistical analysis of graphaesthesia displayed no significant difference between ASC and control groups suggesting that the high error rate was more indicative of an issue in the application of the test. Seven errors occurred with the number four, indicating it was a poor choice in this test. The Heidelberg scale instructions for testing of graphaesthesia would have provided a more reliable test. In the Heidelberg scale the letter X, ☐ (a square), O (a circle), and number 3, are presented on a sheet of paper and then the symbol is drawn with the participant's eyes closed. The participant then chooses the symbol from the sheet.

The motor sequencing and motor coordination tests had a timed component: fist-edge-palm, rapid pronation/supination, and Ozeretski's test, displayed issues in the examiner conduction of the tests. In the neuroexam-trials a stopwatch was provided to time the tests over a standard number of iterations. However, when it came to the study execution of these tests the examiner found it difficult to count iterations, hesitations or errors, as well as time the conduction of the test. The accurate timing of the test suffered as a result, and timing data

could not be incorporated into the study. The qualitative feedback regarding slow and precise movements was instead used. The test was designed in this manner as validation of timed motor movements and normative curves have been established in child and adolescent measures of function in the PANESS(61) as well as the Zurich Neuromotor Assessment.(153,154) A limited amount of normative data exists in timed motor tests of adults, particularly in older cohorts.(155–158) The NES instructions request a set number of iterations of completed movements but do not time the tests. The problems encountered in the motor sequencing tasks was disappointing, as the prior research had indicated that adults with ASC performed poorly in these tasks.(29–32) Despite the difficulties in the conduction of the timed motor tests the qualitative data suggests that fast and accurate motor sequencing tasks are more difficult for participants with ASC, and potentially speed is sacrificed to allow accuracy. Slow and deliberate qualitative comments were made regarding 71% of participants with ASC compared to 20% of the controls.

The examiner also reported difficulty in quantifying the tone and clonus examination as he found it difficult to interpret a true increase in tone compared to the participant finding the sensory input difficult and being unable to allow passive limb movements.

One of the issues that became apparent during the running of the study was the determination of when it was clinically appropriate to refer a participant for further medical review. In some cases, multiple 'hard' signs present such as deviation on poking out tongue, positive Romberg's with sway to the left in conjunction with the positives in the 'soft signs' more commonly associated with ASC in the literature, such as saccades and FEP. These cases highlighted the need for further research to ultimately lead to pragmatic guidelines for clinical decision making in the neuroexam in adults with ASC. In such cases, it was discussed with the examiner as to his clinical opinion of the necessity for referral. If no referral was deemed necessary, then no feedback about the examination was given. No participant was referred for further examination.

Feedback was not generally given to participants on the results of the neuroexam. A single exception occurred when the Ishihara testing indicated that a participant was colour-blind. The participant was provided with feedback on this specific test with the recommendation of follow-up with his own GP if he was concerned regarding the probability of colour-blindness. A formal referral was not provided on this occasion as it was deemed that he was otherwise healthy and not in need of a medical work-up. General feedback detailing the results of the study will be emailed to participants who indicated interest in receiving an update on the results.

The protocol could potentially be made shorter by removing tests such as the Ishihara tests for colour blindness, and unless clinically indicated, tests such as the Fukuda step test, Dix-Hallpike test, and otoscope examination. In a future protocol, filming of the actions would prove beneficial and allow for more than one-rater of the examination. This is an issue in clinical practice as it is similarly difficult for a single examiner to simultaneously count errors, hesitancies, and number of iterations of a complete set of actions.

5.3. Neuroexam Analysis

5.3.1. Mental Status

The mental status section of the neuroexam consisted of 14 scored tests. The analysis of this group did not display any significant between ASC and control group differences, either over the whole group, nor in any individual tests.

5.3.2. Motor Sequencing

All motor related results have been grouped into one section. See section 5.3.8 Motor, Gait, and Coordination.

5.3.3. Extinction

All participants scored 100% on the extinction tasks of: line bisection, face-hand test, and visual extinction. As these tasks test for relatively gross neurological deficits, it is not surprising that deficit was not displayed in either group.

5.3.4. Cranial Nerves

The cranial nerves section displayed a between group statistically significant difference (*p*=.001, r=.207). Tests which only the participants with autism scored atypical results were: saccades, muscles of facial expression, facial sensation, jaw jerk reflex, dysarthria, and poke out tongue. Saccades and muscles of facial expression both individually showed strong between group significance.

