Investigating working memory impairments in individuals with autism spectrum disorder.

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Abstract

Autism spectrum disorders (ASD) are lifelong neurodevelopmental disorders characterized by communication difficulties, social impairment and fixated interests along with repetitive behaviours. Although neuropsychological impairments are not part of diagnostic criteria, many people with ASD experience significant cognitive impairments. Executive function deficits are commonly experienced by individuals with ASD, and WM which plays an important role in human cognition and a central role in executive function has been reported to be impaired in individuals with ASD. Studies examining whether individuals with ASD experience significant WM impairments have produced inconsistent findings thus it is not clear whether WM deficits are commonly experienced by individuals with ASD. Therefore, Chapter 2 investigated whether individuals with ASD experience significant impairments in WM and whether there are specific domains of working memory that are impaired while controlling for age and IQ as potential moderators. The findings of this chapter indicate that across the lifespan, individuals with ASD demonstrate large impairments in WM across both phonological and visuospatial WM domains when compared to healthy individuals.

The importance and role of working memory to everyday tasks is well established, but research has yet to investigate if the WM deficiencies reported on cognitive tasks are translated to difficulties with everyday life. To investigate this question, Chapter 4 explored whether individuals with ASD experience significant everyday WM related difficulties and if they are everyday concern of adults with ASD. 111 males with ASD between the ages of 18 and 35 who were recruited through the National Health Service Greater Glasgow and Clyde, completed the WMQ, a self-assessment questionnaire. This finding reveals that individuals with high functioning autism display significant impairment in WM related difficulties in everyday life.

It is evident from Chapter 3 and 4, that WM deficiencies is a definite problem in individuals with ASD. With WM impairments being present in multiple psychiatric disorders, there has been urgent need for effective treatment options. While both pharmacological and non-pharmacological approaches have shown positive results, both are far from leading to a significant improvement in WM in patients with ASD. In the last 15 years, there has been a growing interest in the use of non-invasive brain stimulation methods such as transcranial direct current stimulation (tDCS) as a way of improving WM in typically developed

individuals and in clinical populations. In chapter 5 a phase II trial was conducted to evaluate the adverse effects of tDCS and investigate whether anodal tDCS lead to an improvement in working memory accuracy scores when administered over the left DLPFC when compared to sham in adults with high functioning autism. Additionally, we investigated whether the observed effect of tDCS over the left DLPFC and working memory scores is dependent on polarity anodal (positive) versus cathodal (negative) stimulation). A random sample of 50 male participants consisting of 25 individuals with HFA and 25 typical developed (TD), between the ages of 18-35 with a mean age of 24.33 (*SD*=3.80) took part in this study. All self-reported that they had normal or corrected vision, normal colour vision and passed the tDCS safety screening process. Participants underwent three experimental conditions: anodal, cathodal and sham stimulation. One session involved anodal stimulation over the DLPFC (F3) with the cathode placed over the contralateral supraorbital area. The next session involved the same protocol but the cathode electrode was placed over the DLPFC and the anode over the contralateral supraorbital area. The third and final session involved sham stimulation where the current was 'ramped-up' for 30 seconds and then ramped down to 0 milliamps over 30 seconds. Participants performed the 3-back working memory task pre, during and post stimulation; tDCS was then applied at a current of 1.5 milliamps for 15 minutes. The findings of this study demonstrated that anodal tDCS for 15 minutes at an intensity of 1.5 mA led to an improvement in WM performance scores when administered over the left DLPFC when compared to baseline, cathodal and sham stimulation of the same area in adults with HFA.

The results of this thesis provide evidence of significantly impaired WM in the literature and everyday life in individuals with ASD. Moreover, it also provides evidence for the possible therapeutic application of tDCS for WM impairments.

Author's Declaration

I hereby declare that I am the sole author of this thesis, except where the assistance of others has been acknowledged.

It has not been submitted in any form for another degree or professional qualification.

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Publications

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Abbreviations

ABC	The Aberrant Behavior Checklist
ADHD	Attention Deficit Hyperactivity Disorder
ADI- R	Autism Diagnostic Interview-Revised
ADOS-G	Autism Diagnostic Observation Schedule – Generic
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
ATEC	Autism Treatment Evaluation Checklist
ATMT	Advanced Trail Making test
AQ	Autism Quotient
BDC	Backward digit recall
BR	Block recall
CANTAB	Cambridge Neuropsychological Test Automated Battery
CARS	Childhood Autism Rating Scale
CBZ	Carbamazepine
CC	Central Coherence theory
CD	Childhood Disintegrative Disorder
CFQ	The Cognitive Failure Questionnaire
CGAS	Children's Global Assessment Scale
CI	Confidence interval
CTT	Consonant Trigrams Test
DC	Diagnosed by a clinician
DLPFC	Dorsolateral Prefrontal Cortex
DMO	Dextromethorphan
DR	Digit recall
DSM	Diagnostic and Statistical Manual
EDT	The Executive Dysfunction theory
EEG	Electroencephalography
EF	Executive Function
F-BDC	Forward and backward digit recall
FSIQ	Full scale intelligence quotient
fMRI	Functional Magnetic Resonance Imaging
FW	Finger Windows
GABA	Gamma-Aminobutyric acid
GHB	Gamma-hydroxybutyrate
HFA	High Functioning Autism
I^2	Index of heterogeneity
ICD-10	International Classification of Diseases 10^{th} Edition

LFA	Low Functioning Autism
LNS	Letter-Number Sequencing
IQ	Intelligence quotient
MRS	Magnetic resonance spectroscopy
MTS	A visuo-spatial delayed match-to-sample task
N	Number
NHS	National health service
NHSGGC	National Health Service Greater Glasgow and Clyde
NIBS	Non-invasive brain stimulation
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl D aspartate
OCD	Obsessive–Compulsive Disorder
PAF	Peak alpha frequency
PCP	Phencyclidine
PDD	Pervasive Developmental Disorders
PDD- NOS	Pervasive-Developmental Disorder – Not Otherwise Specified
PFC	Prefrontal Cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PM Task	Prospective memory task
POP	Preparing to Overcome Prepotency
PWS	Phonological word-span task
RCTs	Randomized controlled trials
REC	Research Ethics committee
RS	Rett's syndrome
RSAB	The Rating Scale of Attentional Behaviour
RT	Reaction times
S-TWM	Three-word short-term memory task
SD	Standard deviation
SEM	Standard error of the mean
SMD	Standardised mean difference
SOPT	Self-ordered pointing task
SSRI	Selective Serotonin Reuptake Inhibitor
STM	Short-term Memory
SWMT	Spatial working memory task
TD	Typically developed
tDCS	Transcranial Direct Current Stimulation
ToM	Theory of Mind
TMS	Transcranial magnetic stimulation
TRT	Time reproduction task
VVT	Variant-visual-pattern test

UK	United Kingdom
US	United States
WASI	The Wechsler Abbreviated Scale of Intelligence
WCC	Weak Central Coherence
WM	Working Memory
WMS-III	Wechsler Memory Scale
WMT	Working memory training
WMQ	Working Memory Questionnaire
WRAML	Wide Range Assessment of Memory and Learning

1 Introduction

This chapter will provide an overview of Autism spectrum disorder (ASD) and working memory. It will discuss some of the main points in the literature regarding the two, as well as address and review their significance and the relationship between each other. Finally, this chapter will conclude with addressing the current issues in literature and research regarding working memory and ASD, as well as how we can address and fill any gaps identified in research.

1.1 Autism spectrum disorder

Autism spectrum disorder (ASD), first described by Leo Kanner (1943) and Hans Asperger (1944), is a neurodevelopmental disorder characterised by communication difficulties (e.g. not knowing when it is ones turn to speak and failure of normal back-and-forth conversation), social impairment (e.g. failure to make eye contact) and fixated interests along with repetitive behaviours (e.g. inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour, lining up toys or flipping objects, echolalia, idiosyncratic phrases), and are considered the core features of the diagnostic criteria for ASD (American Psychiatric Association, 2013). Autism and related disorders were under an umbrella term of Pervasive Developmental Disorders (PDD) in the DSM-IV (American Psychiatric Association, 1994), which consist of Autistic Disorder (AD), Asperger's Disorder (AS), Pervasive-Developmental Disorder – Not Otherwise Specified (PDD-NOS), Childhood Disintegrative Disorder (CD) and Rett's Disorder (RS). The most recent version of the DSM (DSM-V; American Psychiatric Association, 2013) has several changes from its previous iteration, the DSM-5 combines four independent diagnoses, AD, AS, PDD-NOS and CD— into a single label of ASD, as they are thought to have the same essential symptoms, but at varying degrees of severity and are best thought of as a single disorder on a wide spectrum. The DSM-5 also combines social and language deficits into a single measure, collapsing the triad of impairments defined in the DSM-IV into two. In order to diagnose an individual with ASD, an individual must have persistent impairments in reciprocal social communication and social interactions, and restricted, repetitive patterns of behaviours, interests or actives. In addition, these symptoms should be present from early childhood and significantly limit or impair everyday functioning and are not better explained by intellectual disability or global

developmental delay. This may differ from one country to another as the United States (US) uses the DSM (American Psychiatric Association, 2013) while the 10th version of the International Classification of Diseases (ICD-10) (World Health Organization, 1992) is being used by the majority of the world. The ICD-10 diagnosis of autism is still under the umbrella term of PDD, which includes: childhood autism, atypical autism, RS, other childhood disintegrative disorder, AS, other pervasive developmental disorders and pervasive developmental disorder, unspecified (World Health Organization, 1992). However, these may also be subject to change as the ICD-11 comes into effect by member states on the 1st of January 2022 (WHO, 2018).

Due to unestablished biomarkers, the diagnosis of ASD is dependent on multiple behavioural assessments additional to the consultation of a clinician which involves a parent interview (e.g. Autism Diagnostic Interview-Revised (ADI-R: Lord, Rutter, & Le Couteur, 1994)) and observation of the individual (e.g. Autism Diagnostic Observation Schedule – Generic (ADOS-G: Lord et al., 2000)). However, the diagnosis of ASD may be challenging as it is frequently associated with other comorbidities. In a study by Simonoff et al. (2008), they reported that 70% of individuals with autism in a population-based sample had at least one co-occurring disorder, and 40% had at least two. Within this sample, the most common co-occurring conditions were social anxiety disorder, attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder. In addition, the Center for Disease Control and Prevention (2012) have stated that approximately 50% of children with autism also have an intellectual disability. This lead the National Institute for Health and Care Excellence (NICE, CG128, 2011) to stress the importance of these conditions when an individual with autism is being diagnosed or assessed for their needs.

Due to the changes of the DSM-IV to DSM-V, Guthrie et al (2013) published a comprehensive study, examining whether the DSM-V criteria were tapping into the right indicators by investigating the factor structure of autism symptoms in toddlers, to aid understanding of the phenotype during the development period that represents the earliest manifestation of autism symptoms. A sample of toddlers between the 12 and 30 months of age diagnosed with ASD were examined. Confirmatory factory analyses were conducted comparing the relative fit of 4 distinct factors (DSM-V, DSM-IV, 1-factor, and an alternative 3-factor model proposed by van Lang et al). Findings revealed that the 1-factor model provided the poorest fit, followed by the DSM-IV model and the van Lang et al. model. The

DSM-V provided the best fit to the data relative to other models and a good absolute fit. As discussed above, with the advent of the DSM-V, ASD diagnosis became more prevalent. Williams et al, (2014), examined ASD autism rates between 1965 and 2012, and found, although there are increased rates, the current DSM-V diagnostic criteria are more discerning. These results are married in Heurta et al., (2012), who found the DSM-V criteria almost twice as discerning as the DSM-IV when comparing the two diagnostic categories. Further, Heurta et al., (2012), suggest using data from multiple input sources, such as clinical observation and parents.

There have been a number of studies examining and comparing the old DSM-IV and the new DSM-V categories. Aiding in the DSM-V criteria are statistical studies, looking at factors and categories. For example, Mandy et al., (2012), used confirmatory factor analysis to conclude the DSM-V categories of repetitive behaviours and social communication deficits were demonstrated in the data for high functioning ASD children. Guthrie et al., (2013), also used confirmatory factor analysis, and concluded that the new DSM-V diagnostic categories are the best for data in toddlers. Kim et al., (2014) argue that the new DSM-V criteria of ASD and social communication disorder were almost a perfect overlap with the DSM-IV categories PDD. Guthrie et al., (2013), using confirmatory factor analysis, found almost the same results as Kim et al., although in toddlers, rather than teens.

1.2 Aetiologies of ASD

One of the most frequently asked questions by patients, parents and the scientific community, is what causes ASD? While the exact cause or causes of autism still remain unclear, research has suggested that ASD is caused from multiple factors such as genetic and environmental. There is substantial evidence on the link between ASD and genetics; studies have shown high heritability of autism in twins at around 90% (Bailey et al., 1995). This was also supported in a Swedish study, where the researchers found that individual likelihood of ASD and autistic disorder increased with increasing genetic relatedness and heritability of ASD and autistic disorder were estimated to be approximately 50% (Sandin et al., 2014). Despite the studies on heritability, the gene or genes linked to autism has not been identified. Thus, autism is believed to be polygenic (Hertz-Picciotto et al., 2006). In a study by Muhle, Trentacoste and Rapin (2004), investigating the genetics of autism, their findings suggests Cytogenetic

abnormalities at the 15q11-q13 locus are fairly frequent in people with autism and thought to be one of the possible causes of autism. Moreover, among other candidate genes that could be possible for autism are the FOXP2, RAY1/ST7, IMMP2L, and RELN genes at 7q22- q33 and the GABAA receptor subunit and UBE3A genes on chromosome 15q11-q13. Variant alleles of the serotonin transporter gene (5-HTT) on 17q11-q12 and oxytocin receptor at 3p25-p26 are also more frequent in individuals with autism than in non-autistic populations.

Research also shows that certain environmental factors may increase the risk of autism in people who are genetically predisposed to the disorder. For example, research has shown that birth complications have a distinct dimension of risk associated with autism, such as prolonged labour, prematurity and vaginal bleeding (Brimacombe, Ming and Lamendola, 2007; Leavey, Zwaigenbaum, Heavner and Burstyn, 2013) as well as children with older parents are at higher risk of autism (Durkin et al., 2008; Kong et al., 2012). Additionally, a study conducted by Cheslack-Postava, Liu and Bearman (2011) found that children born after shorter intervals between pregnancies were at increased risk of developing autism; the highest risk was associated with pregnancies spaced <1 year apart. Moreover, there is also evidence of the ingestion of certain medication during pregnancy may lead to an increased risk of autism. In 2013, a study by Christensen and colleagues found that exposure to valproate, a medication used for the treatment of epilepsy and other neuropsychological disorders, during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring.

Nevertheless, with all these findings this demonstrates the complexity of ASD as a disorder as we are nowhere near knowing the exact cause of it. No two people with autism are exactly alike, thus there may be multiple causes for autism. While genetics plays a large factor, there is probably not a single cause for ASD, but rather a combination of causes.

1.3 Theories in ASD

There are multiple cognitive theories that try to explain ASD. While there are vast number of theories out there, the three majorly recognised theories that have dominated the literature in ASD are The Theory of Mind (Baron-Cohen, Leslie, & Frith, 1985), The Theory of

Executive Dysfunction (Cumine et al, 2009; Hill, 2004), and The Theory of Weak Central Coherence (Frith, 1989, 2003; Frith & Happé, 1994; Happé, 1999).

1.3.1 Theory of Mind

One of the most recognised and acknowledged theories of autism is Theory of Mind (ToM; Baron-Cohen, Leslie, & Frith, 1985). This theory refers to the notion that individuals with ASD lack the ability to interpret the mental states (i.e. beliefs, intents, desires, emotions, attitudes) of other individuals. Furthermore, it is difficult for them to comprehend that other individuals have their own plans, thoughts, and points of view. The False Belief task is the most common methodology to examine ToM (Wimmer & Perner, 1983). This task is designed to measure whether the individual is able to understand that another's mental representation of the situation is different from their own, the task (commonly known as the 'Sally-Anne task') involves playing out a scene using two dolls (Sally and Anne), Sally places a marble into a basket and leaves the room, while she is out of the room Anne takes the marble and places it into a box. When Sally returns, the child is asked where Sally would look for the marble, thereby inferring the mental state of the doll. The child passes the task if he/she answers that Sally will look in the basket, as that where Sally placed the marble, the child fails the task if they answer that Sally will look in the box, where the child knows the marble is. Baron-Cohen et al. (1985) found that 80% of children diagnosed with autism failed the task and concluded that these children had a deficit in their theory of mind. The theory was updated in 1995 by Simon Baron-Cohen due to it receiving criticism that 20% of autistic individuals actually passed tests of false belief, showing that the deficit is not universal (Happé, 1994). By using evidence from the more difficult second-order false belief task (the belief of one person based on the thoughts of another) Baron-Cohen (1989) found that 90% of typically developing children (mean chronological age 7.5 years) passed the task, in addition to 60% of the children with Down syndrome (mean verbal mental age of 7.5 years), however none of the children with autism passed (mean verbal mental age of 12.2 years). Baron-Cohen (1995) concluded that although some individuals with autism were able to pass the first-order task, they were unable to complete the second order task therefore did not have a fully representational theory of mind.

1.3.2 The Theory of Executive Dysfunction

The Executive Dysfunction theory (EDT) suggest that individuals with ASD have impairments in their executive functions, which includes planning and organising, working memory, initiating behaviour or activity, switching focus, self-regulation and impulse control (Cumine et al, 2009; Hill, 2004) which contribute to individuals with ASD experiencing difficulties with motivation, coping with change, self-regulation and control as well as an impact on practical daily life skills that rely on good self-organisation and planning such as dressing, shopping, and cooking. A major strength of the EDT is that it clarifies some of the non-social symptoms not covered by the previous theories of ASD such as a need for sameness, a difficulty switching attention, a tendency to perseverate and a lack of impulse control (Rajendran & Mitchell, 2007). There has been strong indications that EDT and ToM are related as showed by Russell et al., (1991) where they developed an executive function task (The Windows Task) that included deception, in this task a participant can win a desired object (chocolate) by pointing to one of two boxes, one of which can be seen to contain the chocolate. However, in order to win the chocolate, the participant must point to the empty box, that is the one without the chocolate. The Widows task relates executive function (EF) to ToM due to participants must control the impulse to point directly at what they want and be deceptive as the other participant can win the chocolate if they do not win. Russell et al., has noted that the reason children with autism fail the task is because they act impulsively in relation to the location of the chocolate and not due to them failing to take account of Sally's mental state (the ToM task).

1.3.3 The Theory of Weak Central Coherence

The Weak Central Coherence (WCC, Frith, 1989, 2003; Frith & Happé, 1994; Happé, 1999)) also known as the Central Coherence theory (CC), suggests that individuals with ASD have a detail-focused cognitive style causing individuals with ASD to have difficulties to comprehend context or focus on small parts rather than seeing the "big picture" such as derive overall meaning from a mass of details. An individual with strong coherence would see an endless expanse of trees, would see "the forest" while a person with weak coherence would see it as each individual tree by itself.

Many of the cognitive theories of ASD account for the individuals and the disorders deficits, the WCC theory would account for their strengths. This theory has been used to try to explain that some individuals with ASD are “savant” (display extraordinary skills in certain areas; Howlin, Goode, Hutton, & Rutter, 2009), such as mathematics, music, and engineering etc. and attempts to explain some of the social and non-social features of autism. due to that weak coherence and looking into things individually allows them to focus on extreme details that others might overlook. For example, when a task requires the person to extract the “big picture” individuals with ASD would have trouble, however, when the task requires the individual to extract extreme detail from surrounding masses of information, an ASD individual would perform well.

WCC theory has received some criticism and challenge due to the theory originally stated that deficits in global processing caused the superior local processing observed in individuals with ASD, yet, multiple studies have demonstrated that individuals with ASD have intact global perception (Heaton, 2005; Mottron et al., 1999; Mottron, Burack, Iarocci, Belleville, & Enns, 2003). This led to the theory to be updated in three ways (Happé & Frith, 2006). First, WCC is a deficit of superior local processing, rather than poorer global processing. Second, WCC is considered a cognitive style and not that individuals with autism have a deficit or dysfunction in addition that these cognitive styles are biases to attend to detail however, they may be able to extract overall meaning. Third, WCC is viewed as one part of cognition in autism, in place of trying to explain all the characteristics of autism (for review see, Rajendran & Mitchell, 2007). An important note that should be made here is that the cognitive theories of autism presented here all focus on certain symptoms of ASD but unsuccessfully explain the wide range of ASD symptoms.