Saccades had the largest between group effect size (*p*=.008, r=.643) of any test. The atypical saccade results only occurred in participants with autism (*n*=4), and all were all in the vertical orientation. Smooth pursuits and saccadic movements have been extensively researched within the field as a method of elucidating the brain regions which may behave differently in individuals with ASC to those who are TD. For useful reviews of vision in autism see Johnson *et al* (2016)(159) and Bakroon *et al* (2016).(160) The saccade task in the neuroexam is a voluntary saccade task as the patient is being asked to rapidly redirect their focus between two spaced fingers in a horizontal plane and then a vertical plane. In the meta-analysis performed by Johnson *et al* (2016) they determined that in voluntary saccade tasks there was no difference between ASC populations and controls except in saccade dysmetria. Saccade dysmetria is a reduction of accuracy in the fixation of the visual target, either undershooting or overshooting the goal. The studies in the literature use computerised visual targets and electrooculography to track eye movements which give considerably more accurate information than in our saccade screening task. The errors noted in the vertical saccade task in this study may be accounted for by the examiner noting saccade dysmetria in the execution of the task. The literature is notable for consistently reporting individuals with autism performing significantly more errors in anti-saccade tasks,(159,160) however anti-saccade tasks are not easily tested in the neuroexam. Mosconi *et al* (2010)(161) in a study of unaffected first-degree relatives of individuals with autism found that they also exhibited saccade abnormalities compared to controls, including saccade dysmetria.

The muscles of facial expression test also had a significant difference between groups (*p*=.027, r=.537) with several of the participants with ASC (n=3) being unable to perform the actions, whereas none of the control group exhibited difficulty in this test. The test gave verbal instructions, as well as the examiner demonstrating the actions: smile, wrinkle forehead, close eyes tight, blow out cheeks, show teeth, pull down sides of bottom lip. The test is not capable

of discriminating between a bilateral muscular weakness and an inability to perform imitation of facial expression. A unilateral muscular weakness or paralysis is apparent through asymmetry. A bilateral weakness or paralysis of facial muscles would be unusual.

The group difference displayed in our study is very likely to represent difficulty in action imitation. Action imitation has been extensively discussed in the literature.(68,70,72,162–175) Williams, Whiten, and Singh (2004)(163) in a comprehensive systematic review of action imitation in ASC and concluded that imitation deficit existed in autism. The persistence of imitation deficit into adolescence and adulthood has been less well studied. Frietag *et al* (2006) (170) found group differences between participants with ASC (14-22 y) in upper and lower facial imitation. Yoshimura *et al* (2015)(172) in a study of adults with ASC response to dynamic and static images of angry and happy faces also found group differences where the ASC group performed imitation poorly compared to controls. The Yoshimura *et al* (2015) work included an element of social responsiveness in the design, rather than a direct imitation. This kind of study is a result of the debate regarding mirror neurons theory of autism. This theory hypothesises that mirror neurons, used to related observed actions to motor codings, are dysfunctional in autism.(176) The mirror neuron basis of imitation deficit has been critiqued in several studies.(165,167,175,177) Biscaldi *et al* (2014),(178) in one of the few studies that performed a comparison across developmental trajectories, found that whilst imitation of facial movements and non-meaningful gestures were impaired in ASC, the deficit improved with age.

5.3.5. Coordination and Balance

All motor related results have been grouped into one section. See section 5.3.8 Motor, Gait, and Coordination.

5.3.6. Deep Tendon Reflexes

The deep tendon reflexes group did not display any statistically significant differences across the entire group of tests, (p=.103, r=.125) nor in any individual subtest.

5.3.7. Sensory Tasks

The current study did not demonstrate a significant difference between the autism and control groups in any of the sensory domains tested. This was expected in the dermatome testing of light and sharp touch, and the vibration testing. The testing of proprioception did not demonstrate between group statistical significance but one of the proprioceptive tasks: finger-

to-nose (dominant hand) (p=.028, r=.535), and finger-to-nose (both hands) (p=.008, r=.457) displayed a large effect size and between group differences in the performance of the test. Participants with ASC scored less accurate movements than the control group. Curiously, the non-dominant hand, in this case the left hand as all participants were right-handed, did not record significant between group differences.

The sensory integration tasks of graphaesthesia, stereognosis, and two-point discrimination have been reported in the literature as demonstrating difference between autism and control groups,(29–31,109) but no significant difference was found in the current work.

There is limited data on actual neurological testing of sharp and dull touch and vibration in the literature.(109,179–182) Our study did not show significant between group differences in the dermatome testing of light touch, pinprick and right/left sensation. Minshew, Goldstein, and Siegal (1997)(182) performed tests of sensory perception in 33 adolescents and adults with ASC (IQ> 80), compared with controls. The tests included light touch and pinprick, sharp and dull discrimination, graphaesthesia, and joint position sense. Similar to our study, their study showed virtually no errors in either group in the detection of light or sharp touch, or the discrimination between the two. However, they did find significant difference in graphaesthesia. Minshew and Hobson (2008)(109) repeated and expanded this work, with 60 participants with ASC (IQ>80), in a large age range of 8-54 years, and additionally included a sensory sensitivity questionnaire (SSQ) for both the participants, and their parents or caregivers. The neurological testing included the Luria-Nebraska Battery, Tactile Functions Domain (183) and Reitan-Klove Sensory Perceptual Exam.(184) The tests included were light touch and pinprick, sharp and dull discrimination, graphaesthesia (finger-tip writing, wrist shape drawing), stereognosis, and joint position sense, sensory neglect through double simultaneous stimulation (visual, auditory, and tactile). They found no correlation between the sensory sensitivities, as reported by participants or parents, and the neurological testing. The testing of sensory neglect between groups was not significant. Our study tested sensory neglect only for the visual and tactile domains, and similarly did not show any significant between group difference. Consistent with Minshew's previous work, no significant difference in light touch and pinprick, and sharp and dull discrimination was found. They did find significant group differences in the composite scores for graphesthesia and stereognosis (p<.001) as well as for the stereognosis tasks as analysed individually. They did not find any significant difference in

joint position sense, however as the pre-screening for the study eliminated those who scored poorly in motor speed, and motor praxis, the participants with sensorimotor integration issues were effectively removed from the design.

Cascio *et al* (2008)(185) in a small study of eight adults with ASC compared to controls found that the two groups were comparable in the threshold force required to detect light touch on the thenar eminence and forearm, and similarly comparable in warm and cool detection. Vibrotactile detection was comparable on the thenar eminence, but had a significant difference on the forearm, with participants with ASC demonstrating a lowered threshold for detection. The standard method of testing vibration in a neuroexam is on the boney aspects of fingers or toes, hence differences are unlikely to be detected. This study found no difference between groups in the detection of vibration on the fingers. The Cascio *et al* (2008) study also found heat and cold pain thresholds were lower for the ASC group compared to controls.

Previous work has found significant between group differences, particularly in graphaesthesia and stereognosis.(109,182) The NES subscale of sensory integration (audio-visual integration, graphaesthesia, stereognosis, tactile extinction (face-hand test), right/left confusion) in the Manouilenka *et al* (2013)(31) study was reported as significant. The Hirjak *et al* (2014)(29) study reported significance between the ASC group and controls in the Heidelberg subscale of right/left and spatial orientation (right/left orientation, graphesthesia, face-hand test, stereognosis) but not in the following study performed in 2016.(30) Our study reported no differences between the groups in stereognosis and tactile extinction (face-hand test), and as mentioned previously, the graphaesthesia protocol was not reliable. There were right/left orientation errors recorded in both groups, but the analysis determined these differences were not significant.

Proprioception (joint position sense) is a contentious subject in the literature with debates on whether or not a proprioceptive deficit exists in autism.(69,186–193) It is difficult to assess proprioception without incorporating motor function, gait, and balance as all these systems are reliant on the accurate reporting of joint position. The finger-to-nose test in the format presented in the protocol, is a measure of the accuracy of a person's internal representation the location of their limbs in space (proprioception) without visual input. The finger-to-nose test displayed statistically significant difference between the ASC and control groups (p=.028, r=.535) , whilst the proprioception test section, consisting of two other tests of joint position

sense as well as the finger-to-nose test, was not significant (*p*=.078, r=.154). The finger-to-nose findings in the current study are broadly consistent with the Hirjak *et al* studies, in which they reported significance in complex motor acts Heidelberg subscale, of which the finger-to-nose test is an element. The Manouilenka *et al* (2013) study showed significance for the motor coordination NES subscale, of which the finger-to-nose test is an element.