1.4 Brain differences in ASD

Neuroimaging studies have shown that there are a number of brain regions that are thought to have an association with ASD, mainly the frontal lobes (Carper & Courchesne, 2000; 2005), prefrontal cortex (Prior & Hoffman, 1990), the parietal lobes (Courchesne et al., 1993), the cerebellum (Courchesne, 1997) and the medial temporal lobe structures (Salmond et al., 2005). Individuals with ASD are reported to have larger brain volumes on average when compared to typically developed individuals (Stanfield et al., 2008). However, this noted

difference may not persist into adulthood (Amaral, Schumann, & Nordahl, 2008). This noted increase in brain size appeard to be due to an increase in grey and white matter in young children (Courchesne et al., 2001) and the increase in grey matter may persist into adulthood (Hyde, Samson, Evans, & Mottron, 2010). In a recent study Catani and colleagues (2016) revealed that autism spectrum disorder was associated with significantly reduced fractional anisotropy in regions that included frontal lobe pathways. The participants had altered development of white matter connections in the left side of the brain, the arcuate bundle, which is involved in language. The changes in the arcuate bundle which connects areas of the brain involved in understanding words and regions related to speech production, were particularly severe in those who had a significant history of 'delayed echolalia', which is very common in ASD which is the repetition of phrases, words or parts of words. In addition, findings showed that male adults with autism spectrum disorder have regional differences in brain anatomy, which correlate with specific aspects of autistic symptoms and which is linked to aberrant developmental trajectories of the frontal networks that persist in adult life.

In 1943, Kanner stated that five of the eleven children studied had unexpectedly large heads in his definition of autism (Kanner, 1943). This observation has been mentioned and confirmed in multiple studies such as the study by Bolton et al. (1994) where they found that 22% of 87 children and adults with autism had head circumference above the 97th percentile. In addition, Bailey et al. (1995) showed that 42% of autistic twins below the age of 16 years in their study had a head circumference above the 97th percentile. Imaging and post mortem studies have shown that this is due to increased brain volume (Bauman, 1996; Piven et al., 1995). In 2007, Webb and colleagues examined the rate of head circumference growth of a group of boys with ASD and a group with developmental delay over the first three years of life. They found that there was a significantly higher rate of growth in the ASD group, specifically an increase in occipitofrontal circumference between 7 and 10 months.

A meta-analysis conducted by Redcay and Courchesne (2005) revealed brain size in autism was slightly reduced at birth, dramatically increased within the first year of life, but then plateaued so that, by adulthood, the majority of cases were within normal range. These findings showed a period of pathological brain growth and delay in autism that is largely restricted to the first years of life, before the typical age of clinical identification. Moreover, studies have identified brain hyperconnectivity at the whole-brain and subsystems levels across long- and short-range connections (Lynch et al. 2013; Supekar et al. 2013; Uddin et al.

2013). Brain hyperconnectivity may result in the isolation of the neural systems involved in high-level cognitive processes, thus, contributing to the core deficits of ASD, such as cognitive functions, social and emotional processing and communication, and speech (Courchesne and Pierce 2005; Courchesne et al. 2007; Lynch et al. 2013; Supekar et al. 2013; Uddin et al. 2013).

Cortical thickness has also been investigated in ASD with results indicating an increased thickness in children (Hardan, Muddasani, Vemulapalli, Keshavan, & Minshew, 2006), and reduced thickness in adults (Hadjikhani, Joseph, Snyder, & 21 Tager-Flusberg, 2006). There has also been reports of differences in specific brain regions such as small cell size and increased cell density in the limbic system, fewer Purkinje cells in the cerebellum, and enlargement of the amygdala (see Amaral et al., 2008, and Bauman & Kemper, 2005, for review). It is important to note that these findings have to be interpreted within the context of brain development as structural differences evident in early childhood may be absent, or even reversed, by adulthood (Amaral et al., 2008).

1.5 Treatments of ASD

Autism has been regarded as a biological disorder that emphasises social interaction and language deficiencies for many decades. There is a tension around the notion that autism is a biomedical condition that researchers should develop treatments for or if it is a way of life (Bagatell, 2010). However, to give the historical context to this thesis, I am going to briefly review work that has been done to develop ways to mitigate the effects of difficulties with social functioning and communication. In 1997, Freeman found that early diagnosis of autism plays a vital role in the prognosis as our understanding of ASD has grown tremendously since the initial work of Kanner in 1943. Early diagnosis of ASD provides access to appropriate services which results in a better quality of life for the individuals. Parents of a child with ASD play a crucial role in supporting their child and improving their skills and by providing an early diagnosis it offers the opportunity for parents to understand the difficulties their child has and facilitates the ability to focus treatment efforts. In addition, Freeman (1997) states that the most important thing to remember when attempting to evaluate any treatment program is that every child with autism is an individual and what is appropriate for one child may or may not be appropriate for another. In a study conducted by

Forest and colleagues (Forest, Horner, Lewis-Palmer & Todd, 2004) they found that the children that received intervention services during the preschool years are better prepared to face future academic challenges and to continue to develop cognitively and socially.

Interventions traditionally involve behavioural treatments, medicines or both. Behavioural therapies used to treat children with ASD include Applied Behaviour Analysis and Pivotal Response Training, while adolescents and adults benefit from other interventions with a behavioural component such as Cognitive Behavioural Therapy. Medication may be prescribed to treat some of the symptoms or conditions associated with ASD. Melatonin used to treat sleeping problems, selective serotonin reuptake inhibitor (SSRI) used to treat depression, anticonvulsant used to treat epilepsy, methylphenidate used to treat ADHD and antipsychotics used to treat aggressive and challenging behaviour that could result in self-harming.

Over the last decades, many approaches proposed as treatments for ASD and some even boldly hailed as a 'cure'. These include holding therapy, megavitamins, music therapy, auditory integration therapy, facilitated communication, sensory diets, sensorimotor integration therapy, play therapy, Gentle Teaching, experimental brain surgery, immunosuppressant therapy, and secretin to name a few. Many of these treatments were promising enough to even progress to rigorous scientific testing in controlled clinical trials (Bodfish, 2004). When it comes to treatment, Freeman (1997) drew guidelines for evaluating various treatments for children diagnosed with autism: 1. Approach any new treatment with hopeful scepticism. Remember the goal of any treatment should be to help the person with autism become a fully functioning member of society. 2. Beware of any program or technique that is said to be appropriate for every person with autism. 3. Beware of any program that thwarts individualization and potentially results in harmful program decisions. 4. Be aware that any treatment represents one of several options for a person with autism. 5. Be aware that treatment should always depend on individual assessment information that points to it as an appropriate choice for a particular child. 6. Be aware that no new treatment should be implemented until its proponents can specify assessment procedures necessary to determine whether it will be appropriate for an individual with autism. 7. Be aware that debates over the use of various techniques are often reduced to superficial arguments over who is right, moral, ethical and who is a true advocate for the children. This can lead to results that are directly

opposite to those intended including impediments to maximizing programs. 8. Be aware that often new treatments have not been validated scientifically.

1.6 The importance of Autism research

ASD has been researched since it was first introduced, but there is still a great deal that we do not understand about this disorder. In recent years, the prevalence of ASD has been going up across the world (for review see Fombonne, 2009 which shows a best estimate of ASD = 60 to 70/10,000 (0.6 to 0.7%, or 1 child in 150). While it is unclear why the sudden increase in prevalence has occurred, growing awareness and diagnostic substitution may be contributing to the apparent rise (Wazana, Bresnahan and Kline, 2007). By researching ASD, we can better understand the disorder, and thus develop ways to improve the quality of life of individuals with ASD as ASD is a lifelong disability which contributes to significant difficulties on the individuals and their families, schools, and society (Amendah et al., 2011).

Further rationale for studies focused on autism arises from its economic costs. Here, a study undertaken by Buescher, Cidav, Knapp, Mandell (2014) sought to establish the economic cost of the lifetime impacts of autism spectrum disorders in the US and the United Kingdom (UK), noting that the disorders had serious effects on health, wellbeing, social integration, and overall quality of life. The researchers considered variables such as autism prevalence, intellectual disability, and place of residence, combined with average yearly costs of support and services alongside the opportunity costs arising from lost productivity. The findings indicated that the lifespan costs of autism were $2.4 million in US and $2.2 million in the UK for individuals with intellectual disability. The direct and indirect economic impact of autism alongside the health impacts on individuals and emotional suffering among carers underpin the need for heightened research in the field. Furthermore, the publication of small, underpowered clinical trials and studies with flawed research designs has made autism literature difficult to interpret and judge the clinical and scientific significance of the findings (Thurm and Swedo, 2012) and thus, high-quality autism research is not only necessary but crucial in order to help identify potential treatments and provide basic understandings of developmental processes of ASD.

1.7 Cognitive impairments in ASD

One of the cognitive impairments proposed to underlie some of the symptoms of ASD is executive dysfunction (Happé and Ronald, 2008; Hill, 2004; Russell, 1997). Researchers have suggested that ASD is characterised, at least in part, by executive difficulties associated with the integrity of the frontal lobe (Baron-Cohen et al., 1999; Casanova, Buxhoeveden, Switala, & Roy, 2002; Horwitz, Rumsey, Grady, & Rapoport, 1988; Luna et al., 2002; Penn, 2006; Russell, 1997). Poor impulse control, difficulties switching attention, perseveration and preference for sameness are all traits of ASD and executive difficulties caused by from frontal lobe damage (Baddeley & Wilson, 1988; Hill, 2004; Rajendran & Mitchell, 2007). Executive dysfunctions have been particularly related to the restricted, repetitive behaviours and interests of individuals with ASD (Happé and Ronald, 2008; Hill, 2004; Russell, 1997), as well as difficulties in communication and reciprocal social interaction (Damasio & Maurer, 1978). It is evident that executive function (EF), an umbrella term for functions such as control functions related to the inhibition of prepotent responses, shifting mental sets, initiation and monitoring of action, impulse control, planning, working memory (WM), and cognitive flexibility (Hill, 2004), plays an important part in everyday life, and deficits in executive functions are commonly experienced by individuals with ASD (Hill, 2004; Geurts, Corbett and Solomon, 2009; Geurts et al., 2004). Researchers have suggested that EFs are best conceptualised as distinct functions that are only loosely related. Of these executive functions, WM is considered to be one of the core EFs that control cognitive performance (Blair, Zelazo, & Greenberg, 2005; Fletcher, 1996; Pennington, Benneto, McAleer, & Roberts, 1996; Pennington & Ozonoff, 1996; Rapport, Chung, Shore, Denney, & Isaacs, 2000; Zillmer & Spiers, 2000) thus, WM does not only play a vital role in executive functioning but also has a high impact on daily life.

1.8 Working memory in everyday life

The importance and role of WM to everyday tasks is well established. WM plays a crucial role in everyday functioning (Goldstein, 2014) and high-level cognition, including reading (de Jong, 2006), arithmetic (Bull and Espy, 2006; Swanson and Beebe-Frankenberger, 2004; DeStefano & LeFevre, 2004), comprehension (Friedman & Miyake, 2004), problem solving (Engle, Tuholski, Laughlin, & Conway, 1999; Passolunghi and Siegel, 2001; Beilock &

DeCaro, 2007), reasoning (Kane et al., 2004; Crone et al., 2009), navigation (Garden, Cornoldi and Logie, 2001), cognitive flexibility (for reviews see Baddeley, 1986, 1992) and general fluid intelligence (Gray, Chabris and Braver, 2003; Unsworth et al., 2009). Moreover, WM is considered to have an essential role in social cognition and interpersonal interactions. A study by Phillips and colleagues (2008) explored the role of verbal WM in decoding emotions. They found that the process of labelling the emotions portrayed on facial expressions places high demands on WM resources. In another study, Bankó, Gál and Vidnyánszky (2009) suggest that humans can retain fine-grained information related to facial emotions and identity in short-term memory with high precision. As a result, it can be assumed that the impairment in WM may lead to deficits of emotional processing.

Furthermore, WM is also thought to play an important role in language development. Gathercole and Baddeley (1990) investigated the phonological memory skills of a group of children with disordered language development that were compared with those of two control groups, they found that the language-disordered children were poorer at repeating single nonwords and recalling word lists than even the younger children of matched verbal abilities. Gathercole and Baddeley proposed that the deficit of phonological storage in working memory may underpin the poor memory performance of the language-disordered children and could play a central role in their disordered language development. Moreover, deficits in WM are closely associated with learning deficits observed in daily classroom activities. Gathercole (2008) stressed that the majority of children with poor WM are slow to learn in both primary and secondary school years in the areas of reading, math and science. These students have difficulties with normal social relationships with peers, reserved in group activities, poor academic progress in reading and maths, difficulties in following instructions, problems with learning activities that require both storage and processing, place-keeping difficulties and appears to be inattentive, to have short attention span, and to be distractible.

1.9 What is Working Memory?

The distinction between short-term memory (STM) and working memory (WM) is important. STM refers to a cognitive system that is used for holding sensory events, movements, and cognitive information, such as digits, words, names, or other items for a brief period of time (Kolb and Wishaw, 2009). It has been suggested that an average person can store between 5

and 9 chunks of information in their STM, this is referred to as The Magical Number Seven, Plus or Minus Two (Miller, 1956). Although they are conceptually different, the use of the terms STM and WM in literature is not always strict. STM and WM are different theoretical concepts that are assumed to reflect different cognitive functions. At a superficial level, working memory seems functionally indistinguishable from short-term memory, which is to temporarily store information in an activated state. However, short-term memory is a subset of working memory, (i.e. working memory = short-term memory + attention).

WM is a cognitive temporary storage system with a limited capacity that is responsible for holding information for processing and the maintenance plus manipulation of information and requires reactivation in order to avoid rapid decay of information. There have been several models developed to explain the ability to temporarily store information and use it since Miller's (1956) important work on The Magic number 7 (plus or minus two). Most models of working memory agree on the fundamental processes of working memory of encoding, maintenance and retrieval. However, models differ in the way in which these processes are applied. Working memory models can be divided into two categories 1) models that view working memory as a complete system in itself with connections to other systems (e.g. Baddeley & Hitch, 1974; Baddeley, 2012), 2) models that conceptualise working memory as part of a larger cognitive architecture that incorporates several aspects of higher order cognition (e.g. Cowan, 1999; 2001; Cowan, Elliot, Saults, Morey, Mattox, Hismjatullina, & Conway, 2005).

The most commonly and frequently used and referred to model of WM is that presented by Baddeley, the multiple component model (Baddeley, 1986; 1992; Baddeley & Hitch, 1974) (Figure 1). The model is a three-component model of working memory that is comprised of the 'central executive' an attentional control system, concerned with information control and monitoring information processing, and two subsidiary slave systems supporting the central executive, the 'phonological loop' and the 'visuospatial sketchpad' (Fig. 1). The phonological loop holds the verbal information by using a temporary storage system and refreshes the information by using a subvocal rehearsal system. The visuospatial sketchpad serves the function of integrating spatial, visual, and possibly kinaesthetic information into a unified representation which may be temporarily stored and manipulated (Baddeley, 2003). The central executive is also assumed to have several components including focusing, dividing and switching attention (Baddeley, 1996; 2002; Baddeley, Emslie, Kolodny, & Duncan,

1998). In 2000 Baddeley introduced a fourth component to his working memory system, namely the ‘‘episodic buffer’’. This component is assumed to be a limited capacity system that depends heavily on executive processing and capable of binding together information from a number of different sources. While the central executive is concerned with attentional control, the episodic buffer is principally concerned with the storage of information. The episodic buffer is episodic in the sense that it holds information into chunks or episodes and it is a buffer in the sense of providing a way of combining information from different modalities into a single multi-faceted code. Baddeley argued that the episodic buffer is controlled by the central executive, which is able to retrieve information from the store in the form of conscious awareness, or reflect on that information and, where necessary, manipulate and modify it (Baddeley, 2000; 2003).

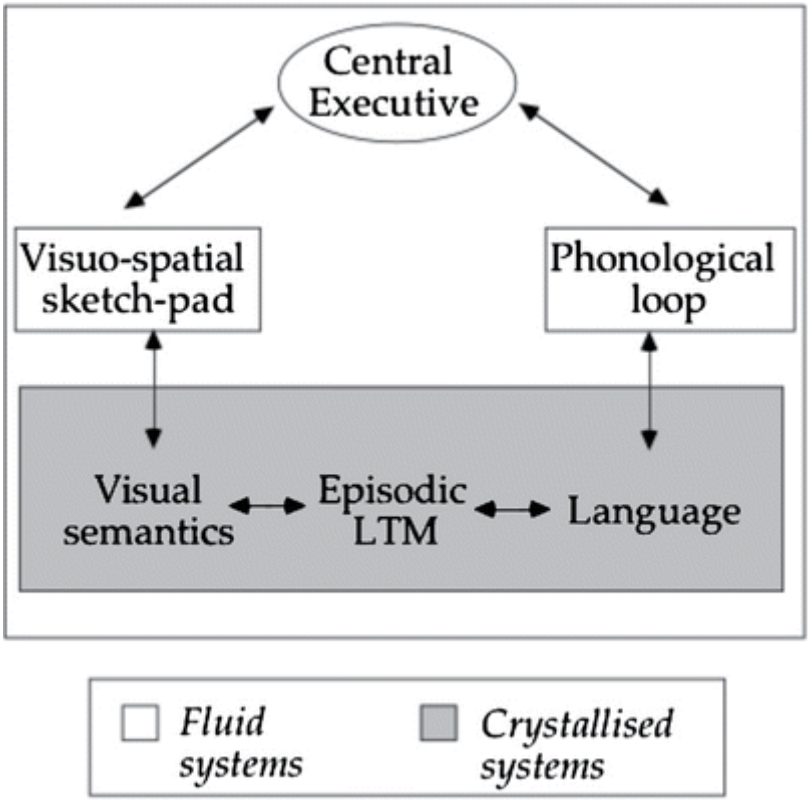


Figure 1 Baddeley’s working memory model.

While Baddeley’s WM model is the most frequently used model, some prefer the alternative framework to working memory provided by Cowan, the Embedded Process Model (Figure 2) (Cowan, 1999; 2001; Cowan, Elliot, Saults, Morey, Mattox, Hismjatullina, & Conway, 2005). The Embedded Process Model of working memory rely on five principles.

1. That working memory information comes from hierarchically arranged processes consisting of long-term memory, the subset of long-term memory that is currently activated, and the subset of the activated component of memory that is currently in the focus of attention and awareness.
2. The focus of attention is capacity limited whereby four chunks can be held in memory at any one time and activation is time limited, that activation of information within working memory will decay unless reactivated through rehearsal.
3. The focus of attention is controlled conjointly by voluntary processes (a central executive system) and an involuntary process (the attentional orienting system).
4. Stimuli with physical features that have remained unchanged over time and are of no key importance to the individual, still activate some features of memory, but they do not elicit awareness.
5. Awareness influences processing. In memory it allows new episodic representations to be available for explicit recall (Cowan, 1999; Cowan, Day, Saults, & Keller, 1992).

Unlike Baddeley's WM model, Cowan accounts for a limit in the capacity of attentional focus across the areas of active long-term memory. Cowan considered working memory to be part of short-term memory and long-term memory, and that representations in working memory are a subset of representations in long-term memory (Cowan, 1988;1995;1999;2001).

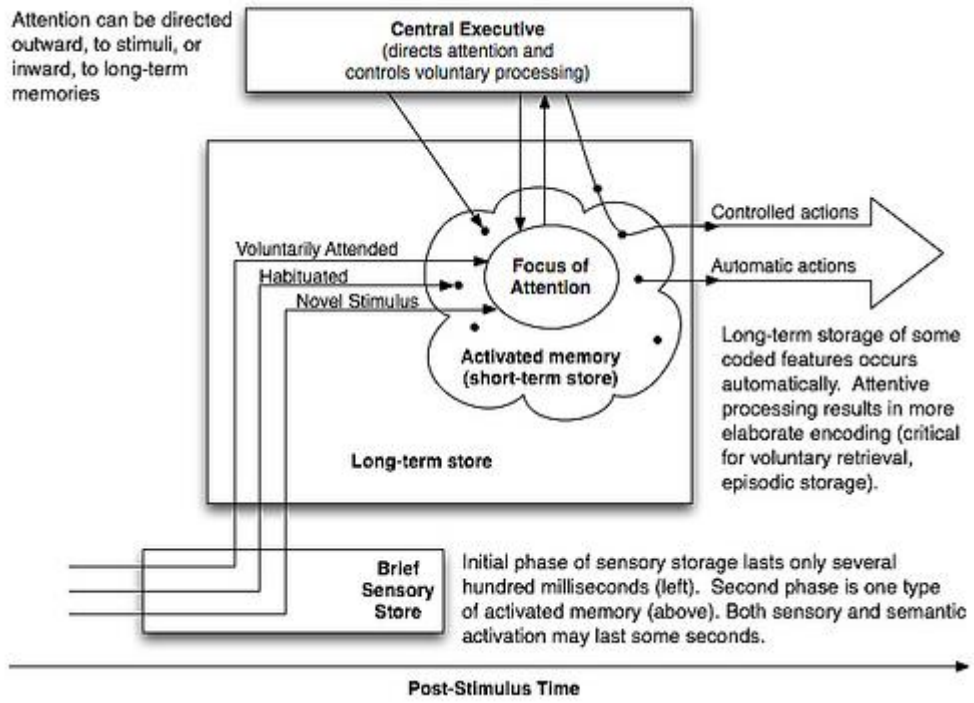


Figure 2 Cowan's working memory model.