In the protocol, the participant is seated with eyes closed, the arm is held in forward flexion at shoulder height and the participant touches the tip of their nose. The test protocol was written in reference in the NES test of finger-to-nose and additionally based on Notermans *et al* (1994)(107) basis for quantifying ataxia. In our grading system a value of: 'two' indicated that the participant had touched the tip of their nose; 'one' was recorded for touching on nostrils or bridge of the nose; and 'zero' for any other location. The test was performed bilaterally. In Notermans *et al* (1994) study participants with cerebellar ataxia performed equally poorly, compared to controls, on finger-to-nose with eyes opened and eyes closed. Whereas only the eyes closed condition, was able to discriminate between those with sensory neuropathy and controls. No gender, age or dominant hand effects were detected.

5.3.8. Motor, Gait, and Coordination Tasks

Analysis was performed of the neuroexam tests as grouped into functional subscales. The subscale of motor coordination and balance (finger-to-nose-to-finger (FNF), rapid pronation/supination, Romberg's test, and Fukuda step test) found statistically significant difference between the ASC and control groups (*p*=.029, r=.187). Applying the analysis according to the NES subscale of motor coordination (tandem walk, pronation/supination, finger-to-nose) note that the NES subscale uses finger-to-nose, rather than FNF. A moderate effect size between groups was reached (*p*=.004, r=.311). This increase in statistical significance was driven primarily by the inclusion of the rapid pronation/supination task (both hands) (*p*=.033, r=.366) and the finger-to-nose (*p*=.008, r=.457) tests. Both of which displayed significant group differences as individual tests summed across both hands. The rapid pronation/supination task did not display significant between group differences when analysed per hand, (left: *p*=.232, r=.290, right: *p*=.081, r=.423) only when the analysis was performed across both hands (*p*=.033, r=.366).

Individuals who displayed slow motor performance within the neuroexam would consistently have examiner qualitative comments in the following tasks: motor sequencing tasks (fist-edge-palm (FEP), Ozeretski's tests), rapid pronation/supination task, and the FNF task. The qualitative data demonstrates these comments were made for 71% (n=5) of the ASC group performed the tasks slowly compared to 20% (n=2) of controls.

The motor sequencing tasks of FEP and Ozeretski's tests did not display statistically significant differences due to the issues in recording timed responses, but the qualitative data suggests a difference exists. The motor sequencing tasks are used to test for motor perseveration, as might occur in a frontal lobe lesion. Boks *et al* (2000)(194) in a meta-analysis of neurological soft signs in schizophrenia pooled the control group data to report on prevalence of soft signs in a normal adult population. They found 15.6% (*n*=212) of controls performed poorly in FEP, and 16.7% (*n*=254) performed poorly in Ozeretski's test. These results are consistent with our findings, notwithstanding our small sample size.

The motor sequencing tasks (FEP, Ozeretski's test) are grouped within the complex motor tasks subscale in the NES inventory, and separated in the Heidelberg inventory between complex motor tasks for FEP, and motor coordination for Ozeretski's test. By either inventory classification, these tests have demonstrated a statistically significant difference between autism and control groups in the literature.(29–31) Within neuropsychological studies of autism, there has been little direct analysis of motor sequencing, but rather in neuropsychological executive function tests (195) of planning and inhibition such as the Tower of Hanoi, Stroop test, Wisconsin card sorting test,(55) and the Trail Making Test.(56)

The finger-to-nose-to-finger (FNF) did not show a statistically significant difference between the ASC and control groups, however the examiner's comments on this test recorded that the motor control of this action was slow, and on occasion with pauses, with the same participants who performed slowly in the motor sequencing tasks also demonstrating difficulty in this task. This test required the seated participant to touch their nose and then the examiner's finger as rapidly as possible for ten iterations. The examiner held his finger at arms-length from the participant and moved his finger vertically and horizontally, to ensure pronation and supination of the participant's arm, but remained within the same plane of distance from the participant. It is unfortunate that timed responses were not available in this study, as the analysis of the time taken to perform this action may have been more revealing of the between group

differences, rather than to complete the action at all. This test examines fine motor control for a visual target. Swaine *et al* (2005)(196,197) developed timed normative values for 15-34 year old healthy participants over 5 iterations, in the range or 4-5.5 seconds. Amer *et al* (2012)(103) found that the rapid FNF discriminated between cerebellar disease patients and controls in the exhibition of errors in accuracy, such as past-pointing and intention tremor. Our protocol was based on the Amer et al (2012) description of FNF that was not timed but did report accuracy.

A study released this year (198) recorded reaching movements in children and adults with ASC compared to controls. These movements were analysed by a computational model in millisecond timeframes to detect sensorimotor noise. The participants with ASC displayed speed fluctuations in movement that were not detectable to the naked eye and analysis of the movements were able to discriminate both adults and children with ASC from controls. First-degree relatives of the ASC group also displayed greater levels of sensorimotor noise compared to controls.

The analysis of gait did not show a significant difference between groups in the current study. Prior work analysing gait and postural control in children and adolescents with ASC suggest that both are impaired compared with controls,(25,59,68,70,72,74,75,168,171,189,199–207) particularly when computational analysis allows quite specific comparisons of each part of the gait cycle or postural sway in balance tasks.(74,75,205,208) The detection of these subtle anomalies in gait and postural control are unlikely to be obvious in a neuroexam in healthy young adults with ASC. The research to date has focussed on the analysis of infants and children therefore little is known regarding the impact of gait or postural difference in autism as individuals age.

Motor control is complex, requiring more than the simple muscle strength to perform a motor action. That action must be planned and integrated with the sensory information to perform a smooth, skilled action. A large body of work indicates that motor control and coordination is impaired in autism. See Fournier *et al* (2010)(73) for a meta-analysis of motor coordination in autism, and also Gowen and Hamilton (2016)(205) for a review of motor abilities. Hannant, Tavassoli, and Cassidy (2016)(204) give a comprehensive discussion of the role of sensorimotor integration in autism.

The current diagnostic definitions do not include any concepts of problems with motor coordination, sequencing or sensorimotor integration, hence primary care clinicians are unlikely to be aware of the evidence and debates surrounding skilled motor movements. In a recent study (209) 6.9% of adults with ASC (*n*=1,237) reported they had been diagnosed with dyspraxia compared to 0.8% (*n*=6,765) of controls. The effects of sensorimotor issues in adults with ASC has not been well studied. Travers *et al* (2017)(210) performed a longitudinal study (8 years) of manual motor ability from childhood to mid-adulthood (5-40 y) using grip strength measures and found that over a third of ASC participants exhibited at least one measurement of grip strength below the 10th percentile compared to age-matched norms and that manual motor performance was associated with adaptive daily living skills.

5.3.9. Summary

These preliminary results demonstrate that the interpretation of the neuroexam when testing for pathology in an autism population requires some care in interpretation. Whilst there may be an expectation of certain tests, such as saccades, giving unusual results there remains the question of what is normal for the individual and how many atypical results in a given section are an indicator of pathology. If all test results are assumed to be the result of autism alone, there is little diagnostic value in performing a neuroexam. Guidelines for primary care clinicians as to which specific tests may give unusual results, and parameters defining what constitutes a normal for autism, would be beneficial in both aiding clinicians and their patients in detecting pathology. Further work is required to determine the prevalence of atypical results in a variety of age ranges in autism. The prevalence of co-occurring conditions in autism mean that pragmatic clinical tools are required to care for the adult ASC population. Pharmacotherapy frequently prescribed to individuals with ASC have been shown to have an increased risk of cardiovascular issues (211) that can lead to stroke and its neurological impacts. Events such as minor stroke or transient ischaemic attacks (TIA) require careful neurological evaluation to assess treatment and potential causes. If these events are ignored as being attributable to autism the long-term individual prognosis is negatively impacted. The preliminary work (22) on Parkinsonism in a relatively young (>39 y) ASC population indicate that testing capable of discriminating between motor difficulties in autism and the development of Parkinson's disease is required.

5.4. Limitations

The primary limitations of this study were on the reliance on self-reporting of autism diagnosis and severity. It would be useful to have qualified clinicians conducting interviews with gold standard instruments for diagnosis of autism such as the Autism Diagnostic Interview – Revised (ADI-R)(212) or the Autism Diagnostic Observation Schedule (ADOS)(213) for the assessment of traits and severity. This was not performed because, as a pilot study, the primary objective was to determine the tolerance and uptake of the neuroexam. The addition clinical psychological assessments would have significantly extended the time required for participant involvement and made the issue of tolerance to the neuroexam less clear. The second reason was purely pragmatic, as the study did not have the resources to include psychological testing.

Additionally, gathering of more detailed demographic data such as the precise age, level of educational attainment, and any first-degree relatives with autism or other neurodevelopmental conditions would be useful in future work to allow for confounders of the neuroexam. Confounding factors for the neuroexam include age, IQ, educational level, dominant handedness, and gender. These factors can potentially affect the results of a neurological physical examination. Age can affect executive function, balance, and speed and coordination of motor movements.(156,214) High IQ or educational attainment can compensate for declines in executive function (215) whereas low IQ can affect the comprehension of the requirements of the examination. Educational attainment has been demonstrated to have effects on the performance of motor sequencing tasks such as the fist-edge-palm test.(216) Dominant handedness is important in tests of complex motor sequencing, as people usually perform tasks faster with their dominant hand.(217) The effects of gender on the neurological exam is not well studied, but it has been suggested that there are gender based differences in speed of tasks such as finger tapping and the grooved pegboard test.(156) The age range was controlled and the gender and handedness of the participants was recorded, however as this was a pilot study and as such was underpowered for hypothesis testing these factors were not taken into account in the statistical analysis.