1.10 Neural basis of working memory

Neuroscience research has made remarkable progress in understanding the involvement of the prefrontal cortex (PFC) in human memory. Functional magnetic resonance imaging (fMRI) studies have demonstrated PFC activity during WM task performance (D'Esposito et al., 1995; Fiez et al., 1997; Jonides et al., 1993; Petrides, Alivisatos, Meyer, & Evans, 1993). The dorsolateral region, a specific region of the PFC, is considered to play a crucial role in WM, evidence from brain-imaging research has demonstrated the critical role of the dorsolateral PFC (DPFC) in WM (Curtis and D'Esposito, 2003; D'Esposito, Postle and Rypma, 2000; Marshuetz et al., 2000). More specifically, the left DPFC (DLPFC) has been supported by multiple studies demonstrating the region significance in WM, such as the study by Barbey, Koenigs and Grafman (2012) where they demonstrated the importance of the DLPFC in WM as their findings showed that DLPFC damage was associated with deficits in the manipulation of verbal and spatial knowledge and supported by Tsuchida and Fellows (2009) study where they found evidence for lesions in the prefrontal cortex led to impaired performance in an n-back WM test. Additionally, Muller and Knight (2002) suggest that processes supporting WM are distributed along ventral and dorsal lateral prefrontal cortex,

D'Esposito, Postle, Ballard and Lease (1999) found that during a WM manipulation task there was greater activity in the DLPFC. Furthermore, fMRI studies reported activity within the DLPFC during tests of working memory [for meta-analytic reviews, see (Owen et al., 2005; Wager et al., 2004; Wager and Smith, 2003)]. The conclusion to draw from these studies is the crucial role that the PFC and specifically the DLPFC plays in WM.

1.11 Testing working memory

Early tasks to examine WM required individuals to learn sequences of numbers (Miller, 1956; Ryan, 1968). Recently, studies have adapted a more complex task which involves not only short-term storage but also some processing components. The following WM tasks are among the most common widely used tools to examine working memory in cognitive psychology.

1) The counting span, where participants are presented cards with green and yellow dots and are asked to count the number of green dots on each card and say out loud the counted sum. After a certain amount of cards (starting with a span size of 1 and going up to 5), participants are asked to remember the number of dots they counted for each card, starting with the first card and going in order. Responses are given verbally (Case et al., 1982; Conway, Kane, Bunting, Hambrick, Wilhelm & Engle, 2005).

2) The reading span tasks, where participants are required to read a series of unconnected sentences aloud and to remember the final word of each sentence of a series (grouped according to the total number of sentences) participants are required to recall the memorized end-of-sentence words in their original order by a blank card at the end of a series. The number of sentences is increased until the participants reading span is found or the maximum number of words are recalled correctly (Daneman & Carpenter, 1980) and

3) The operation span, where participants are required to read and verify a simple math problem (e.g. is (6/2)-3=3?) after which they read a word after the “operation” such as SNOW. After a series of problems and words has been presented, the participants recall the words that followed each operation. The number of operation-word strings in a sequence is

increased and decreased to measure the participant's operation span (McCabe, 2008; Turner & Engle, 1989; Unsworth & Engle, 2005).

Performance on WM measures have demonstrated a relationship with multiple cognitive abilities such as attentional control (Shipstead, Harrison, & Engle, 2015), fluid intelligence (Jaeggi et al., 2008), mathematics proficiency (Miller & Bichsel, 2004), language and reading comprehension (Daneman & Green, 1986; Daneman & Merikle, 1996), reasoning ability (Kyllonen & Christal, 1990), and achievement in school (St. Clair-Thompson & Gathercole, 2006). The majority of research investigating WM task performance often utilise the n-back task as it is a widespread measure of working memory in clinical and experimental settings, where the participants need to recognise and respond of whether each new stimulus matches the stimulus shown n steps earlier in the sequence. The n-back test was first introduced by Wayne Kirchner in 1958, it was used to assess age differences in memory tasks of "rapidly changing information", when the load of n is 2 or more, it is not enough for participants to store the stimulus representation in mind. The episodic buffer needs to continuously update to keep track of the current stimulus and what it needs to be compared to. To achieve this, the participants need to maintain and manipulate information in WM. Ever since, majority of research investigating WM, often utilise the n-back WM task (for review of studies using n-back paradigm, see (Owen et al., 2005).

1.12 Working memory and psychiatric disorders

Cognitive deficits are usually not the focus of psychiatric disorder studies, while most focus on traditional symptoms of the disorder, cognitive deficits are equally important and severely compromise quality of life (Millan et al., 2012). WM deficits are consistently present in a number of psychiatric disorders, such as major depression (Castaneda et al., 2008; Gorwood et al., 2008; Marazziti et al., 2010), bipolar disorder (Goodwin et al., 2008; Kurtz and Gerraty, 2009), schizophrenia (Barnett et al., 2010; Galderisi et al., 2009), ASD (Boucher et al., 2012; Barendse et al., 2013; Hill and Frith, 2003; Kercood et al., 2014) , ADHD (Vaidya and Stollstorff, 2008; Uekermann et al., 2010), obsessive–compulsive disorder (OCD) (Burdick et al., 2008; Sayin et al., 2010), post-traumatic stress disorder (Liberzon and Sripada, 2008), panic disorder (Gordeev, 2008), generalized anxiety disorder (Coles, Turks and Heimberg, 2007), Parkinson's disease (Beato et al., 2008; Graceffa, Carlesimo, Peppe

and Caltagirone, 1999; Lee et al., 2010) and Alzheimer's disease (Baddeley et al., 1991; Belleville, Howard, Serge, 2007; Yetkin et al., 2006). Therefore, due to WM playing an important role in both healthy and clinical populations, interventions focused on WM improvement are highly sought after (Rabipour & Raz, 2012).

1.13 Working memory and ASD

Despite WM's vital role in many higher cognitive functions, few researchers and clinicians investigate WM in individuals with ASD. Understanding the relationship between ASD and WM could provide vital insights into the disorder's neural basis, which would prove valuable in establishing interventions against ASD and related neurodevelopmental disorders. Executive function problems are found throughout the spectrum and throughout development (from early childhood to adulthood) (Luna et al. 2007), but are not seen as core deficits, however, WM deficits in individuals with ASD appear to result in numerous problems associated with behaviour regulation, cognitive flexibility, abstract thinking, and focusing and sustaining attention (Hughes, Russell, & Robbins, 1994; Ozonoff & McEvoy, 1994; Ozonoff, Pennington, & Rogers, 1991). Moreover, research has found that WM impairment is strongly associated with deficits in communication, play and social relationships found in individuals with ASD (Gilotty et al., 2002; Oliveras-Rentas et al. 2012) as well as restrictive and repetitive symptoms of ASD (Lopez et al. 2005; Sachse et al. 2013).

Furthermore, research has suggested that WM deficits in ASD may be explained by a neural basis. A study by Koshino, Kana, Keller, Cherkassky, Minshew, and Just (2007) investigated brain activation and functional connectivity in individuals with high-functioning autism and a control group, employing functional magnetic resonance imaging (fMRI) to image an n-back WM task that involved photographic face stimuli. The researchers established that the group with autism had lower activation in the inferior left prefrontal area, which is involved in WM maintenance and verbal processing, as well as similar low activation in the right posterior temporal area, which is associated with mind processing. Further, the autism group showed activation in a different fusiform area location when compared to the control group. The connectivity results of the study indicated lower connectivity in the frontal areas and normal connectivity in the posterior cortical regions. Koshino, Carpenter, Minshew, Cherkassky, Keller, and Just's (2005) study entailed a similar fMRI approach evaluating brain activation

in a high-functioning autism adult group compared with an age-matched control group, but this time studying n-back WM task involving letters. The fMRI findings indicated that adults with autism employed visual codes to perform the task, in contrast to the normal group's reliance on verbal codes. The adults with autism demonstrated higher right lateralized activation in the parietal and prefrontal regions while their counterparts in the control group had more activation in the left parietal regions. In addition, the autism group had higher activation in the posterior regions such as the occipital and inferior temporal regions. These findings suggest that WM processes unfold differently in individuals with autism. Yet, the research on WM deficits in individuals with ASD however has been inconsistent. While there are studies demonstrating that individuals with ASD have impaired WM, there are studies that have failed to observe any WM impairments in individuals with ASD compared with typically developing individuals (Morsanyi and Holyoak 2010; Ozonoff and Strayer 2001).

Within this thesis, the following terms will be used: low-functioning autism (LFA) (referring to those with Autistic Disorder, classic autism or childhood autism), high-functioning autism (HFA) (referring to those with Asperger's Disorder or Asperger's syndrome), and Autism Spectrum Disorder (referring to those with either autism, Asperger's syndrome).

2 Aims of thesis and research questions

2.1 Aims

The aims of this thesis were formulated based on the existing literature discussed in chapter one.

The overall aim of this thesis was to investigate whether individuals with ASD demonstrate significant impairments in WM (in both domains, phonological and visuospatial), investigate whether individuals with ASD experience significant everyday WM related difficulties and explore the development of a potential treatment plan in regards to improving WM in individuals with ASD.

These aims were addressed by conducting three studies which aimed

1. To systematically review and analyse the available literature on WM and ASD
2. To determine whether individuals with ASD experience significant everyday WM related difficulties.
3. To investigate whether transcranial direct current stimulation (tDCS) leads to improvements in working memory in adults with high functioning Autism.

2.2 Research question

In order to address the above aims of this thesis, the following research questions were developed. Research question 1 in relation to the first aim was addressed in chapter three, by undertaking a systematic review and meta-analysis of the literature. Research question 2 in relation to the second aim was addressed in chapter four. Research questions (3 and 4) in relation to the third aim were addressed in chapter 5, through conducting a randomised controlled trial.

1. To determine whether individuals with ASD experience significant impairments in WM and whether there are specific domains of working memory that are impaired.
2. To determine whether individuals with ASD experience significant everyday WM related difficulties and if they had everyday concern of adults with ASD
3. To evaluate the adverse effects of tDCS and investigate whether anodal tDCS led to an improvement in working memory accuracy scores when administered over the left DLPFC when compared to sham in adults with high functioning Autism.

4. Are the observed effects of tDCS over the left DLPFC and working memory scores dependent on polarity anodal (positive) versus cathodal (negative) stimulation)?

3 A meta-analysis of working memory in individuals with autism spectrum disorders

This chapter will present a review of the available evidence on WM in individuals with ASD. This review will aim to expand on previous knowledge of WM in ASD and give us an accurate examination of the current literature to whether WM impairments are an issue for individuals with ASD.

3.1 Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by communication difficulties, social impairment and fixated interests along with repetitive behaviours (American Psychiatric Association, 2013). The symptoms of ASD are evident from young age; usually in children aged two or three, with a higher prevalence in boys than in girls (Levy, Mandell and Schultz, 2009). Autism has become one of the most prevalent and common developmental disabilities, the Center for Disease Control and Prevention (2012) notes that the incidence of ASD has been increasing in the general population in recent years in the United States of America (USA), with the new estimate of 1 in 68 children having an ASD being roughly 30 percent higher than previous estimates reported in 2012, 1 in 88 children. In the United Kingdom (UK), according to Brugha et al. (2012) 1.1% of the population in the UK had an ASD compared to 2009 when it was found 1% of the population studied had an ASD (Brugha et al., 2009). ASD has significant negative impact on the quality of life of the individual (Billstedt, Gillberg and Gillberg, 2005). A meta-analysis (Van Heijst and Geurts, 2014) concluded that across the lifespan, quality of life is lower for people with ASD when compared to people without ASD. The impairments associated with ASD mean that many people with ASD remain dependent on others for support, such as parents, siblings, and other carers (Howlin, Goode, Hutton and Rutter 2004). Thus, many parents of people with ASD are concerned about what to expect from the future and what will happen to their family members when they will not be able to take care of them anymore (Eaves and Ho, 2008).

Impairments in cognitive abilities are not part of the classification of ASD. However, clinicians and researchers often make a distinction between low-functioning autism (LFA) with an intelligence quotient (IQ) below 65 or 70, and high-functioning autism (HFA) with an IQ above 65 or 70. Although neuropsychological impairments are not part of diagnostic criteria, many people with ASD experience significant cognitive impairments (Sergeant, Geurts and Oosterlaan, 2002; Hill, 2004; Geurts, Cobett and Solomon, 2009). Executive function deficits are commonly experienced by individuals with ASD (Geurts, Verté, Oosterlaan, Roeyers and Sergeant, 2004; Hill 2004; O'Hearn, Asato, Ordaz and Luna, 2008). Executive function is an umbrella term for a set of cognitive processes that includes, WM, inhibition, planning, impulse control, and shifting set as well as the initiation and monitoring of action (Hill, 2004).

WM plays an important role in human cognition and a central role in executive function (Pennington, 1994). The most commonly used cognitive model of WM is the revised WM model (Baddeley, 2012), which is based on the model developed by Baddeley and Hitch in 1974. The core of the model involves the central executive, concerned with information control and monitoring information processing (attention control center), an episodic buffer enables information integration from the sub-components of WM and long-term memory. Executive functions allow one to engage in purposeful and independent behaviours such as suppressing irrelevant information, shifting among multiple tasks, and revising and monitoring information held in long-term memory. The model also involves two storage systems- the phonological loop and the visuospatial sketchpad- supporting the central executive. The phonological loop provides temporary storage for phonological information while the visuospatial sketchpad allows temporary storage and manipulation of visual and spatial information. Other aspects of the model include the role of attention in WM and the concept of temporal duration when performing memory tasks. However, based on this revised WM model of Baddeley, WM is not only important but also essential for successfully navigating in the social world (Barendse et al., 2013).

Gathercole and Baddeley describe WM as a short-term memory system that controls temporary processing and storage of information (Gathercole and Baddeley, 2014). The importance and role of WM in everyday tasks is well established. WM plays a crucial role in supporting various complex high-level cognition activities such as language comprehension and long-term learning (Gathercole and Baddeley, 2014), reasoning (Kyllonen and Christal,

1990), reading comprehension (Daneman and Carpenter, 1980; Just and Carpenter, 1992), mental arithmetic (Hitch, 1978), and problem solving (Engle, Tuholski, Laughlin and Conway, 1999). As a temporary storage system under an individual's attentional control, WM allows processing of complex cognitive information and plays central roles in social cognition, interpersonal interactions, and language comprehension. These roles make WM highly relevant in ASD because the disorder primarily concerns the cognitive domains involved in social impairments, communication problems, and repetitive activities (Barendse et al., 2014). Studies have shown that WM deficits in individuals with ASD are associated with learning disabilities (Alloway, 2006), difficulties associated with behaviour regulation (Hughes, Russell and Robbins, 1994), cognitive flexibility, focusing and sustaining attention (Ozonoff, Pennington and Rogers, 1991), abstract thinking (Ozonoff and McEvoy, 1994), communication and socialising (Gilotty et al., 2002; Oliveras-Rentas et al., 2012) as well as restrictive and repetitive symptoms (Lopez, Lincoln and Ozonoff, 2005; Sachse et al., 2013). Therefore, it is important to obtain a clearer and more accurate understanding of WM impairments in individuals with ASD as impairments in WM are associated with difficulties in everyday life and can have a negative impact on the quality of life.

Studies examining whether individuals with ASD experience significant WM impairments have produced inconsistent findings. Joseph, Steele, Meyer and Tager-Flusberg (2005) examined verbal encoding and rehearsal strategies in the service of working memory in high-functioning children with autism and a comparison group. They found that while the two groups were equal in verbal rehearsal skills, the autism group performed significantly less in the verbal test, suggesting that children with ASD are deficient in the use of verbal mediation strategies to maintain and monitor goal-related information in working memory. Steele and colleagues tested high-functioning individuals with ASD on the Cambridge Neuropsychological Test Automated Battery (CANTAB) compared to a matched group of typically developing controls. Their findings suggest deficits in spatial working memory abilities in ASD and that these deficits are significant when tasks impose heavier demands on working memory (Steele, Minshew, Luna and Sweeney, 2007). Moreover, Morris et al. (1999) investigated spatial working memory in ASD using the Executive Golf Task, where they found that The ASD group showed a substantial deficit on spatial working memory. Yerys and his team found a significant correlation between Consonant Trigrams Test (CTT) performance and everyday working memory, as CTT performance in children with ASD was

significantly worse than in matched age and IQ controls (Yerys et al., 2010). So, several prominent studies have found that individuals with ASD experience WM impairments.

On the other hand, some studies have not reported significant WM impairments in individuals with ASD, Ozonoff et al. (2001) investigated working memory in individuals with high-functioning autism, Tourette syndrome and a typically developing control group. No group differences were found across three tasks and five dependent measures of working memory, and it was concluded that working memory is not one of the executive functions that is seriously impaired in ASD. In another study, Russell and colleagues (1996) were unsuccessful in finding any significant group differences between children and adolescents with ASD as well as individuals with moderate learning difficulties and controls which were matched on mental age and on three measures of working memory capacity. Moreover, Faja and Dawson tested in 23 children with ASD without intellectual disability and 20 typically developing children matched on IQ and age on a backward digit span, and found that performance did not differ between groups (Faja and Dawson, 2013). Finally, the study by Griffith, Pennington, Wehner, & Rogers (1999) which investigated spatial working memory in very young children with ASD and control groups matched on age, and verbal and nonverbal ability found no group differences across eight tasks which appeared to require working memory.

As described above, the findings from research on WM impairments in ASD has been inconsistent. One meta-analysis looking at WM in ASD has been published (Wang et al, 2017). The authors reported a significant WM impairment and suggested that this impairment was not associated with age or IQ. They also demonstrated that spatial WM was more severely impaired than verbal WM and the component of cognitive processing (maintenance vs. maintenance plus manipulation) did not affect the severity of WM impairments. This initial meta-analysis flags up the relevance of research on WM and ASD. However, there were significant limitations in the methods used for the meta-analysis. A systematic literature search was not used to identify potential studies; only two search terms were used "Asperger+ working memory" and "autism + working memory". A literature search that is not comprehensive can lead to relevant studies being missed and biased results from meta-analyses. In order to include studies that used error rate as the measure of WM, Wang et al. (2017) converted error rate into accuracy by assuming that error rate and accuracy have an opposite direction relationship. For example, if the error rate was 0.8 they converted it to an

accuracy score of -0.8 (personal communication). This method is problematic as studies that have measured error rate and accuracy found that ASD participants' accuracy scores did not differ from the control group however the ASD participants made more errors (Joseph el at., 2005; Kaufmann et al., 2013). For studies that had used more than one than one WM task, Wang et al. (2017) state that they calculated effect sizes for each WM task and then combined these into an unweighted average effect size. However, they excluded WM tasks from the average effect size calculation if participants with ASD did not demonstrate impairments on these tasks. For example, two studies measured reaction time and accuracy (Cui et al, 2010; Koshino et al, 2008) but the participants with ASD only had impairments on reaction time so the accuracy scores were excluded. Selection of studies based on the direction of the results creates bias and, in this case, will have inflated the overall effect size of the meta-analysis. These methodological weaknesses fall well short of guidance on the methods and reporting of systematic reviews and meta-analyses (Moher et al, 2009), and threaten the validity of the findings in the previous meta-analysis by Wang and colleges.

We previously explained the potential importance of WM in the daily functioning and quality of life of individuals with ASD. Our aim in this study is to determine whether individuals with ASD experience significant impairments in WM and whether there are specific domains of working memory that are impaired. We will also evaluate age and IQ as potential moderators of WM impairments in individuals with ASD.

To achieve these aims, in this systematic review and meta-analysis, we will address the limitations in the previous study (Wang et al, 2017) by adopting a more systematic and comprehensive search of the available literature, including more rigorous inclusion criteria that controls for matching participants on IQ and age (i.e., no significant difference between the groups) a more stringent selection process to identify relevant studies, avoiding bias by not using study results as the basis for inclusion, and analysing WM accuracy and error rates scores separately, as accuracy and error rate do not necessarily have an opposite relationship (i.e. if accuracy is high, error rate is low). Additionally, looking into only one of the outcomes would reduce the amount of studies included significantly as studies sometimes only report 1 of the outcomes. This was done in order to achieve a more accurate examination of the topic of WM impairments in individuals with ASD.

3.2 Method

This study was conducted in adherence with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Moher et al, 2009).

3.2.1 Literature search

We conducted a literature based search and manual cross referencing of English language empirical studies relating to both ASD and WM using four electronic databases EMBASE (OVID), MEDLINE (OVID), PsychINFO (EBSCOHOST), and Web of Science from 1986 to May 2017 (subsequent to a previous review by Wang et al. (2017)). Search terms were combinations of the following 'autis', 'asperg', 'pervasive development disorder', 'kanner', 'childhood schizophrenia', 'child development disorders', 'Rett', 'working memory', 'memory capacity', 'memory span', 'short-term memory', 'N-back', 'memory', and 'digit span'. The full search Medline search strategy is illustrated in appendix A. The reference lists of retrieved studies were also examined to identify relevant papers.

3.2.2 Inclusion criteria

Studies were eligible for this review if they met the following inclusion criteria:

- Published in peer-reviewed journals in English
- Included people with ASD
- Used ADOS (Lord et al., 2000), ADI- Revised (Lord, Rutter and Le Couteur, 1994), 3Di (Skuse et al., 2004) or a clinician as a method to diagnosis ASD
- Matched the groups on age, gender and IQ or where there was no statistically significant difference between the groups
- Data reported clearly and sufficiently such as mean scores and standard deviation
- Compared ASD groups to TD groups
- Included a valid test of WM, the appropriateness of including tests as measures of WM was determined by referring to Lezak (1995) or Baddeley, Wilson and Watts (1995)

Research studies were not eligible for this review if they met the following exclusion criteria:

- Conference papers/abstracts
- Review papers
- Unpublished data, grey literature
- Non-English language papers.

3.2.3 Selection of studies

The lead researcher (AH) performed the literature search and removed any duplicate studies. The titles and abstracts were screened independently by two authors (AH and CM) and disagreements about inclusion resolved at a consensus meeting. For records retained after screening, the full text was obtained, read in full and both researchers (AH and CM) independently completed an inclusion checklist. If there was any disagreement between the inclusion checklists for a paper final list decided decision about inclusion was made following a consensus discussion.

3.2.4 Data extraction

The following data were extracted by the lead researcher to assess the methodology quality and data synthesis:

- Authors, year of publication
- Number of subjects
- Full scale IQ
- Age
- Gender
- Instruments used to assess WM
- WM scores (where there was multiple task being used, we chose the more challenging task, for example, they study by Williams et al. (2014) where multiple loads of the N-Back WM task were used (1-Back, 2-Back and 3-Back). The 3-back results were chosen as the 3-back is what is commonly used as a load when using N-back WM task which also happens to be the more challenging task.)
- The method of diagnosis was recorded for the ASD groups.

3.2.5 Quality assessment

To check the quality of the studies, we used the Standard Quality Assessment Criteria for Evaluating Primary Research Papers tool for quantitative studies developed by Kmet, Lee, and Cook (2004). Each study was assessed against 14 criteria-oriented items. Criteria 5 (if interventional and random allocation was possible, was it described?), 6 (if interventional and blinding of investigators was possible, was it reported?) and 7 (if interventional and blinding of subjects was possible, was it reported?), were not considered during the quality assessment as they are applicable to studies assessing interventions. If the study met the criteria it was scored as 2; 1 if it partially met the criteria; and 0 if it did not meet the criteria. A total score for each study was calculated by adding the score across the criteria and dividing by the total possible score (22). The assessment was completed by two authors (AH and CM) for each study to improve reliability. There was complete agreement between the two reviewers.

3.2.6 Data analysis

Meta-analyses were performed using Comprehensive Meta-analysis version 3.0 (Biostat, Englewood, NJ, USA). Effect sizes were calculated (using means, standard deviations and sample sizes) based on the pooled standardised mean difference (SMD), expressed as Cohen's d (Cohen, 1988) and 95% confidence interval (CI). Although studies measured the same outcome of WM, due to the different methodological tests to assess WM, it was necessary to standardise the results on a uniform scale (in order to combine results in the meta-analysis). The effect size was calculated as the difference in mean change between the ASD group and the TD/comparison group divided by the standard deviation pooled between the two groups. Effect sizes were interpreted as small (d = 0.20), moderate (d = 0.50) and large (d = 0.80).

WM was divided into subgroups via the following WM constructs, phonological and visuospatial, consistent with the gold-standard criterion recommendations (Higgins et al., 2008). Study results were pooled using an inverse variance weighted method of random effects analysis (DerSimonian and Laird, 1986). The significance and degree of heterogeneity were calculated using Cochrane's Q statistic and I^2. Cochrane's Q statistic provides a measure of the variance between the effect sizes (with $p < 0.05$ illustrating evidence of

heterogeneity) while I^2 provides a measure of the amount of variance between the studies in terms of heterogeneity, as described by Higgins et al. (2003). The degree of heterogeneity was measured by the I^2 statistic, with $I^2 \geq 50\%$ indicating substantial heterogeneity. In accordance with the Cochrane handbook for reviews and to explore possible potential heterogeneity, subgroup analysis (post hoc) was conducted for variation in sample characteristics including moderator variables age and IQ considering all our meta-analysis had 10 or fewer studies.

Publication bias was investigated using visual inspection of funnel plots of the SMD against the standard error of the SMD of the included studies and using the linear regression approach described by Egger et al. (1997). This method examines the association between effect size and standard error for each study and takes into account the sample size and effect size.

3.3 Results

Of a total of 8868 studies, 273 duplicate studies were removed, 7995 articles were excluded on reviewing the title and abstract. For the remaining 600 full text articles, those that were conference papers, review articles or not in English, were excluded. We identified a total of 29 papers that evaluated WM performance for individuals with ASD; 16 investigated accuracy as a measure of participants working memory performance, while 13 investigated participant error rates. Five studies were excluded for not reporting the statistics efficiently, such as the means and standard deviations of each group, eight studies were excluded for not matching participants on IQ or there was a significant difference between the two groups, one study was excluded for not measuring full scale IQ, one study was excluded for not having a matched age and IQ control group, one study was excluded for not having a control group, finally, one study was excluded for not measuring the IQ of the control group. Studies where we were not able to contact the authors and/or access their data were excluded from this review. The articles were obtained from 11 different journals and were published between 2001 and 2015. A total of 29 papers containing 34 studies were retained for inclusion in the review and data synthesis. Based on the WM model by Baddeley (2012) results were categorised based on which aspect of WM was tested, phonological or visuospatial. Figure 3 shows the study selection process.

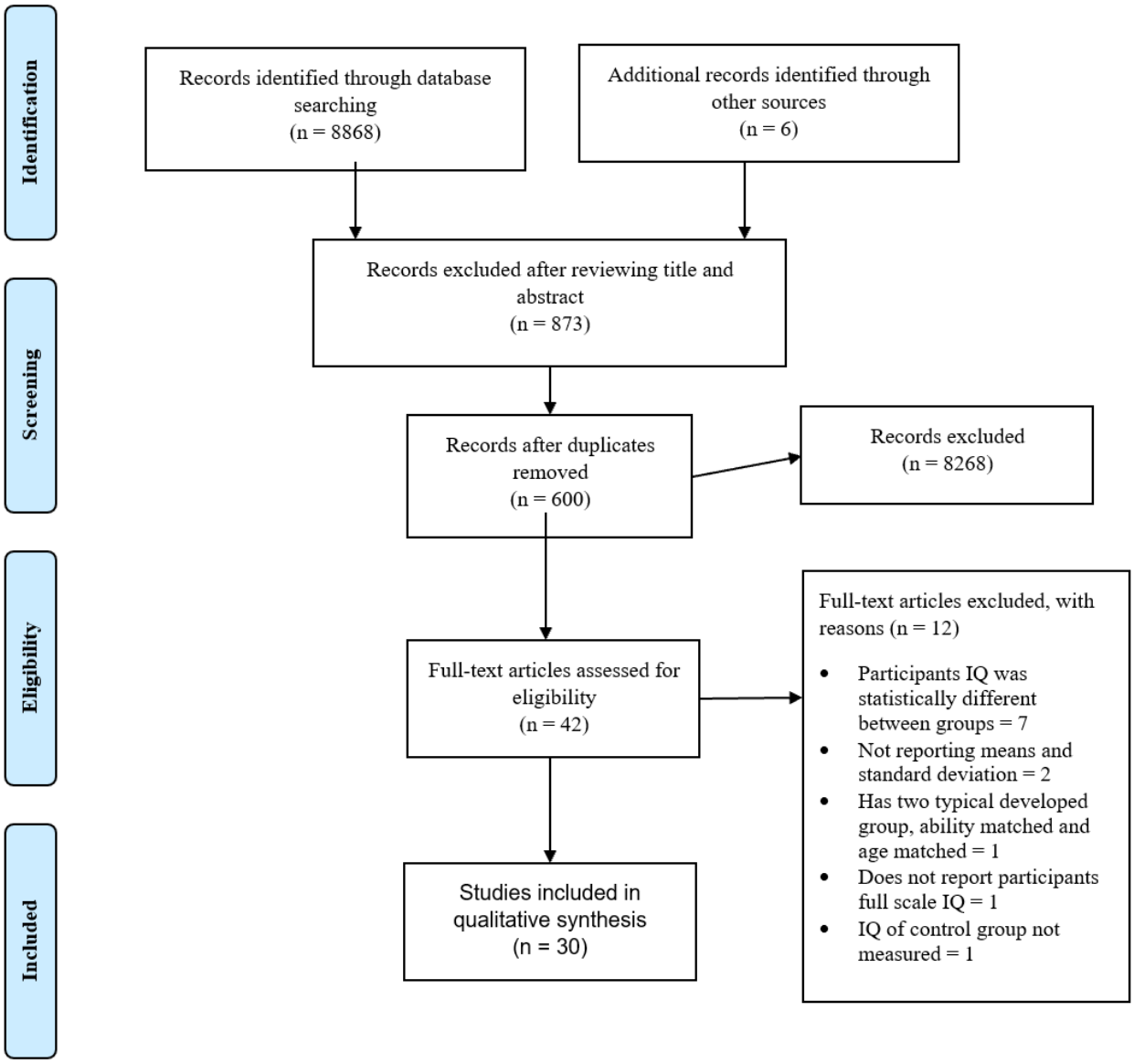


Figure 3 Flow diagram of study selection process in accordance with the PRISMA statement

3.4 Phonological working memory

3.4.1 Accuracy in phonological working memory

Out of the 34 studies, nine studies were identified testing accuracy in phonological WM. A summary of the study characteristics of the nine studies is presented in Table 1. The studies were published between 2001 and 2013 in nine different journals. A total of 447 participants were recruited (226 ASD, 221 TD) across the nine studies, with a mean total ASD sample size of 25.1 and TD sample size of 24.5. Participants' ages ranged from 11 to 31 years with the mean age of ASD participants of 20.7 years and TD participants' ages ranged from 11 to 38 years with the mean age of 21.2 years. All nine studies compared ASD participants with TD participants with all participants' IQ scores being above 70.

Table 1. Main characteristics of accuracy in phonological working memory studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assessment
Gonzalez-Gadea et al., 2013	0.13	0.09	23	33.00	21	28.29	5.61 (1.31)	5.43 (1.47)	37.43	37.14	DC	BDC
Gracia-Villamisar et al., 2002	-2.98	0.26	16	23.50	16	21.19	48.13 (16.77)	86.88 (7.58)	42.75	43.69	DC	DR
Ham et al., 2011	-0.40	0.10	19	12.10	23	12.00	98.60 (20.20)	107.00 (21.60)	106.00	111.40	ADOS	DR
Maister et al., 2011	-0.61	0.14	15	11.80	15	11.20	30.30 (9.00)	36.10 (10.10)	39.70	40.00	ADI-R	PWS
Minshew and Goldstein, 2001	-0.42	0.05	52	22.33	40	21.55	1.72 (1.44)	2.36(1.62)	92.88	96.53	ADI and ADOS	S-TWM
Poirier et al., 2011	-0.96	0.14	16	31.60	16	34.80	0.64 (0.20)	0.81 (0.15)	100.30	102.40	ADOS	F-BDC
Schuh et al., 2012	-1.27	0.13	18	12.00	18	13.00	16.00 (2.00)	18.00 (1.00)	105.00	104.00	ADI and ADOS	LNS
Williams et al., 2006	-0.22	0.05	38	11.68	38	12.16	8.61 (3.33)	9.26 (2.61)	103.82	107.18	ADI and ADOS	WRAML
Williams et al., 2005 b	-0.20	0.06	29	28.73	34	26.53	10.86 (3.07)	11.38 (2.24)	105.86	109.65	ADI and ADOS	WRAML

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; S-TWM: Three-word short-term memory task; WRAML: WMS–III, the Wide Range Assessment of Memory and Learning; DR: Digit recall; BDC: Backward digit recall; F-BDC: forward and backward digit recall; PWS: Phonological word-span task; LNS: Letter-Number Sequencing subtest from the Wechsler Intelligence Scale for Children, 4th Edition.

The combined WM scores from the nine studies were significantly lower in the ASD group than the typical developed group (*d*: -0.67, 95% CI -1.10 to -0.24, p<0.05). There was substantial heterogeneity between studies (Q-statistic = 36.82, df = 8 (p < 0.05); I^2 = 78.27%). As only nine studies were identified as testing accuracy in phonological WM, publication bias was not assessed. This was due to the limited number of studies to provide adequate power of reliability of tests to detect for presence of publication bias (Higgins and Green, 2011). Representative forest plots from the phonological WM meta-analyses are shown in Figure 4.

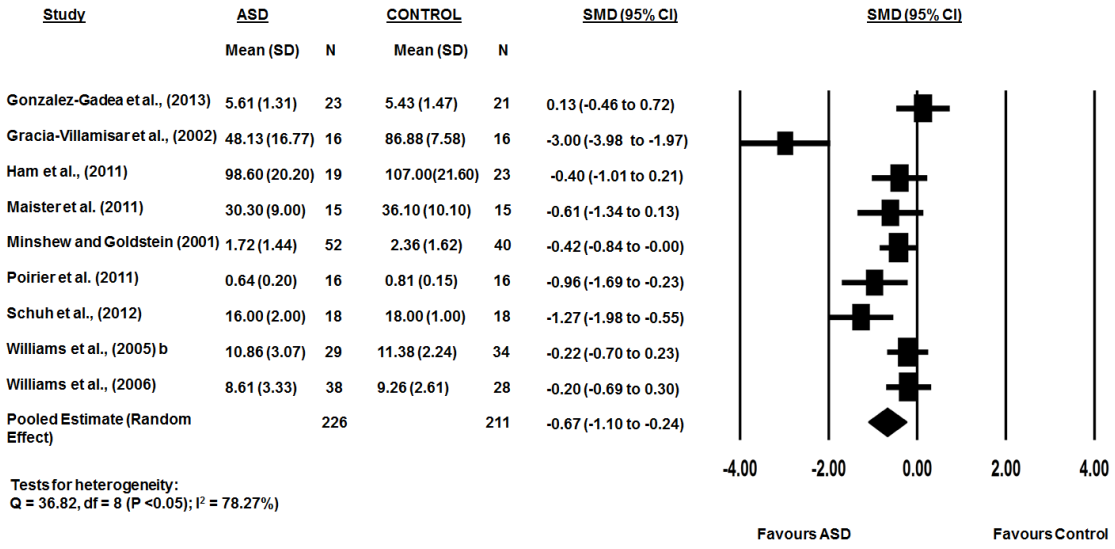


Fig. 4. Accuracy in phonological WM between ASD and typically developing controls.

3.4.2 Error in phonological working memory

Out of the 13 studies, two studies were identified testing error in phonological WM. A summary of the study characteristics of the two studies is presented in Table 2. A total of 80 participants were recruited (45 ASD, 35 TD) across the two studies, with a mean total ASD sample size of 22.5 and TD sample size of 17.5. Participants' ages ranged from 10 to 31 years with the mean age of ASD participants of 20.9 years and TD participants ages ranged from 11 to 32 years with the means age of 21.5 years. Both compared ASD participants with TD participants with all participants' IQ scores being above 70.

Table 2. Main characteristics of error rate in phonological working memory studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assessment
Williams et al., 2014	0.68	0.12	17	31.06	17	31.92	0.21 (0.32)	0.05 (0.09)	114.10	117.70	ADOS and DC	PM Task
Yerys et al., 2011	2.22	0.15	28	10.89	18	11.07	65.36 (11.50)	43.11 (7.00)	113.90	118.90	DC, ADI and ADOS	CTT

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; PM Task: Prospective memory task; CTT: Consonant trigrams test.

The WM error rates scores from the two studies were significantly lower in the TD group than the ASD group (*d*: 1.45, 95% CI -0.07 to 2.96, p=0.06). There was substantial heterogeneity between studies (Q-statistic = 8.84, df = 1, (p<0.05); I2 = 88.69%). Publication bias was also not assessed for studies testing error in phonological WM. Representative forest plots from the phonological WM meta-analyses are shown in Figure 5.

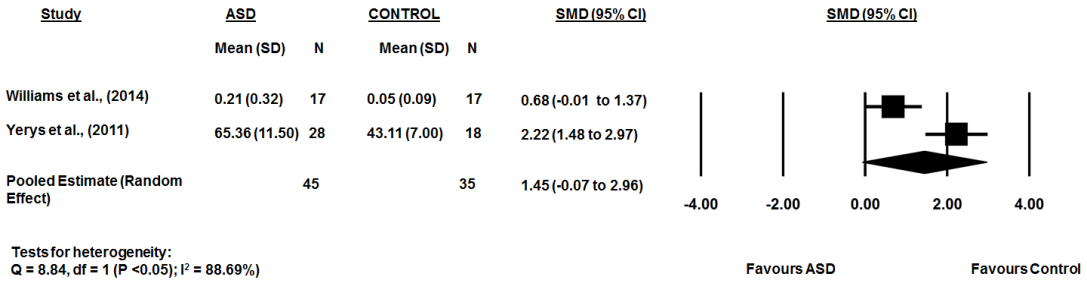


Fig. 5. Error rate for ASD and typical developed controls groups in phonological WM.

3.4.3 Subgroup analysis of phonological working memory

The results above show that there was a significant impairment in both accuracy and error rate in phonological WM in people with ASD. However, to examine whether this effect was consistent across lifespan and to explore the variation in effect sizes post-hoc subgroup analysis was performed using age and IQ as moderators (Table 3). Age was dichotomised into children (< 18 years) and adults (≥ 18 years). There were four studies that investigated accuracy in phonological memory in children and five phonological memory in adults. There were no between group differences in age (Q = 0.25; p = 0.62) for accuracy in phonological WM (adults: *d* -0.79, 95% CI, -1.53 to -0.04 vs child: *d* -0.57, 95% CI, -1.01 to -0.13). Mean IQ of study participants was dichotomised (average 90-109; high average 110-119). The accuracy phonological WM scores for all participants was reported as all having a mean average IQ and therefore not divided into subgroups. Moreover, as only two studies measured error in phonological WM, subgroup analysis was not conducted.

Table 3. Subgroup analysis phonological working memory**.**

Study or Subgroup					**Heterogeneity**			
	K	SMD	95% CI	p-value	Q_{model}	P-value (Q_{model})	I^2	$Q_{between}$ (p-value)
Phonological Accuracy								
Adult	5	-0.79	-1.53 to -0.04	0.038	30.74	<0.001	86.99	0.25 (0.62)
Children	4	-0.57	-1.01 to -013	0.0111	6.08	0.11	50.66	

Note: K = number of studies; SMD = standardised mean difference; CI = confidence interval; Q_{model} = heterogeneity statistic for the model; I^2 = index of heterogeneity beyond within-study sampling error; $Q_{between}$ = between-groups heterogeneity statistic

3.5 Visuospatial working memory

3.5.1 Accuracy in visuospatial working memory

Twelve studies tested accuracy in visuospatial WM. A summary of the study characteristics of the twelve studies is presented in Table 4. The studies were published between 2005 and 2015 and included 12 different journals. A total of 656 participants were recruited (305 ASD, 351 TD) across the 12 studies, with a mean total ASD sample size of 23.5, and TD sample size of 27. Participants' ages ranged from 11 to 63 years for ASD with a mean of 25.4 years, and TD age ranged from 10 to 63 with a mean age of 25.4 years. All twelve studies compared ASD participants with TD participants with all participants IQ scores being within typical range of 70 or greater.

Table 4. Main characteristics of accuracy in visuospatial working memory studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean Age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assess-ment
Brenner et al. (2015)	-0.45	0.08	27	12.68	25	13.41	9.54 (2.80)	10.82 (2.91)	101.31	106.96	ADI and ADOS	TRT
Crane et al. (2013)	-.067	0.08	28	41.57	28	40.53	10.16 (3.13)	11.89 (1.92)	117.18	115.11	DC	WMS-III
Cui et al. (2010)	-0.93	0.13	12	7.46	29	7.37	8.00 (1.76)	9.28 (1.19)	100.03	108.31	DC	BR and VPT
Geurts and Vissers (2012)	-0.88	0.10	23	63.60	23	63.70	6.60 (1.70)	8.10 (1.70)	109.50	109.80	DC	WMS-III
Jiang et al. (2014)	-1.96	0.14	21	11.00	21	10.90	1.51 (0.30)	2.01 (0.20)	110.50	111.90	ADI and ADOS	SWMT
Maister et al. (2011)	-0.38	0.14	15	11.80	15	11.20	12.30 (2.50)	13.10 (1.60)	39.70	40.00	ADI and DC	MST
Nakahachi et al., 2006	-0.51	0.10	16	28.00	28	28.30	31.90 (12.30)	37.40 (9.70)	101.00	103.00	DC	ATMT
Schuh et al. (2012)	-1.00	0.13	18	12.00	18	13.00	9.00 (2.00)	11.00 (2.00)	105.00	104.00	ADI and ADOS	FW
Williams et al. (2005) a1	0.13	0.07	31	26.58	25	26.76	570.03 (128.91)	554.08 (121.34)	108.65	109.76		N-Back
Williams et al. (2005) a2	-0.32	0.07	24	11.75	44	12.39	576.79 (127.26)	623.14 (150.98)	109.67	109.95	ADI and ADOS	N-Back
Williams et al. (2005) b	-1.58	0.08	29	28.73	34	26.53	7.28 (3.02)	11.85 (2.79)	105.86	109.65	ADI and ADOS	WMS-III
Williams et al. (2006)	-0.47	0.05	38	11.68	38	12.16	8.63 (2.83)	9.92 (2.66)	103.82	107.18	ADI and ADOS	WMS-III

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; BR: Block recall; ATMT: Advanced Trail Making test; VVT: variant-visual-pattern test; MTS: A visuo-spatial delayed match-to-sample task; FW: Finger Windows subtest from the Wide Range Assessment of Memory and Learning; WMS-III: Wechsler Memory Scale; SWMT: Spatial working memory task; TRT: The time reproduction task.