5.5. Future Research

Future research would benefit from a longer recruiting period to increase the number of participants so that comprehensive statistical analysis could be performed. Ideally the future work would also include the application of standardised intelligence measures, such as the Wechsler Adult Intelligence Scale – Revised (WAIS–R),(218) testing of dominant handedness by tools such as the Edinburgh Handedness Inventory,(219) and collection of a full medical history and clinical interview with measures of autism traits and severity for all participants.

Including different age ranges and participants with different severity of ASC would make the results more applicable to a greater population. This would require the extension of the current protocol to accommodate variation in verbal skills and intellectual functioning.

Filming the neuroexam and having more than one examiner rate the results would allow the inter-rater reliability to be established. Performing test-retest metrics would additionally lend power to the strength of the analysis.

5.6. Conclusion

The healthcare needs of individuals with ASC are complex and present a significant challenge for primary care providers. This study attempted to create and apply a standard neuroexam protocol to both assess the tolerability of the protocol to individuals with ASC and to assess the neuroexam results. The protocol was well tolerated with the group that chose to participate. This group had advantages in their capability to tolerate the neuroexam as they could perform fluent verbal communication, had no intellectual disability and could understand the neuroexam process, and had chosen to participate in the study after being given detailed information about the process. The protocol was well accepted amongst these participants; however, these results cannot be extended across the whole spectrum of autism.

The recruitment was quite successful amongst participants who identified themselves as being Asperger's Syndrome, indicating that the social media advertising with Tip of the Asperg was well received. The neuroexam participants with ASC had good representation between males and females (4:3). The inclusion of scheduled breaks into the protocol was utilised by the autism group only, and provided for a period of relief from sensory stimulation.

The neuroexam protocol ran smoothly with the exceptions of the graphaesthesia test and the timed components of the motor exam. The graphaesthesia test can be replaced with the version as used in the Heidelberg inventory or other validated tools. The timed motor tests can be filmed to improve precision of analysis of the movements and timing of the complete set of iterations. Other studies have used computerised equipment to allow greater precision in timing components. This study intended to minimise any specialised equipment, to make it as broadly application as possible to primary healthcare providers. With the greater availability of tablets and other touchscreen devises the addition of touchscreen recording could deliver an accessible solution to the precision difficulties in future work.

The neuroexam presents a considerable challenge in defining guidelines for the suspicion of pathology in the autism population. Due to the heterogeneity of presentation in autism, there will be no absolutes in the interpretation. The results gathered in this preliminary work demonstrated atypical results in motor coordination and cranial nerves. Sensory issues were not demonstrated in the current study, other than how proprioception informed motor coordination. A subset of the neuroexam, which specifically tests key areas of function, much as the NES was developed to discriminate schizophrenia, may provide a manageable tool for collecting baseline neurological function for individuals with autism. Another approach that is commonly used to improve sensitivity and specificity is to provide a guide of how many combined positive tests within a category are indicative of pathology.

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1 Appendix A: Ethics Approval

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MACQUARIE University
SYDNEY·AUSTRALIA

24 May 2017

Dear Dr Whillier

Reference No: 5201700410
Title: *The Neurological Examination of High-Functioning Autism Spectrum Adults: Pilot Study*

Thank you for submitting the above application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)).

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated May 2015) (the *National Statement*).

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:
http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research
2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol and associated documents must be submitted to the Committee for approval before implementation.

It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au
Yours Sincerely

Professor Tony Eyers

Chair, Macquarie University Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Details of this approval are as follows: Approval Date: 5 May 2017

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Correspondence responding to the issues raised by the HREC (Medical Sciences)	N/A	Received 5/5/2017
Revised Human Research Ethics Application form	N/A	Received 5/5/2017
Summary Protocol	1.1*	5/5/2017
Poster	1.0*	12/4/2017
MQ Participant Information and Consent Form (PICF)	1.1	5/5/2017
Qualtrics Online Screening Questionnaire	1.0*	12/4/2017

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