The combined WM scores from the 12 studies were significantly lower in the ASD group than the TD group (*d*: -0.73, 95% CI -1.04 to -0.42, p < 0.05). There was a substantial heterogeneity between studies (Q-statistic = 36.40, df =11 (P <0.05); I^2 = 69.75%) with a statistically insignificant publication bias (Egger's linear regression P=0.09; Figure 6). Representative forest plots from the phonological WM meta-analyses are shown in Figure 7. Comparison of Figures 2 and 5 appear to suggest that there is a greater impairment in the visuospatial domain when measuring accuracy.

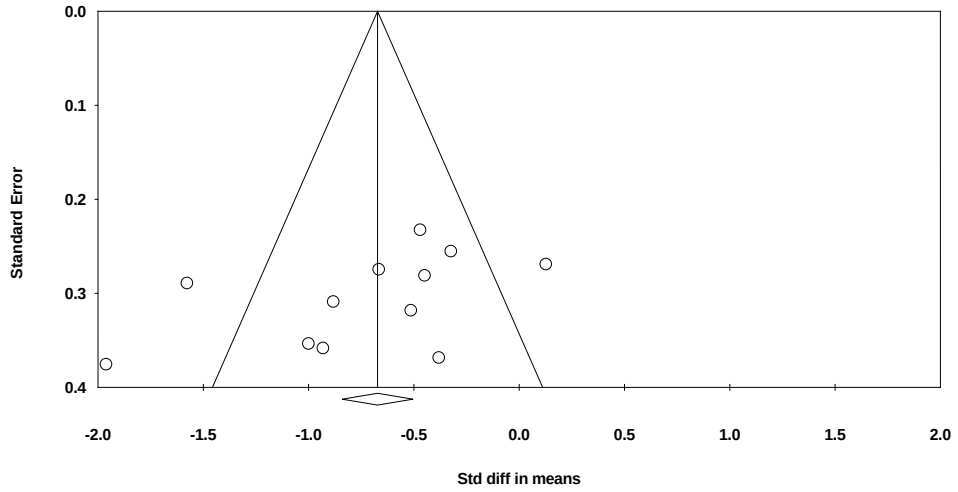


Fig. 6. Funnel plot for accuracy in visuospatial working memory, Egger's linear regression P=0.09. SMD effect size plotted against standard error. The circles represent the studies in the analysis. The vertical line represents the population effect estimate and the diagonal lines represent the 95% confidence intervals.

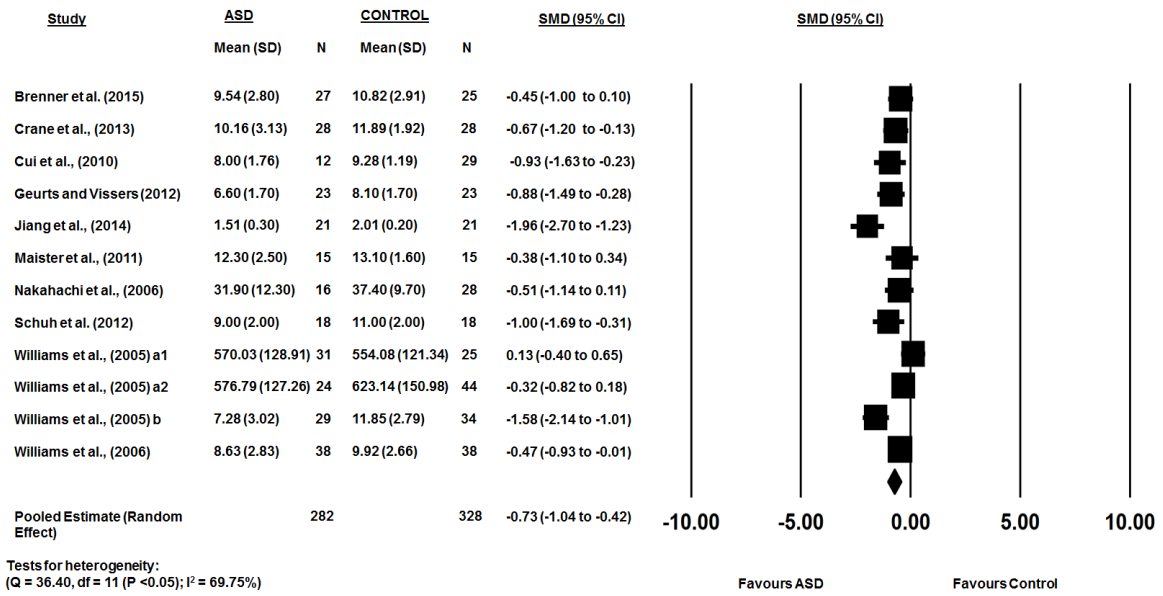


Fig. 7 Accuracy in visuospatial WM between ASD and typically developing controls.

3.5.2 Error in visuospatial working memory

Eleven studies tested error in visuospatial WM. A summary of the study characteristics of the eleven studies is presented in Table 5. The studies were published between 2005 and 2014 and published between nine different journals. A total of 691 participants were recruited (342 ASD, 349 TD) across the eleven studies, with a mean total ASD sample size of 31.1, and TD sample size of 31.7. Participants' ages ranged from 8 to 28 years, with the ASD mean of 13.8 (range 8-24), and TD mean age of 14.4 (range 8-28). All twelve studies compared ASD participants with TD participants with all participants IQ scores being within typical range of 70 or greater.

Table 5. Main characteristics of error rate in visuospatial working memory studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assessment
de Vries and Geurts 2014	0.44	0.03	79	10.70	71	10.30	9.60 (6.10)	7.30 (3.90)	109.30	107.70	ADI and DC	N-Back
Happe et al., 2006	0.59	0.07	32	10.90	32	11.20	46.90 (8.80)	42.30 (6.60)	99.70	106.80	DC	CANTAB
Jospeh et al., 2005	0.70	0.09	24	8.11	24	8.11	5.60 (2.70)	3.90 (2.10)	96.00	92.00	ADOS, ADI and DC	SOPT
Kaufmann et al., 2013	0.57	0.21	10	14.70	10	13.80	24.60 (19.50)	14.60 (15.60)	102.30	109.50	ADOS and ADI	CANTAB
Koshino et al., 2008	-1.01	0.21	11	24.50	11	28.70	12.50 (2.90)	15.90 (3.80)	104.50	108.60	ADOS and ADI	N-Back Faces
Landa and Goldberg 2005	1.02	0.12	19	11.01	19	11.00	52.70 (17.90)	35.80 (15.30)	109.70	113.40	ADOS and ADI	CANTAB
Sachse et al., 2013	0.99	0.08	30	19.20	28	19.90	33.30 (22.20)	15.60 (11.80)	105.30	109.30	ADOS, ADI and DC	CANTAB
Sinzig et al., 2008	-0.54	0.10	20	14.30	20	13.10	-0.62 (1.31)	0.01 (1.00)	112.00	113.00	DC	CANTAB
Solomon et al., 2009	0.98	0.10	22	182.00	23	191.00	0.26 (0.20)	0.11 (0.09)	107.00	113.00	ADOS and DC	Pop task
Steele et al., 2007	1.02	0.08	29	14.83	29	16.93	0.17 (0.11)	0.08 (0.06)	107.80	110.80	ADOS and ADI	CANTAB
Verte et al., 2006	0.90	0.03	66	8.70	82	9.20	21.1 (7.70)	14.90 (6.20)	101.50	112.20	ADI and DC	SOPT

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; CANTAB: Cambridge Neuropsychological Test Automated Battery; POP: Preparing to Overcome Prepotency; SOPT: Self-ordered pointing task.

The combined WM error rate scores from the eleven studies were significant lower in the TD group than the ASD group (*d*: 0.56, 95% CI 0.25 to 0.88, p<0.05). There was a substantial heterogeneity between studies (Q-statistic = 36.01, df = 10 (P < 0.05); I^2 = 72.23%) with statistically insignificant publication bias (Egger's linear regression P=0.4; Figure 8). Representative forest plots from the visuospatial WM meta-analyses are shown in Figure 9.

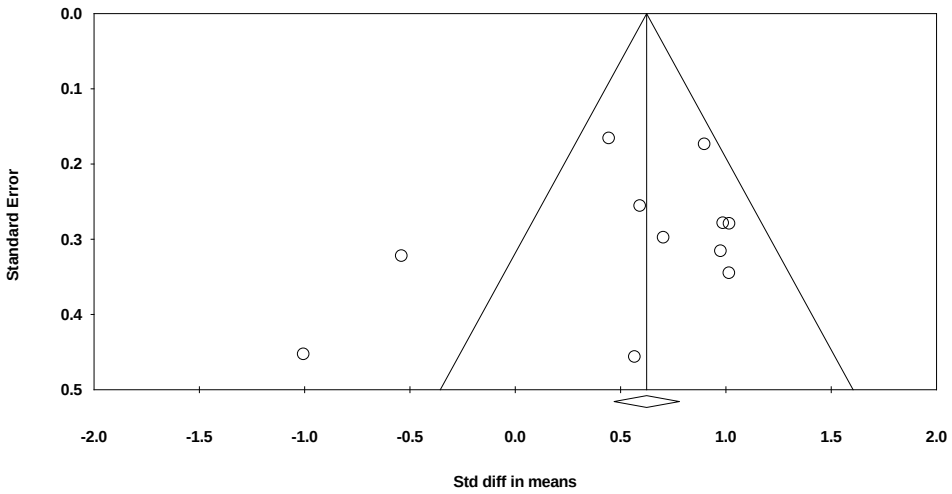


Fig. 8. Funnel plot for error rate in visuospatial working memory, Egger's linear regression P=0.4. SMD effect size plotted against standard error. The circles represent the studies in the analysis. The vertical line represents the population effect estimate and the diagonal lines represent the 95% confidence intervals.

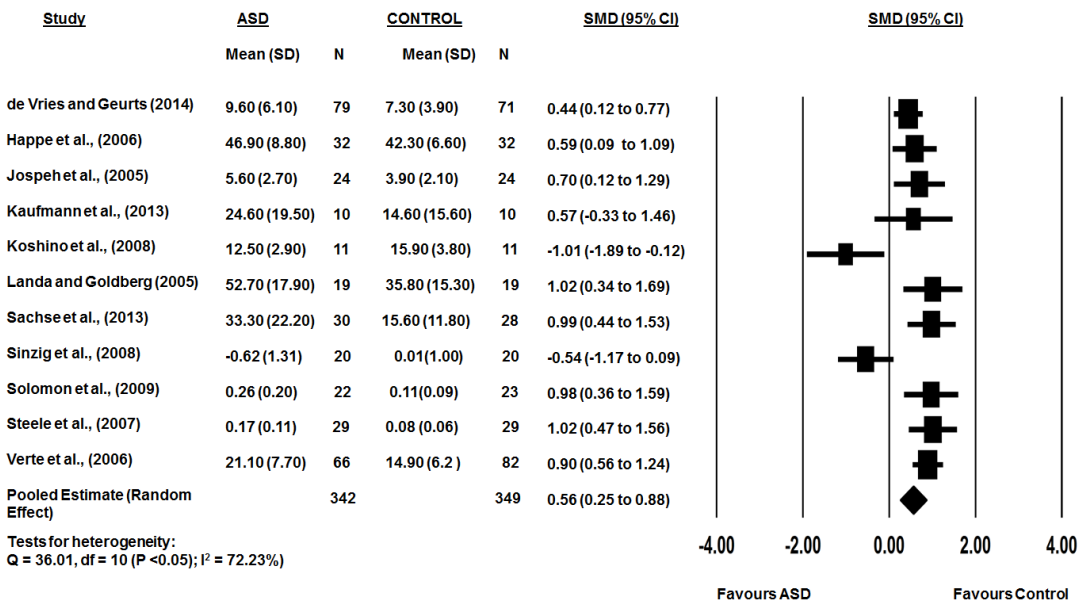


Fig. 9. Error rate in visuospatial WM between ASD and typically developing controls.

3.5.3 Subgroup analysis of visuospatial working memory

Eight studies investigated visuospatial accuracy in children, four in adults and nine studies measured visuospatial error rate in children, two in adults, presented in Table 6. There, were no between group differences in age (Q = 1.67; p = 0.20) for accuracy in visuospatial WM (adults: *d* -0.47, 95% CI, -0.91 to -0.03) vs child: *d* -0.86, 95% CI, -1.27 to -0.46) or in age (Q = 0.38; p = 0.54) for error in visuospatial WM (adults: *d* 0.02, 95% CI, -0.93 to 1.97 vs child: *d* 0.64, 95% CI, 0.35 to 0.92).

Two studies included participants categorised as having high average IQ (*d*: -1.29; 95% CI -2.56 to -0.02) and ten studies included participants with average IQ (d: -0.62; 95% CI -0.93 to -0.32) in accuracy visuospatial WM. There was no between group difference in accuracy in visuospatial WM (Q = 1.00; p = 0.32). Three studies involved participants categorised as having high average IQ (d: 0.48; 95% CI -0.53 to 1.49) and eight studies with participants with average IQ (d: 0.61; 95% CI 0.30 to 0.92) in error visuospatial WM. There was no significant between group difference for error in visuospatial WM (Q = 0.05.; p= 0.81).

Table 6. Subgroup analysis visuospatial working memory**.**

Study or Subgroup					**Heterogeneity**			
	K	SMD	95% CI	p-value	Q_{model}	P-value (Q_{model})	I^2	$Q_{between}$ (p-value)
Visuospatial Accuracy								
Adult	4	-0.47	-0.91 to -0.03	0.037	7.22	0.07	58.44	1.63 (0.220)
Children	8	-0.86	-1.27 to -0.46	<0.001	25.58	0.001	72.63	
Average IQ	10	-0.62	-0.93 to -0.32	<0.001	23.88	0.004	62.31	
High Average IQ	2	-1.29	-2.56 to -0.02	0.046	7.75	0.005	87.09	1.00 (0.32)
Visuospatial Error rate								
Adult	2	0.02	-1.93 to 1.97	0.982	14.06	<0.001	92.89	0.38 (0.54)
Children	9	0.64	0.35 to 0.92	<0.001	21.27	0.006	62.40	
Average IQ	8	0.61	0.30 to 0.92	<0.001	20.26	0.005	65.44	
High Average IQ	3	0.48	-0.53 to 1.49	0.351	14.91	0.001	86.59	0.05 (0.81)

Note: K = number of studies; SMD = standardised mean difference; CI = confidence interval; Q_{model} = heterogeneity statistic for the model; I^2 = index of heterogeneity beyond within-study sampling error; $Q_{between}$ = between-groups heterogeneity statistic

3.6 Quality assessment

Assessment scores were converted to a percentage score, scores ranged from 81 to 100 %. Nineteen studies were assessed as very good quality and were scored 22/22 = 100 % and 21/22 = 95%. Ten studies were assessed as good quality and were scored 20/22 = 91%, 19/22 = 86%, and 18/22 = 81%. Results are presented in Table 7 along with scores from the quality assessment checklist. All papers were considered of sufficient quality.

Table 7. Quality assessment.

Study	Question / objective sufficiently described?	Study design evident and appropriate?	Method of subject/ comparison group selection or source of information/ input variables described and appropriate?	Subject (and comparison group, if applicable) characteristics sufficiently described?	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	Sample size appropriate?	Analytic methods described/ justified and appropriate?	Some estimate of variance is reported for the main results?	Controlled for confounding?	Results reported in sufficient detail?	Conclusions supported by the results?	Total score	Percentage
Brenner et al. (2015)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Crane et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Cui et al. (2010)	2	2	2	2	2	0	2	2	2	2	2	20	91%
de Vries and Geurts (2014)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Geurts and Vissers (2012)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Gonzalez-Gadea et al., (2013)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Gracia-Villamisar (2002)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Ham et al., (2011)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Happe et al., (2006)	2	2	2	2	2	1	2	2	2	2	2	21	95%
Jiang et al. (2014)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Jospeh et al., (2005)	1	2	2	2	2	2	2	2	2	2	2	21	95%
Kaufmann et al., (2013)	2	2	2	2	2	0	2	2	2	2	1	19	86%
Koshino et al., (2008)	1	2	2	2	2	0	2	2	2	2	2	19	86%
Landa and Goldberg (2005)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Maister et al. (2011)	2	2	2	2	2	2	2	2	2	2	2	22	100%

Minshew and Goldstein (2001)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Nakahachi et al., (2006)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Poirier et al. (2011)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Sachse et al., (2013)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Schuh et al. (2012)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Sinzig et al., (2008)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Solomon et al., (2009)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Steele et al., (2007)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Verte et al., (2006)	1	2	2	2	2	2	2	2	0	2	2	19	86%
Williams et al (2006)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Williams et al. (2005a)	1	2	2	2	2	2	2	2	2	2	2	21	95%
Williams et al. (2005b)	0	2	2	2	2	2	2	2	0	2	2	18	81%
Williams et al., (2014)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Yerys et al., (2011)	2	2	2	2	2	2	2	2	2	2	2	22	100%

Note: 2 = Yes, 1 = Partial, 0= No, N/A = Not applicable.

3.7 Discussion

The analyses demonstrated relatively large and statistically robust overall effect sizes, indicating significantly impaired performance when investigating accuracy and error rate among individuals with ASD across age groups which is consistent with previous research (Boucher et al., 2012; Barendse et al., 2013; Kercood et al. 2014).

Working memory deficits in ASD were found across diverse methods to measure WM and different outcomes of working memory. Therefore, the present study indicates that working memory deficits in ASD are independent of the specific modality of the task. The publication bias results suggest that studies of working memory in ASD are equally likely to be published regardless of magnitude or statistical significance. Therefore, the probability that these results would be altered by including unpublished studies, studies there were not in English; studies that did not consider IQ or compared ASD to another clinical population is low. These findings are consistent with our hypothesis that individuals with ASD experience impairments in WM and support the growing view that cognitive and executive abnormalities may be just as important as the core symptoms in ASD, which demonstrates the significance and the importance of investigating working memory in ASD and the difficulties arising from these deficits. Exploratory post hoc subgroup analyses were conducted to investigate the effects of sample characteristics on the effect sizes for each outcome. Moderator variables (age and IQ) however, did not explain a significant amount of the between study variation.

There are a number of differences between the current meta-analysis and the one conducted by Wang and colleagues. By adopting a more extensive search of the available literature and a more stringent inclusion criteria the results of the literature search of the current meta-analysis found 8868 studies in the initial search compared to the 499 studies found by Wang et al. Moreover, a number of studies considered in the current meta-analysis, which met the inclusion criteria of Wang and colleagues, were not included in their meta-analysis. The studies that are present in their meta-analysis and not in the current one are due to those studies not meeting our inclusion criteria of matching participants on IQ and age. Therefore, the results presented here provide a less biased, and more comprehensive, synthesis of studies examining working memory in ASD.

Wang and colleagues found that there was a significant impairment in WM in individuals with ASD when investigating accuracy. The moderation results showed that visuospatial WM was more impaired than verbal WM and cognitive processing (maintenance vs. maintenance plus manipulation) did not explain the severity of the impairment. While they did conduct a meta-regression on IQ and age and found that they are not predictors of the impairment in WM, it is unreliable to draw such a conclusion while not controlling for IQ and age in the meta-analysis, as some of the studies included in their analysis did not control for IQ and age between their participants (Table. 7). Similar to Wang, we found differences in WM accuracy that were not moderated by IQ and age. However, we found a larger effect size in both visuospatial (*d*: -0.73) and phonological (*d*: -0.67) WM showing a medium effect size compared to Wang (visuospatial, *d*: −0.72 and phonological, *d*: −0.44) showing a medium and a low effect size. Since Wang converted error rate scores into accuracy, this is the first study to show differences in WM error rates. This shows that individuals with ASD make more errors on WM task compared to the TD controls. This is important as a few studies show that while testing WM performances, ASD participants did not differ on their accuracy from the TD controls, however, made more errors. Therefore, this demonstrates that accuracy is not the only way to identity WM weaknesses, which could mean that ASD individuals are not only having impairments choosing the correct response but identifying them as well.

While there was an observed effect size difference between visuospatial (*d*: -0.73) and phonological (*d*:-0.67), we could not run a subgroup meta-analysis as the data in the groups was not independent (i.e. the same study participants contribute to more than one of the subgroups in the forest plot; (Higgins, Thompson, Deek and Altman, 2002)). Wang and colleagues conducted meta-analysis on WM type (spatial vs verbal) although the data was also independent as evident from their forest plots, which is another concern with the validity of their findings. There may be multiple explanations for the suggested larger impairment in visuospatial memory compared to phonological memory impairment. It may be that visuospatial tasks are more challenging simply due to the task being less familiar for automatic response. Letters or numbers are typically used to test phonological memory and that may be one of the reasons that visuospatial memory exhibits more impairments, since phonological tests can be associated to spoken and written material that may be used or observed in everyday life.

Another explanation for the observed larger impairment in the visuospatial domain in ASD individuals is that there may be another underlying cause such as using different brain regions

during WM tasks. Functional magnetic resonance imaging (fMRI) studies have demonstrated prefrontal cortex (PFC) activity during WM task performance (D'esposito et al., 1995; Fiez et al., 1996, Jonides et al., 1993; Petrides, Alivisatos, Meyers and Evans, 1993) and the left dorsolateral prefrontal cortex (DLPFC), a specific region of the PFC, is considered to play a crucial role in WM (Barbey, Koenigs and Grafman, 2013; Tsuchida and Fellows, 2009; D'Esposito, Postle, Ballard and Lease, 1999,for meta-analytic reviews, see Owen, McMillan, Laird and Bullmore, 2005; Wagner and Smith, 2003; Wager, Jonides and Reading, 2004). fMRI studies have also investigated WM in individuals with ASD, for example, Koshino et al. (2005) examined brain activation of a group of adults with high-functioning autism during an n-back working memory task with letter. Their results demonstrated that individuals with ASD exhibited similar activation in the right hemisphere compared with the control group in contrast to substantially less activation in the left hemisphere in the dorsolateral prefrontal cortex and the inferior frontal gyrus. Individuals with autism showed more right lateralized activation in the prefrontal and parietal regions, whereas the control group demonstrated more activation in the left than the right parietal regions. In addition, individuals with ASD had more activation than the control group in the posterior regions including inferior temporal and occipital regions. Luna and college (2002) investigated the abnormalities in prefrontal circuitry and their effects on spatial working memory, they found that individuals with ASD demonstrated significantly less task-related activation in dorsolateral prefrontal cortex and posterior cingulate cortex in comparison with healthy subjects during a spatial WM task. This has been supported further by multiple studies such as the studies by Vogan et al. (2018) that investigated neural correlates of verbal WM using a one-back letter matching task with four levels of difficulty. They found that neural patterns of activations differed significantly between TD and ASD groups. TD group had activation in the lateral and medial frontal, as well as superior parietal brain regions, while the ASD group showed little recruitment of frontal and parietal regions. In addition, the study by Silk et al. (2006) demonstrating that individuals with ASD displayed less activation in lateral and medial premotor cortex, dorsolateral prefrontal cortex, anterior cingulate gyrus, and caudate nucleus during a visuospatial mental rotation task. Future research should consider these observed differences in WM impairments and investigate them fully in order to clarify this issue.

Furthermore, EEG studies have demonstrated that compared with TD individuals, individuals with ASD typically display a diffuse network pattern with diminished activity in task-related regions and increased activity in task-unrelated regions (Takarae, Minshew, Lunda and Sweeney, 2007; Pierce et al., 2001; Müller et al., 2001). However, individuals with ASD demonstrate functional underconnectivity in anterior-posterior connections when there is no task involved (Cherkassky,

Kana, Keller and Just, 2006) and reduced connectivity involving the medial prefrontal cortex and the left angular gyrus (Kennedy and Courchesne, 2008). On the other hand, studies have reported, a lack of deactivation in task-related regions during rest and also been demonstrated in individuals with ASD (Kennedy, Redcay and Courchesne, 2006). These "under-activation vs over-activation" hypotheses have been rather inconsistent and a gap in the literature that should be acknowledged.

Given that WM allows individuals to maintain information actively in a readily accessible format, various researchers have investigated its relationship with wider intellectual ability measures, such as fluid intelligence and scholastic aptitude (Jaeggi, Buschkuehl, Jonides and Perrig, 2008). Such research provides various viewpoints explaining the relationship between the two constructs. For instance, Engle et al. (1999) and Colom, Flores-Mendoza, and Rebollo (2003) investigated the WM- intelligence association and found that WM is strongly related with intelligence. In light of the WM correlation with intelligence, we ensured that our inclusion criteria included only studies that matched groups on IQ or there was no significant difference between the groups, thus, eliminating intellectual weakness as a cause of impaired WM. Therefore, the results of the study suggest that working memory deficit is not simply attributable to IQ deficits. However, Poirier et al. (2011) note that when participant groups are matched on verbal IQ as measured by the Wechsler scales, group differences on WM tasks may be underestimated because the test on which participants are matched (i.e., the WAIS), includes a sub-test of short-term/working memory (the digit span). In other words, participants might partly be matched on the domain that is of interest. While Poirier and colleagues took this into consideration and matched their participants on WAIS scores that purposefully excluded the digit span sub-tests while other studies did not, thus, this could be a critical methodological issue that future studies should take into consideration.

3.7.1 Strengths and limitations

Despite that there have been a number of comprehensive reviews of WM and ASD (Boucher et al., 2012; Barendse et al., 2013; Kercood et al. 2014; Wang et al., 2017), this is the first comprehensive review and meta-analysis of the current literature that investigates WM in ASD, while controlling for confounders such as age and IQ. We also divided WM into constructs, phonological and visuospatial, which consistent with the criterion recommendation (Higgins and Green, 2008), which is aimed to minimise heterogeneity and improve reliability in the results found. By conducting separate meta-analysis on the different possible outcomes of WM (accuracy and error rate) it allowed us to have a clear conclusion on the results of whether there are significant impairments in

individuals with ASD. As the WM tasks used in experiments are not often identical, the search strategy used was vital. Using a large number of relevant key terms in the literature search allowed us to gain access to a wide range of studies. We ensured that our search strategy was inclusive of any studies that specifically state the testing of working memory despite the terminology used for the task. We also used the most commonly used understanding of working memory (Baddeley, 2012).

Using stringent criteria for inclusion in the meta-analysis lead the study to have some limitations. Some of the limitations of the study were that only published and English language studies were included in this review excluding studies that can potentially meet the inclusion criteria. Another limitation of the study was that we reviewed studies that tested older ASD individuals even though research has shown that WM is among the cognitive functions that decline with age (Park et al. 2002; Hertzog et al, 2003). However, we felt it was important to investigate if the WM impairment is displayed across the life span of ASD individuals.

Due to the small number of studies included in this review, in particular phonological WM in ASD in comparison to matched TD, results should be interpreted with caution (Higgins, Thompson, Deek and Altman, 2002). Furthermore, there are some factors that contributed to the large heterogeneity found in this meta-analysis. A large range of methods used to measure WM, and the outcome measured of each method (apart from accuracy and error rate). For example, the study by Williams et al. (2005) where they reported the accuracy mean as 570 for the ASD group using an N-back task compared to the study by Cui et al. (2010) reporting the ASD group mean as 8 using a Block recall task. Another factor that could have contributed to the large heterogeneity is the is the different age groups used, for example the study by Gonzalez-Gadea et al. (2013) looked at adults with a mean age of 33 in the ASD group and a mean of 38 in the control group, compared to the study by Ham et al. (2011) where they looked at children with a mean age of 12 for the ASD and control groups. However, variation between studies is expected and was accounted for using the random effects model, which assumes heterogeneity.

It is important to note that the WM tasks across the studies were not matched and this must be considered when making any conclusion drawn from the current review as the results on the task may be influenced by psychometric properties of the test itself. In addition, individuals with ASD often have many comorbidities, such as Attention deficit hyperactivity disorder (Jang et al., 2013), learning difficulties (e.g. dyslexia) (Baird et al., 2006), and obsessive-compulsive disorder

(Postorino et al., 2017). Most of the studies in this review did not control for such confounders (or reported that they did) and thus these concurrent disorders may have contributed to the WM impairment observed.

3.7.2 Theoretical and clinical implications

Nevertheless, despite the study's limitations, as evident by the effect size the findings from this study will have important implications for people with ASD. WM impairments impact upon academic achievement (Gathercole and Pickering, 2000; Gathercole, Pickering, Knight and Stegmann, 2004; Jarvis and Gathercole, 2003) because many academic activities depend on WM such as remembering instructions, solving problems (mental arithmetic), controlling impulses and focusing attention (Kellogg, 2001; Passolunghi and Siegel, 2001). Therefore, academic progress of children and young people with ASD may be impaired due to WM impairments described in this study. WM impairments also has an impact on everyday life as it is plays a crucial role for several everyday functions such as the development of theory of mind (Davis and Pratt, 1995), navigation Garden, Cornoldi and Logie, 2002), every day problem solving (Siegel, 1994), reading skills (de Jong, 1998; Gathercole and Baddeley, 1990) and language development (Meyer and Lieberman, 2012). Moreover, it has been demonstrated that WM deficiencies contribute to social problems in people with ASD (Gilotty et al., 2002) as it is necessary to keep social information constantly changing in WM for social flexibility (Meyer and Lieberman, 2012). WM also encodes emotions observed on faces (Phillips et al., 2008), regulate emotional responses (Schmeichel, Volokhov and Demaree, 2008), slow learning (Gathercole, 2008) and learning disabilities (Alloway, 2006), language development (Gathercole and Baddeley, 2014), and break from restrictive or repetitive behaviours (Lopez, Lincoln and Ozonoff, 2005). These identified WM impairments are relative to TD controls (e.g. worse WM in ASD individuals relative to TD individuals), thus, clinicians should acknowledge that WM is significantly impaired and possibly a core issue in individuals with ASD. Additionally, clinicians should take into consideration that complains in regard to difficulties in everyday life from ASD patients could be related to the impairment of WM. The treatment of WM deficits could therefore improve some of the core cognitive and behavioural deficits characterising ASD.

3.7.3 Future research

The findings of this study help extend the literature on ASD and can be used to develop future studies centred on the most effective way to improve memory and consequently enhance the quality of life for individuals with ASD. Future research should investigate the nature of severity of WM deficiencies in individuals with ASD while controlling for confounding factors, such as comorbid psychiatric or developmental disorders. In the future, it may be possible to examine the results from studies that include individuals with LFA to investigate whether the deficit is present across the spectrum, studies should also consider using larger sample size as many of the studies have a small sample size that could lead the study to being underpowered. Future studies can also investigate if parents or siblings of individuals with ASD also experience WM impairments.

3.8 Conclusion

This review revealed that individuals with ASD display significant impairment in WM in both phonological and visuospatial domains across age groups this is important for the ASD population to help understand the disorder further and inform the development of interventions and intervention studies to improve WM in people with ASD.

4 Assessing everyday life problems related to deficits of working memory in autism spectrum disorder

The meta-analysis and systematic review demonstrated that there are WM impairments in ASD in both phonological and visuospatial domains, however, it is important to investigate if these reported impairments are also observed in everyday applied settings. WM impairments are normally investigated through cognitive testing in laboratory settings; however, we are unsure if these deficits in performance translate to difficulties in everyday life. In order to investigate this matter, we conducted a study looking at reports of everyday WM related difficulties reported by individuals with ASD using the Working Memory Questionnaire (WMQ).

4.1 Introduction

Although research has shown that deficits of WM seem to be a core impairment in individuals with ASD (See Chapter 3), to this date there is no valid measurement of everyday life difficulties related to WM in individuals with ASD. While traditional tests of WM have been beneficial to the understanding WM, the majority of WM tests have been developed for experimental purposes and not clinical applications. While typical cognitive assessments are known for their strict adherence to protocol and high internal validity, as all participants are tested in the same room, given the same test and have the test administered in the same way. At the end, after analysing the results, the researcher would have a glimpse into the participant's cognitive abilities and how well a person can complete standardised cognitive tests in a controlled environment. However, the question remains how well do results from typical cognitive assessments translate to a person's actual functional cognitive ability in everyday life? (Bielak, Hatt and Diehl, 2017).

Research has shown that many patients who perform appropriately on a controlled cognitive task are still demonstrating clinically significant difficulties in everyday life functioning (Eslinger & Damasio, 1985; Shallice & Burgess, 1991). This is thought to be due to the unstructured, open-ended, nature of everyday life situations, while cognitive tasks are well-structured and patients are only required to find the solution to a given problem (Lezak, 1995). Indeed, Yam, Gross, Prindle, and Marsiske (2014) noted that cognitive tasks have face validity but are never precisely the same as what a person might do in his or her everyday life. This was supported by Burton, Strauss,

Hultsch, and Hunter (2006) where they found that traditional cognitive measures did not account for over 50% of the variance in the ability to solve everyday problems. This demonstrates the importance of investigating if cognitive task performance also translates to everyday life as cognitive task seem to have low ecological validity, an aspect of external validity, where the results can be generalised to apply to life outside the lab environment.

The aim of this study is to determine whether reported WM impairments are translated to experiences of difficulties in everyday life in individuals with ASD. We hypothesise that individuals with ASD will have high scores on the WMQ demonstrating significant everyday life difficulties related to WM.

4.2 Participants and Procedure

This study included 111 males with ASD between the ages of 18 and 35 (Mean age 25.7 (SD = 5.52) years). Participants were recruited through the National Health Service Greater Glasgow and Clyde (NHSGGC). Prior to adding the WMQ to the protocol, we read through the WMQ with three service users from the Adult Autism Service, NHSGGC. The service users felt the WMQ provided clear, unambiguous questions that could be easily understood. Accordingly, the WMQ was mailed to potential participants with a FREEPOST return envelope to have the questionnaire mailed back to us. Participants were informed that by agreeing to post back the questionnaire, they were consenting to us holding their information and using it in the study. The WMQ was also posted online to potential participants that were not recruited through the NHSGGC and did not receive the questionnaire by mail. The online questionnaire was only filled in by participants that reported to having an official ASD diagnosis or were identified through the NHSGGC as individuals with ASD. The WMQ was completed by the participants themselves, as a self-assessment questionnaire and the only selection criteria were age 18+ years, declaring to not suffer from other psychiatric or neurological troubles and giving informed consent. Participants anonymously completed the WMQ, as well as a short demographic questionnaire asking for age and gender. The study protocol complied with the Helsinki declaration. Participants were informed of the aim of the study and gave their consent to participate.

4.3 The Working Memory Questionnaire

The WMQ is a self-assessment questionnaire that contains 30 questions, 10 questions each in three different domains: short-term storage (e.g., “Do you find it difficult to remember the name of a person who has just been introduced to you?”); attention (e.g., “Do you find it difficult to carry out an activity in the presence of background noise (traffic, radio or television)?) and executive aspects of working memory (e.g., “Do you find it difficult to carry out a project such as choosing and organising your holidays?). Each question was rated on a five-point Likert-type scale, scoring from 0 (“no problem at all”) to 4 (“very severe problem in everyday life”) for a total score of 120. Higher scores correspond to more difficulties/complaints.

The WMQ validity has been assessed against two other questionnaires which assess cognitive or attention failures in daily living, The Cognitive Failure Questionnaire (CFQ; Broadbent et al., 1982) and The Rating Scale of Attentional Behaviour (RSAB; Ponsford & Kinsella, 1991) and has shown high reliability between the three questionnaires (Vallat-Azouvi et al., 2012).

4.4 Data analysis

4.4.1 Score calculation

For each participant, we calculated the total WMQ score (which can range from 0 to 120). We also extracted the sub scores corresponding to each of the three domains of the WMQ, storage, attention and executive (each ranging up to 40). All statistical analyses were performed using SPSS version 24 statistical software (Chicago, Illinois, USA). Data were reported as means and standard deviations, and significance was accepted at $p< 0.05$.

4.4.2 Cross Sample Comparisons

The scores obtained in the present study were compared to the scores obtained by Vallat-Azouvi et al. (2012) as they are the only study currently that used the WMQ. The mean scores and standard deviations obtained were compared between the two studies using a two-tailed independent sample t-test.

4.5 Results

4.5.1 WMQ results

The mean WMQ scores of the ASD group was 58.1 (SD= 13.31). To investigate the WMQ domains scores, we extracted the scores of each of the scores of the three WMQ domains, storage (M=20.1, SD=5.2), attention (M=20.05, SD=5.47), and executive (M=17.91, SD=4.96). A Pearson correlation was conducted to investigate the relationship between age and scores on the WMQ. Participants showed no relationship between age and scores on the WMQ r (110) =0.006, p=0.95.

4.5.2 Comparisons across Samples

As this study did not investigate the scores of the WMQ on TD individuals, we compared the scores of the 25 TD individuals from the stimulation study (see Chapter 5), as to have a comparison to the results of the TD individuals in the study by Vallat-Azouvi and colleagues (2012). The mean and standard deviation of the TD groups in both studies were very similar, 16.52 (SD=8.75) for the TD group in present study and 17.8, (SD=11.5) for the TD group in the Vallat-Azouvi et al. study. However, the WMQ score for the clinical groups were significantly different, with a mean of 34.5 (SD=22.1) for the brain injury group and a mean of 58.1 (SD= 13.31) for the ASD group.

Moreover, for each of the three domains of the questionnaire, the mean scores were compared between the two studies. In the Vallat-Azouvi et al. study, the mean score for the brain injury group in the storage domain was 11, attention domain was 14, and the executive domain was 9. For the TD group the means was 5 for the storage domain, 7 for the attention domain and 6 for the executive domain. In the current study, mean scores were significantly greater for the ASD group than the brain injury group, with the storage domain having a mean of 20.1 (SD=5.2), attention domain a mean of 20.05 (SD=5.47) and the executive domain having a mean of 17.91 (SD=4.96). However, the TD groups scores were very similar to each other, with the storage domain having a mean of 5.76 (SD=3.15), attention domain a mean of 5.4 (SD=2.42) and the executive domain having a mean of 5.04 (SD=3.25). These results are presented in Table 9.

Table 9 Means and Standard deviation of groups in both studies.

Groups	N	Age in years	Storage domain	Attention domain	Executive domain	Full WMQ scores
ASD	111	25.7 (5.52)	20.1 (5.2)	20.05 (5.47)	17.91 (4.96)	58.1 (13.31)
TD	25	25.36 (4.9)	5.76 (3.15)	5.4 (2.42)	5.04 (3.25)	16.52 (8.75)
Brain injury	69	37.5 (13.4)	11	14	9	34.5 (22.1)
TD	313	43.7 (17.3)	5	7	6	17.8, (11.5)

ASD= Autism spectrum disorder, TD= typical developed, N= number of participants, WMQ= Working Memory Questionnaire.

A paired sample t-test was conducted to compare the scores between each domain. In the ASD group, there was a significant difference between the storage domain and the executive domain ($t=5.17$, $df=110$, $p<0.0001$) as well as the attention domain and the executive domain ($t=4.53$, $df=110$, $p<0.0001$). However, there was no difference between the storage domain and the attention domain ($p>0.05$). Furthermore, an independent t-test was conducted to compare the WMQ scores between the two studies. There was a significant difference between the ASD group and the brain injury group ($t=8.95$, $df=178$, $p<0.0001$), showing that ASD participants reported higher scores on the questionnaire. However, there was no significant difference between the two TD healthy control groups ($t=0.51$, $df=92$, $p=0.61$). There was a significant difference between the ASD group and the TD group ($t=15.79$,$df=135$, $p<0.0001$). Moreover, in the present study we did not find an effect of age on WMQ scores, while the study by Vallat-Azouvi et al. found age to be a main effect.

4.6 Discussion

This is the first study investigating everyday life problems related to deficits of WM in individuals with ASD using the WMQ. The aim of this study was to assess WM-related difficulties in everyday life using the WMQ, a self-administered questionnaire which addresses short-term storage, attentional and central executive aspects of working memory, such as dual-tasking, mental effort and distractibility.

These findings were consistent with our hypothesis that individuals with HFA will report high scores on the WMQ, demonstrating relatively large and significant WM related difficulties in everyday life, which is consistent with previous research literature indicating that individuals with ASD experience WM deficiencies (see meta-analysis, Chapter 3 for review). When looking at the three WMQ domains separately, there was a larger difference in the Storage and Attention domains,

compared with the Executive domain for both clinical groups (ASD and brain injury from the Vallat-Azouvi et al. study), this could be an interesting point to investigate in future research as WM-related difficulties in everyday life could be largely attributed to specific impairments in the Storage and Attention domains. Pearson correlation was conducted to investigate the relationship between age and scores on the WMQ. Age showed no relationship to WMQ scores, this may be due to the age range between both studies, as in the current study we had participants between the ages of 18-35 while Vallat-Azouvi and colleagues had participants between the ages of 20-60+ which lead to them finding that age had a main effect. Overall, this study confirms the strong relationship between individuals with ASD and everyday WM related difficulties. It is important to note is that the study by Vallat-Azouvi et al. (2012) was investigating WM related difficulties in patients with brain injury compared to our population of individuals with HFA. This result and comparison shows that individuals with HFA have significantly more deficits in everyday working memory compared to individuals with brain injury.

4.6.1 Limitations

There are a few limitations to the present study. The first comes from the fact that it is a self-administered questionnaire, raising questions about reliability, particularly in individuals with ASD who may show a lack of self-awareness (Williams, 2010). Another limitation is that all participants were male, native English speakers and between the ages of 18 and 35. It is important to note that the study did not have a control matched TD group and that there may be some individuals that do not have an official clinical diagnosis of ASD as some participants completed the questionnaire and were recruited online. Moreover, there is a possibility that there was a selection bias, as may be only individuals that felt that had WM issues responded back. Nevertheless, despite the study's limitations, the findings from this study will have important implications for people with ASD.

4.6.2 Implications for Individuals with ASD

As WM difficulties can affect the quality of life, understanding how WM could affect everyday life is crucial. To convey the research and theories of WM in ASD is sometimes not clear, as in how do these reported WM impairments affect everyday life? The results from this study sheds light on how WM affects everyday life and could lead people with ASD better understanding the reasons behind some of their difficulties. These findings can also help clinicians better understand that some of the symptoms reported by their ASD patients could be due to WM issues. By having this

understanding and awareness of the possible implications of WM difficulties in everyday life, clinicians can better understand their patients and how to best support them and ultimately help the patients themselves understand their difficulties.

4.6.3 Future research

The findings of this study will help extend the literature on ASD and WM impairments. These findings can be used to develop future studies centred on the most effective way to improve WM, examine the impact of WM on everyday life in individuals with ASD which consequently lead to enhancing the quality of life for individuals with ASD. In the future, it may be interesting to examine the results from younger individuals with ASD to investigate whether the deficit is present across lifespan, studies could also consider using females and the use of healthy a control group matched on age and IQ. Moreover, future studies can also investigate if parents or siblings of individuals with ASD also experience everyday WM-related difficulties.

An important future direction would be for researchers to focus on developing and designing WM tasks based on the role of WM in everyday life. For example, a task where participants are given telephone numbers and they have to remember it, a task that shows pictures of people with their names and having the participant trying to remember the name of the person they just saw, a task that gives various instructions and the participants has to remember them and carry them out, and a task which has the participant make a shopping list and have them recall what is on it. The use of virtual reality in implementing some of these tasks could be a promising venture so as to give the impression of doing these tasks in everyday life and allow assessment of the actual ability to complete tasks relevant to a person's daily life. Indeed, driving simulators have been successful in assessing everyday cognitive ability in older adults (Lees, Cosman, Lee, Fricke, & Rizzo, 2010), and a virtual supermarket has been used to examine the planning ability of those with Parkinson's disease (Klinger, Chemin, Lebreton, & Marie, 2004). Therefore, the findings from these WM tasks would illustrate a better representation of WM impairment as they would translate to difficulties in everyday life, unlike current WM tasks used in research which tests WM based on theoretical models which participants find difficult to relate to as they are not common in daily settings, such as the N-back WM task which calls for participants to recall if a letter presented is similar to the one presented N steps back.

4.7 Conclusion

This study revealed that individuals with HFA report significant impairment in WM related difficulties in everyday life. There was no relationship between individual's age and WM score, i.e., as participants age increase, their WMQ scores increase. This is important for the ASD population to help understand the disorder further and demonstrate that WM impairments are not only based in theory and observed in scientific research on cognitive task, however, it is an everyday persistent issue. These findings help us understand the disorder better to inform us of ways to improve the quality of life in individuals with ASD.

5 A single blind, randomised controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in adults with high-functioning autism

5.1 Introduction

5.1.1 Improving working memory

It is evident from the meta-analysis and the WMQ study, that WM deficiencies are a definite issue for individuals with ASD. With WM impairments being present in multiple psychiatric disorders, there has been a need for effective treatment options.

One of the two most common WM treatments is working memory training (WMT). WMT involves the participant completing exercises on computers which include tasks such as recalling either series of locations such as illuminated lamps on the screen, or lists of digits or letters, either in the order in which they were presented or in the reverse order or recalling specifically where a particular number or digit was in a sequence. The exercise tends to have some form of feedback of the individual's performance such as their current score and their personal best score. Additionally, WMT exercises are programmed to adjust the difficulty of the task to the individual's performance on each trial, if the individual performs poorly on the task, the difficulty will decrease for the next trial and if the participant performance excels, the difficulty will increase.

The most common and empirically researched WMT is Cogmed (www.cogmed.com; Westage, Dunning, Roberts and Adlam, 2017). Cogmed is a computerised training program designed to improve WM by increasing WM capacity in 25 sessions (each lasting 30–45 min) over a 5-week training period through targeting both the storage and storage plus processing/manipulation components of verbal and nonverbal working memory. Each session consists of a selection of various tasks that target the different aspects of working memory. The specific therapeutic component of Cogmed focuses on improving working memory capacity with the use of a game-like interface where the difficulty level of the training is adjusted in real time by the software based on

the trainee's performance. That is, correct trials are followed by trials with greater WM demands, whereas incorrect trials are followed by trials with lesser WM demands. This calibration means that every individual will be training at the very edge of their cognitive capacity. In addition, several components of Cogmed focus on supporting the user's engagement to the Cogmed intervention. Specifically, contingent reinforcement is integrated within the program (e.g., earning small rewards for successful completion of a training-week). Additionally, the training is always supported by a Cogmed-trained coach who makes sure individuals progress through the program and provides a detailed training review, as well as provides support, structure, motivation, and feedback.

5.1.2 The use of working memory training for working memory deficiencies

Previous research has shown that WMT leads to improvements in WM not only in typically developed individuals, but also leads to improvements in individuals with ADHD (Klingberg, Forssberg, and Westerberg, 2002), strokes (Westerberg et al. 2007), multiple sclerosis (Vogt, Kappos, Calabrese, Stöcklin, Gschwind & Opwis et al., 2009), acquired brain injuries (Lunqvist, Grundström, Samuelsson & Rönnberg, 2010), adolescents with a history of extremely low birth weight (LØhaugen, Antonsen, Haberg, Gramstad, Vik & Brubakk et al., 2011), adolescents with intellectual disabilities (Van der Molen et al., 2010), and children with cochlear implants (Kronenberger, Pisoni, Henning, Colson & Hazzard, 2011).

WM was thought to be a fixed cognitive ability, which could not be improved (Engle et al., 1999; Kyllonen & Christal, 1990; Klingberg, 2010), however, studies have found that training on WM exercises improve working memory. The study by Thorell, Lindqvist, Nutley, Bohlin & Klingberg (2009) showed that WM has an effect in four- and five-year olds following a WMT for 15 minutes a day five days a week for five weeks when compared to a control group, which played computer games for the same amount of time. Moreover, in a study by Klingberg Fernell, Olesen, Johnson, Gustafsson, Dahlstrom, et al. (2005) where they looked at the effects of WMT on 53 children with ADHD, aged seven to 12 years. Participants were randomly assigned to use either the treatment computer program for training WM or a comparison program, their findings demonstrated that WM can be improved by training in children with ADHD. In another study by Olesen, Westerberg & Klingberg (2004), participants practiced 90 trials per day for 20, 24 and 30 days, respectively, on three WM tasks. Participants were scanned inside an fMRI scanner before and after training. They found that training significantly improved performance and they found training-induced increases in brain activity in the prefrontal cortex, which was related to working memory.

Despite the promising results WMT has shown in some studies, it has demonstrated unreliable results. The study by Garavan, Kelley, Rosen, Rao and Stein (2000) for instance has found that WM practice for a total of 2 hours and a total of 8 hours lead to improved response times, but not improved accuracy on WM tasks. Additionally, while studies have found improvement in WM performance after explicit training, it was largely domain specific, with no success in finding transfer effects (Butterfield, Wambold, & Belmont, 1973; Ericcson, Chase, & Faloon, 1980). WMT has showed in some cases to not have effect on WM, for example the study by Elliott, Gathercole, Alloway, Holmes & Kirkwood (2010), where they found that WMT that modified and reducing WM load, encouraging memory-aid strategies, and used direct instruction strategies to improve WM skills, did not lead to any improvements in WM. In another study, following a 6-week training program involving online, computerized tests of short-term memory, attention, visuospatial processing, and mathematics, participants WM did not improve compared to the control group (Owen, Hampshire, Grahn, Stenton, Dajani, & Burns et al., 2010).

There also has been studies showing that WMT only has temporary short-term effects, such as the meta-analysis by Melby- Lervåg & Hulme (2013) which reviewed WMT and found that memory training programs appear to produce short-term, specific training effects that do not generalize. Their findings cast doubt on both the clinical relevance of WMT programs and their utility as methods of enhancing cognitive functioning in typically developing children and healthy adults.

While findings have been inconsistent regarding the effects of WMT, a recent meta-analysis by Sala and Gobet (2017) focused on the effects of WM training on cognitive and academic skills in typically developing children, aged three to 16. Their finding suggests that WM training is ineffective at enhancing TD children's cognitive or academic skills and that, when positive effects are observed, they are modest at best. It is well known that individuals who are trained on cognitive tasks improve their performance on those cognitive tasks (Ball et al., 2002), but because the specific task often has little relevance to everyday life, the training technique is not considered a success unless there are corresponding improvements in real-world abilities.

5.1.3 The use of medication for working memory deficiencies

The other common WM treatment is medication. In extreme cases with memory and attention deficit, pharmacologic therapies such as antidepressants and antipsychotics are recommended (Oswald et al., 2007). Many previous studies have documented that psychostimulant medication can improve WM functioning (Holmes, Gathercole, Place, Dunning, Hilton & Elliott, 2010; Barnett, Maruff, Vance, Luk, Costin & Wood et al., 2001; Tannock, Ickowicz & Schachar, 1995; Mehta, Goodyer & Sahakian, 2004; Bedard, Martinussen, Ickowicz & Tannock, 2004). In a study by Wong and Stevens (2012), they looked at the effect of psychostimulant (e.g., methylphenidate or dextroamphetamine/amphetamine combination) in eighteen ADHD individuals, ages 11-17, on working memory. Their findings suggest that psychostimulant medication has widespread effects on the functional connectivity of frontoparietal brain networks, which might be a mechanism that underlies their beneficial effects on WM performance. Moreover, the meta-analysis by Ilieva, Hook and Farah (2015) looked at the magnitude of the effects of methylphenidate and amphetamine on cognitive functions, they found small but significant stimulant enhancement effects on inhibitory control and short-term episodic memory.

However, while medication has demonstrated significant WM improvement, there has been studies showing no difference in performance between the medicated children with ADHD and the control on a spatial WM task (Barnett, Maruff, Vance and Luk, 2001). Additionally, medication may cause adverse effects such as nausea, drowsiness, dry mouth, agitation, behavioural activation, and sleep problem (Oswald et al., 2007) decreased libido, sedation or insomnia, vomiting, and diarrhoea (Khawam, Laurencic and Malone, 2006), in addition to the period of trial and error of finding the best medication for patients. Bringing us back searching for more effective treatment options.

While both pharmacological and non-pharmacological approaches have shown positive results, both are far from leading to a significant improvement in WM in patients with ASD. In the last 15 years, there has been a growing interest in the use of non-invasive brain stimulation methods such as transcranial direct current stimulation (tDCS) as a way of improving WM in typically developed individuals and in clinical populations.

5.1.4 Working memory and transcranial direct current stimulation

Numerous brain stimulation studies have focused on WM and the majority of the studies suggest that tDCS can improve performance and thus brain stimulation techniques offer promise as a possible tool to remediate or enhance WM (Fregni et al., 2005; Ohn et al., 2008). The majority of the research investigating the effects of tDCS on WM task performance, often utilise the n-back task (e.g., Andrews et al., 2011; Berryhill & Jones, 2012; Fregni et al., 2005; Gill et al., 2015; Mylius et al., 2012; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Lally, Nord, Walsh, & Roiser, 2013; Ohn et al., 2008; Teo, Hoy, Daskalakis, & Fitzgerald, 2011; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011; see Berryhill, Peterson, Jones, & Stephens, 2014; Brunoni & Vanderhasselt, 2014 for reviews).

Fregni and colleagues (2005) sought to establish whether anodal tDCS, would have an effect on the performance on a 3-back letter WM task. The study entailed 15 participants who undertook a 3-back WM task based on letters, with anodal stimulation applied on the DLPFC (left dorsolateral prefrontal cortex) at a current of 1 mA for 10 minutes. The findings indicated that left prefrontal cortex anodal stimulation led to increases in the accuracy of task performance, suggesting effects on WM. Additionally, they investigated whether the observed enhancement was due to the focality by applying anodal stimulation to the motor cortex instead of the left DLPFC or polarity by applying cathodal stimulation to the left DLPFC. The findings suggest that the enhancement was dependent on focality and polarity as there was no effect in either of the conditions. As a result, the researchers concluded that left prefrontal anodal stimulation enhanced WM performance, suggesting possibilities for clinical application.

In a similar study, Richmond, Wolk, Chein, and Olson (2014) explored the extent of tDCS learning enhancement on WM training regime, as well as the level to which the learning gains made could transfer beyond the primary WM training task. Fifty-eight participants took part in an adaptive WM training task lasting 10 sessions taken over 2 weeks. The training was concurrent with dorsolateral PFC stimulation and sandwiched by tests measuring various domains associated with WM abilities. The researchers found that tDCS could enhance learning on the verbal aspect of the training, besides enhancing near transfer of learning to other untrained WM tasks. The results indicate that tDCS may apply in bolstering training and transfer gains among people with compromised WM abilities. These findings are consistent with the conclusions made by Boggio, Ferrucci, Rigonatti,

Covre, Nitsche, Pascual-Leone, and Fregni (2006), whose study established that tDCS may have a beneficial impact on WM in Parkinson's disease patients.

Andrews, Hoy, Enticott, Daskalakis, and Fitzgerald (2011) noted the consensus that tDCS applied to the DLPFC could improve WM performances among healthy and clinical subjects. The researchers then sought to establish whether the aforementioned effect of tDCS on WM could be enhanced through cognitive activity during the tDCS procedure. The study involved 10 participants taking part in three situations; an n-back task during anodal tDCS, anodal tDCS while at rest, and an n-back task during sham tDCS. The findings indicated that applying tDCS during an n-back task led to greater improvement WM performance when compared to tDCS at rest and sham tDCS with an n-back task. These findings suggest that tDCS can not only be employed in improving WM but can also be improved through employing adjunctive cognitive remediation tasks. It is important to note that in this study, tDCS did not affect performance on WM tasks during rest.

Multiple systematic reviews and meta-analyses investigated the effect of tDCS on WM. Brunoni and Vanderhasselt (2014) performed a systematic review and meta-analyses of the effects of Non-Invasive Brain Stimulation (NIBS) sham-controlled, randomised studies over the DLPFC. They assessed whether NIBS improved the performance in the n-back task, which is a reliable index for WM. They found that rTMS of the DLPFC significantly improved all measures of WM performance whereas tDCS significantly improved reaction time, but not the percentage of correct and error responses. Moreover, they reported that NIBS effects were greater in clinical samples as compared to healthy volunteers. In another systematic reviews and meta-analysis, Hill, Fitzgerald and Hoy (2016) performed a meta-analysis investigating the effects of anodal tDCS, compared to sham, on WM, as assessed using the n-back, Sternberg and digit-span tasks in healthy and neuropsychiatric cohorts. They also separated the results from tasks performed 'online' (during stimulation) and 'offline' (following stimulation) and assessed the effects of current density and stimulation duration on WM performance. Their findings demonstrated that anodal tDCS enhanced offline WM reaction times in healthy populations, with a trend towards improvement for accuracy, while online WM accuracy in neuropsychiatric populations was improved. Finally, Mancuso, Ilieva, Hamilton and Farah (2016) conducted a meta-analytic review to explore reasons why meta-analyses may have underestimated the effect of tDCS on WM and report a more comprehensive and arguably more sensitive meta-analysis. Their analyses revealed a small but significant effect of left DLPFC stimulation coupled with WM training. Left DLPFC stimulation alone also enhanced WM performance, however, the effect was reduced to insignificant after correction for publication bias.

They conclude that the primary WM enhancement potential of tDCS probably lies in its use during training.

As evident by the literature, the effect of anodal tDCS over the left DLPFC on WM has been found not only in healthy young individuals but also older adults (Seo et al., 2011), people with Parkinson's disease (Boggio, et al., 2006), major depressive disorder and bipolar depressive disorder (Brunoni et al., 2001), depression (Oliveira et al., 2013), ADHD (Nejati et al., 2017), and stroke patients (Jo et al., 2009) as well. It is important to note that tDCS is approved as a rehabilitation method for depression by UK clinical guidance bodies. However, due to a lack of robust evidence of its efficacy, mainly due to small sample sizes and differences in protocols (e.g. montages, current strength, duration), NICE encourages and recommends further research (NICE, 2015).

5.1.5 What is Transcranial direct current stimulation?

Transcranial direct-current stimulation (tDCS) is a non-invasive, brain stimulation technique that uses two electrodes: a cathode (negative terminal through which electrons exit the battery) and an anode (positive terminal through which electrons enter the battery) placed on to a participant's scalp to stimulate specific parts of the brain. Using a battery-driven, constant current stimulator a very low current is then passed through these electrodes placed in sleeves and soaked in a saline solution (NaC1) or mounted using electrode cream (typically made of rubber which serves to diffuse the current over a wider area, and reduce the risk of heating or ionic exchange at the scalp (Nitsche et al., 2008), which modulates neuronal activity and has strong effects on brain activity and excitability (Antal et al. 2011, 2012; Meinzer et al. 2013, 2014). Electrode placement is an important factor in tDCS, the anode is placed over the neural target region (active site) and the cathode is placed over a reference site (a secondary neural region), the reference site is typically placed over one of 3 places, a "dead-spot" (a cephalic location thought to be unimportant to the measured behaviour) common "dead-spots" are orbito-frontal region contralateral to the active electrode (Nitsche & Paulus, 2000, 2001) and the vertex (Chib, Yun, Takahashi, & Shimojo, 2013; Vigano et al., 2013), an extra-cephalic reference electrode: usually on the shoulder or the back (Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007; Muthalib, Kan, Nosaka, & Perrey, 2013), or over the contralateral neural homologue of interest (Brunoni et al., 2013; Kelley, Hortensius, & Harmon-Jones, 2013). Both electrodes must be on the body in order to complete the circuit. Both electrodes have similar current and placed over the scalp, this is a functional definition

and does not imply that the “reference” electrode is physiologically inert. The location of electrode placement typically follows the Electroencephalography (EEG) 10/20 system (Figure 10) for locating areas of the brain for stimulation (Jasper, 1958), although instances of localizing brain regions for stimulation with TMS have been reported (Reis, et al., 2009). The tDCS stimulators have a maximum of 10 mA output, which is below the human pain threshold. Constant current flow between the electrodes can be controlled by the device.

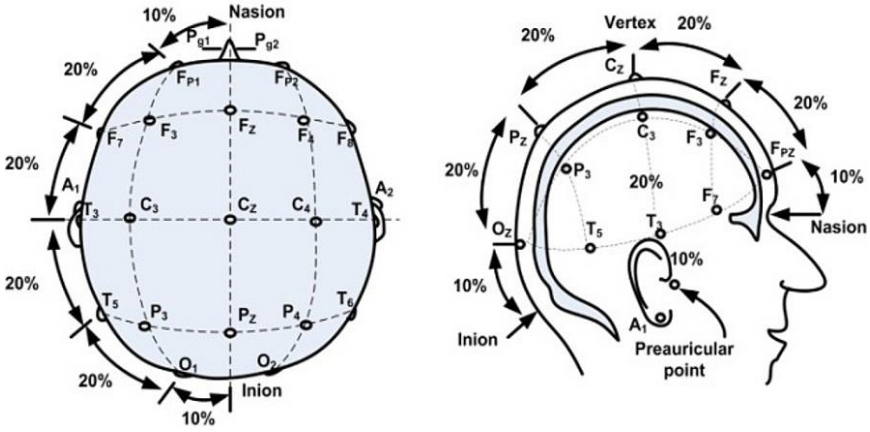


Figure 10. EEG 10-20 measuring system

At the start of a stimulation session most subjects feel a slight tingling sensation under the electrodes, especially when the current is switched on. Subjects usually describe this as being similar to an itching sensation, these effects will be minimised by ramping the current very slowly initially, and down at the end of the session, which usually stops this sensation. Current ramping is also recommended to prevent electrical transients (Nitsche et al., 2008).

tDCS combination studies including brain imaging techniques and brain mapping methods provide invaluable insight on the effects and mechanisms behind tDCS. EEG demonstrates tDCS can modulate resting state alpha and theta frequencies (Ardolino, Bossi, Barbieri, & Priori, 2005; Notturno, Marzetti, Pizzella, Uncini, & Zappasodi, 2014; Pellicciari, Brignani, & Miniussi, 2013). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) suggest anodal stimulation leads to increased blood flow whereas cathodal stimulation leads to decreased blood flow within the primary motor cortex (Lang et al., 2005; Stagg, O'Shea, et al., 2009; Paquette, Sidel, Radinska, Soucy, & Thiel, 2011). Magnetic resonance spectroscopy (MRS) studies suggest anodal stimulation leads to a decrease in inhibitory (GABA) and increase in excitatory (glutamate)

neurotransmitters, whereas cathodal stimulation leads to the opposite effect (Clark et al., 2011; Rango et al., 2008; Stagg et al., 2011, 2009)

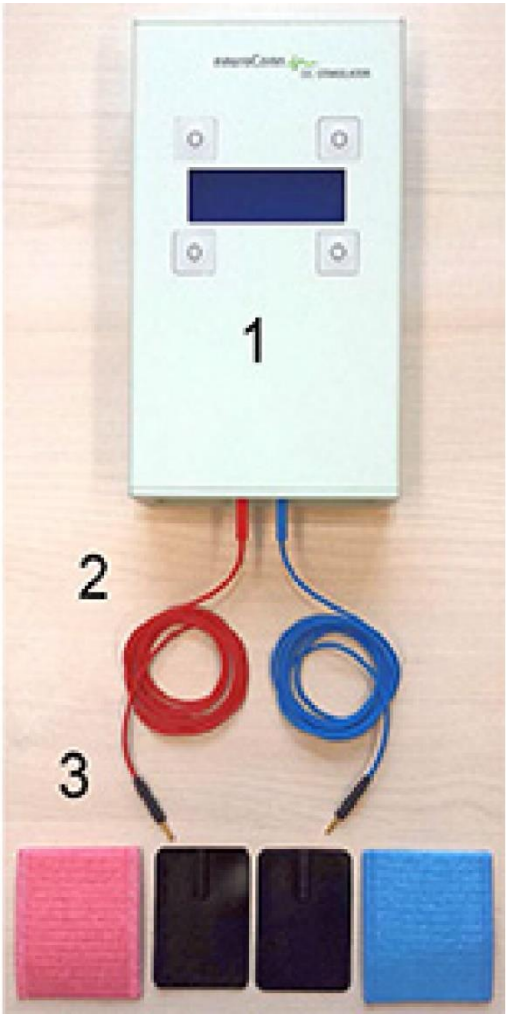


Figure 11. tDCS device. (1) The stimulator, (2) Two standard electrode cables, and (3) Rubber electrodes and sponge pockets for electrodes.

5.1.6 Neuronal mechanisms of transcranial direct current stimulation

While there has been a lot of research on the mechanism of tDCS, since the late 1950's and 1960's (Terzuolo and Bullock, 1956; Bindman et al., 1962; Purpura and McMurtry, 1965; Creutzfeldt et al., 1962) the understanding of the mechanisms by which tDCS generates neural modulation has not been fully described. Recently, the majority of theories explain the mechanism of tDCS depending if it is being delivered (online) or if it has previously been delivered for a long enough duration (offline). The effects of online tDCS stimulation is thought to cause shifts in neuronal membrane

polarity which effects the behavior of single neurons (Radman, Ramos, Brumberg, & Bikson, 2009) and network dynamics (Reato, Rahman, Bikson, & Parra, 2010).
The effects of tDCS induces cortical changes by causing the neuron's resting membrane potential to depolarize or hyperpolarize. When anodal tDCS (positive stimulation) is being delivered it causes depolarization of the resting membrane potential, which increases spontaneous neuronal excitability and activity. When cathodal tDCS (negative stimulation) is delivered it causes hyperpolarization of the resting membrane potential and thus decreases neuron excitability and activity (Nitsche et al., 2008). The anode has the effect of lowering the firing threshold of the neurons and making them more likely to fire, whereas the cathode increases the firing threshold making the neurons less likely to activate (Kim et al., 2014; Stagg et al., 2009; Stagg & Nitsche, 2011).

Pharmacological studies have suggested that the effects of online anodal stimulation depends on calcium and sodium channels but not N-methyl Daspartate (NMDA) or gamma-Aminobutyric acid (GABA) receptors (Nitsche, Fricke, et al., 2003; Nitsche, Liebetanz, et al., 2004). This was demonstrated by a decrease in the stimulation effect following the delivery of calcium and sodium channel blockers, but no impact of stimulatory effect following NMDA or GABA antagonists. It is suggested that it is due to an impact at the neuronal membrane rather than a plastic change at the synapse. Online cathodal stimulation depends on potential modulation at the membrane, this was evident by neither calcium nor sodium channel blockers impacting on stimulation effects (Nitsche, Fricke, et al., 2003), it is suggested that it is due to the neuron being already hyperpolarised thereby abolishing any drug effects. Neither NMDA or GABA interfere with the effects of cathodal stimulation (Nitsche, Fricke, et al., 2003; Nitsche, Liebetanz, et al., 2004) suggesting cathodal effects occur at the membrane rather than at the synapse.

While most researchers commonly explain the choices for certain experimental parameters (e.g. electrode placement location), seldom is this the reason for using online or offline methodologies. Frequently, this decision is based on previous studies or the assumption that both online and offline tDCS generally induces effects in the same direction (Nitsche, Schauenburg, Lang, Liebetanz, Exner et al., 2003; Stagg & Nitsche, 2011). However, it has been suspected that stimulation effects may be interfered with if an irrelevant activity is undertaken during, or directly after, stimulation (Horvath et al., 2014) suggesting that the use of an online or offline procedure may affect different polarity outcomes if an irrelevant task is completed while stimulation is being administered. For example, Nozari et al. (2014) found a facilitatory effect of cathodal stimulation on the Flanker task (post-stimulation) when an unrelated task was performed during stimulation. However, when

participants completed a task posing the same cognitive demands as the Flanker task during stimulation, an inhibitory effect of cathodal stimulation resulted. The reason behind these varying results is still unclear and warrants further exploration, however, these findings should not be overlooked, and every part of the experimental procedure should recorded, including any breaks between tasks.

The effect of tDCS to induce acute neuromodification depends on several important parameters, current density: which determines the induced electrical field strength regarding the electrode area (Purpura and McMurtry, 1965), electrode size, stimulus duration and intensity (Nitsche and Paulus, 2000). Thus, tDCS studies report in the protocols current density, electrode size, and electrode position due to that different current flow direction may results in different effects, stimulus duration and intensity. The effect of the stimulation are increased as the duration and the current strength is increased (Nitsche and Paulus, 2000; Nitsche and Paulus, 2001; Nitsche et al., 2003; Stagg & Nitsche, 2011). During repeated sessions of tDCS, an intersession interval between sessions is added to avoid any unintended carry-over effects. The duration of the interval depends on the stimulation duration. For 4 seconds of stimulation, an interval of 10 seconds is sufficient, for 10 minutes of stimulation, a 1-hour interval between sessions is sufficient, for 1-hour or more of stimulation, an intersession of 48 hours to a week is sufficient (Nitsche et al., 2008).
One of the features of tDCS is it's easier to conduct placebo (sham) stimulation controlled studies. Sham stimulation is a generic term to indicate an inactive form of stimulation (e.g., a very brief or weak one, in some cases no stimulation at all) that is used in research to control for the placebo effect. The subject believes he/she is being stimulated normally, because most subjects feel the itching sensation only initially during tDCS (Siebner et al., 2004) but there should not be any real effects in altering brain functions. A study conducted by Gandiga, Hummel and Cohen (2006) found that ramping up and down for 10 seconds, combined with a 30 second placebo stimulation made real tDCS and the sham stimulation condition indistinguishable. Since stimulators can be programmed to deliver sham protocols, double blind studies are a standard in this field. However, post hoc questioning of subjects is considered important to assess the effectiveness of blinding.
Another feature of tDCS is the ability to achieve cortical changes after stimulation. tDCS in the human motor cortex can be detected for up to 90 minutes post-stimulation (Nitsche and Paulus, 2001). Matsunaga et al., (2004) demonstrated that anodal tDCS over the somatosensory cortex can induced a 60 minute after effect shown by comparing the change in the somatosensory evoked potential (SEP) amplitudes before and after tDCS. The after effects of tDCS depends on the stimulation duration, where at least a 9-13 minutes exposure demonstrated an after-effect (Nitsche

and Paulus, 2000; Nitsche and Paulus, 2001; Nitsche et al., 2003; Ardolino, Bossi, Barbieri and Priori, 2005) and even up to 6-months post-stimulation after multiple consecutive tDCS sessions (Kadosh et al., 2010). The impact of offline stimulation is primarily believed to reflect long-term potentiation- and long-term depression-like shifts at the level of the synapse due to prolonged hyper- and hypo-polarization of membrane potentials during lengthy (>7min) tDCS sessions (Nitsche & Paulus, 2011).

5.1.7 The role of neurotransmitters in tDCS

Neurotransmitters play an important role in the tDCS induced cortical excitability, which resulted in pharmacological studies to be conducted to clarify the molecular and receptor mechanisms of tDCS. In a study conducted by Nitsche et al, (2003) the impact of the sodium channel blocker carbamazepine, the calcium channel blocker flunarizine and the NMDA receptor antagonist dextromethorphan on tDCS induced motor cortical excitability change of healthy human subjects were tested. The results suggest that Carbamazepine and Flunarizine selectively eliminated the excitability enhancement induced by anodal stimulation during and after tDCS. However, the NMDA receptor antagonist dextromethorphan did not alter current-generated excitability changes during a short stimulation, which caused no after-effects, but prevented the induction of long-lasting after-effects. These findings suggest that cortical excitability shifts induced during tDCS depend on membrane polarisation.

Dopaminergic mechanisms take part in NMDA-receptor dependent neuroplasticity, learning and memory processes. The cortical excitability changes induced by tDCS can be altered by blocking D1 and D2-receptors (Nitsche et al., 2006). D2 receptor-antagonist sulpiride abolished the tDCS-induced after effects nearly completely. The co-administration of D1-receptor agonist pergolide and D2- receptor antagonist enhanced and prolonged the tDCS-induced excitability diminution but did not influence the anodal DC-induced neuroplastic changes, suggesting that D2 receptors play a significant role in neuroplastic changes in the human motor cortex compared to that of D1receptors. The results of this study underscore the importance of the dopaminergic system for human neuroplasticity (Nitsche et al., 2006).

In another study, Liebetanz et al., 2002, investigated the combined tDCS of the motor cortex with the application of Na+-channel-blocking carbamazepine (CBZ) and the N-methyl-d-aspartate

(NMDA) -receptor antagonist dextromethorphan (DMO). The results showed that DMO suppressed the post-stimulation effects of both anodal and cathodal DC stimulation suggesting the involvement of NMDA receptors in both types of DC-induced neuroplasticity. On the other hand, CBZ which stabilizes the membrane potential voltage-dependently selectively eliminated anodal effects. It was found that the combined effect of glutamatergic and membrane mechanisms is essential to induce the after-effects of tDCS, and thus, based on these results it was suggested that polarity-driven alterations of resting membrane potentials represent the crucial mechanisms of the DC-induced after-effects leading to alteration of spontaneous discharge and NMDA-receptor activation.

Nitsche et al, 2004 found that the administration of the GABA(A) receptor agonist lorazepam resulted in a delayed, but then enhanced and prolonged anodal tDCS-induced excitability elevation. It was suggested that the absence of the excitability enhancement under lorazepam is caused by a loss of the anodal tDCS-generated intracortical diminution of inhibition and enhancement of facilitation. Nitsche and colleagues (2004) also investigated the impact of D-Cycloserine (CYC) on long-lasting after-effects of transcranial direct current (tDCS)-generated motor cortical excitability shifts. They found that D-CYC selectively potentiated the duration of motor cortical excitability enhancements induced by anodal tDCS. D-CYC alone did not modulate excitability. Table 10 gives a brief overview of the pharmacological approaches to DC stimulation.

Table 10. Pharmacological approaches to DC stimulation

Drugs	Effects	Short-term anodal stimulation	Long-term anodal stimulation	Short-term Cathodal stimulation	Long-term Cathodal stimulation
Carbamazepine	voltage-dependent Na+-channel blocker	-	-	X	X
Flunarazine	Ca++-channel blocker	-	-	X	X
Dextromethorphan	NMDA-receptor antagonist	X	-	X	-
D-cycloserine	NMDA agonist	+	+	X	X
Lorazepam	GABA-A agonist	+	X	X	X
Sulpiride	D2-receptor antagonist	X	-	X	-
Pergolide	D1-receptor agonist	X	X	+	+
Rivastigmine	ACh-estherase inhibitor	-	-	+	+
Amphetamine	increases catecholamine availability	N/E	+	N/E	X

Note: - N/E: not examined, (+): the drug has increased the tDCS-induced effect, (-): the drug has decreased the tDCS-induced effect, (X): no effect.

5.1.8 Safety of tDCS

The risks from tDCS are minimal, the safety of tDCS has been explored by researchers who have suggested that tDCS induces temporary cognitive, mood and/or motor effects with minimal to no negative side effects (Brunoni et al., 2011; Fregni et al., 2006; Gandiga, Hummel, & Cohen, 2006; Nitsche, Liebetanz, et al., 2003). The most common, though rare side effects according to a recent consensus are: headache, dizziness, nausea, itchy sensation as well as irritation under the area of the electrodes (Nitsche et al., 2008). In order to avoid this, special rubber electrodes are placed in sleeves and soaked in a saline solution used as the conducting material or or gel-soaked rubber electrodes. Studies using this technique have not reported problems (Dundas, Thickbroom,

Mastaglia, 2007). Using saline soaked or gel-soaked electrodes also helps electrochemical toxins or toxins caused by electrode dissolution to be kept well away from the patient/participant.

Furthermore, there is a potential for heating effects/burning to occur at the electrode-skin interface. It has been reported in two different tDCS studies (Frank et al., 2010; Palm et al., 2008), which suggested that it has occurred due to using tap water to soak the electrodes rather than saline solution and excessive skin abrasion. In order to avoid this, the widely accepted maximum charge density of 40uC/cm2 is put in place and is not exceeded (Agnew & McCreey, 1987, Nitsche et al., 2003). Following this protocol, it has been found that there is no significant heating effect at the electrode site, as less than 50% of the current is transmitted to the underlying cortex (Nitsche & Paulus, 2000).

Researchers have also suggested ensuring there are no prior skin diseases, cuts or abrasions at the stimulation location prior to stimulation. Mild redness observed under the electrode is not skin damage, but caused by neurally driven vasodilation (Durand, Fromy, Bouye, Saumet and Abraham, 2002). Furthermore, a mild electrical shock has been reported if the current begins or stops suddenly, thus most tDCS devices have a current ramp at the start and the end of each stimulation session. Ramping up and down also prevents dizziness or vertigo occasionally reported after exposure. Although seizures do not appear to be a risk and have not been reported with tDCS, Psychopharmacological agents (including some recreational drugs), lack of sleep, and having a seizure in the past, are factors that can potentially negatively interact with the effects of tDCS (Nitsche et al., 2008).

5.1.9 Autism and tDCS

Casanova et al. (2012) were the first to propose the use of NIBS for ASD patients, based on the possibility that low-frequency repetitive Transcranial Magnetic Stimulation (rTMS) could somehow improve GABAergic neurotransmission. In their study, they used rTMS as a way to improve intracortical inhibition in ASD patients. rTMS was applied once a week over 12 weeks in a group of 25 ASD patients. They reported an increase in gamma activity in the EEG evoked by a visual processing paradigm, with changes in Event Related Potential (ERP), improved error monitoring, and correction function in a visual recognition task after the intervention. Ever since, NIBS techniques, such as rTMS and tDCS, have proven to be effective and safe in treating psychiatric and neurological disorders (Kuo et al. 2014; Lefaucheur et al. 2014). More specifically, NIBS

techniques have been suggested as treatment options for autism (Demirtas-Tatlidede, Vahabzadeh-Hagh, Pascual-Leone, 2013).

The research area of tDCS and ASD is currently limited, however, findings on the relationship between autism and tDCS point to promising possibilities of employing tDCS interventions as a strategy of improving the quality of life of individuals with autism. A number of studies have been undertaken in this area, including Amatachaya et al.'s (2014) research into the effect of anodal tDCS on autistic individuals. The study entailed a double-blind crossover randomised trial involving 20 autism patients who received both sham and anodal tDCS stimulation on the left DLPFC for 20 minutes of five consecutive days. Childhood Autism Rating Scale (CARS), Children's Global Assessment Scale (CGAS), and Autism Treatment Evaluation Checklist (ATEC) sandwiched the tDCS administration. Statistical decrease in CARS and ATEC scores suggest that anodal tDCS over the F3 may be a useful clinical tool in autism. It is important to note that the study had a relatively small sample size and no control group, thus the finding should be interpreted with caution.

In a follow up study, Amatachaya et al. (2015) noted abnormal synaptic connectivity and maturation as being possible autism etiologies, as well as lower alpha activity in autistic children than in normal children. As a result, the researchers investigated the impact of anodal tDCS on peak alpha frequency (PAF) based on ATEC. Using 20 autistic male children randomly assigned to a single session of anodal and sham tDCS stimulation over the DLPFC, the researchers measured pre- to post-session changes in cortical activity impacted by tDCS in PAF and ATEC, as well as pre- and post-session changes in PAF and ATEC. The results indicated that anodal tDCS led to improvements in the social and health/behaviour domains of ATEC, also correlating to significant improvements in PAF on the stimulation site. Overall, these findings demonstrate the need for further research to establish the possibility of employing WM improvement strategies such as tDCS in autism. Again, caution must be taken when interpreting these findings as the study had a relatively small sample size and no control group.

In another study, D`Urso et al. (2015) evaluated the safety, efficacy, and feasibility of inhibitory tDCS for the treatment of behavioural abnormalities of autistic patients. They recruited 12 young adult patients with Autistic Disorder that presented intellectual disability and a majority having a speech impairment. The Aberrant Behavior Checklist (ABC) was administered as the primary outcome measure before and after a 2-week tDCS course entailing 10 daily applications of 20

minute/1.5mA/cathodal over the left DLPFC. Their findings suggest that cathdoal tDCS improved the ABC rating scores for autistic behaviours. There are a number of limitations in this study had that should be considered when interpreting the findings. The study had a very small sample size of twelve patients. Another issue to consider is that patients were undergoing psychopharmacological treatments, which may have had an effect on tDCS giving the potential interaction of tDCS with medications (see section 5.1.7).

In a more recent study, Gómez et al. (2017) wanted to investigate the short-term outcome of NIBS on children with ASD using the total score on the ABC, ATEC, and the ADI. Twenty-four patients with ASD received 20 sessions of NIBS over the left DLPFC. tDCS was used in ASD patients aged <11 years, and rTMS for 11–13-year-olds while having a follow up at one, three, and six months after completing all the sessions of NIBS. They found a significant reduction in the total score on the three clinical scales and was maintained during the first six months after treatment. However, they did not use a placebo stimulation or have a control group for comparison, this warrants caution for any conclusion drawn from these findings. Furthermore, Osório and Brunoni (2019) conducted a systematic review exploring the whether tDCS reduced symptom severity in children and adolescents with ASD. They found preliminary evidence of the potential usefulness of tDCS for treatment of ASD in children and adolescents, suggesting tentative support for reductions in symptom severity and, according to parental reports and clinical observations, improvements in some aspects of language.

While there are some studies exploring the effects of tDCS on individuals with ASD, there is a scarce amount of studies investigating the effects of tDCS on WM in individuals with ASD. Indeed, the study by van Steenburgh, Varvaris, Schretlen, Vannorsdall and Gordon (2017) is currently the only published study examining the effects of tDCS on WM in individuals with ASD. The study entailed single-blind crossover randomized counterbalanced design involving 12 adults with HFA who received left anodal/right cathodal stimulation, right anodal/left cathodal stimulation, or sham stimulation for 40 min at a 1.5 mA intensity on the left and the right dorsolateral prefrontal cortices on three separate days. WM tasks including backward spatial span, backward digit span, spatial *n*-back and letter *n*-back were administered pre and post stimulation. These findings suggest that in adults with HFA, active bifrontal tDCS given during WM tasks improves performance.

Based on the literature, we decided to conduct a phase II clinical trial to evaluate the adverse effects of tDCS in individuals with ASD and TD individuals and investigate whether anodal tDCS lead to

an improvement in working memory scores when administered over the left DLPFC when compared to sham in adults with high functioning autism. Additionally, we also sought to explore whether the observed effect of tDCS over the left DLPFC and working memory scores is dependent on polarity anodal (positive) versus cathodal (negative) stimulation). The trial was set up to compare WM performance on a WM task in individuals with HFA and TD individuals pre, during and post stimulation.

The reason a phase II clinical trial was the appropriate design choice is due to there being only one pervious study looking at tDCS on WM in individuals with ASD, however, it has a very small sample size (12 participants), poor reporting of safety profile and not powered to examine efficacy. A phase II Clinical trial was decided upon due to phase I trials only evaluates safety, determine safe dosage and side effects, which has been researched extensively demonstrating the safety of tDCS (See sections 5.14., 5.1.8 and 5.19). A phase III clinical trial would not be ideal at this stage as it is needed to properly examine efficacy of tDCS on WM in individuals with HFA before an investigation is carried out to confirm the effectiveness, compare it to other treatment options while monitoring side effects in a large scale testing looking at several hundred to several thousand patients.

5.1.10 Study objectives

5.1.10.1 Primary objective

Is to examine the feasibility of a full scale clinical trial on whether anodal tDCS leads to an improvement in WM accuracy scores when administered over the left DLPFC and compared to sham in adults with HFA, while investigating the balance between safety and potential efficacy.

5.1.10.2 Secondary objectives

Are the observed effects of tDCS over the DLPFC and WM scores dependent on polarity anodal (positive) versus cathodal (negative) stimulation?

5.2 Method

5.2.1 Study design

One of the most important things when it comes to tDCS and tDCS research is the design and montage used. Different electrode positions, duration, intensity and ramp up and down, often result in different outcomes and the effectiveness of the technique (Bikson et al., 2010; Moliadze et al., 2010). In order to achieve the best possible design, we referred to the systematic review and meta-analysis of anodal tDCS on WM by Hill, Fitzergald and Hoy (2015) as it provides a more detailed and rigorous examination than other systematic review and meta-analyses in the current literature. Hill, Fitzergald and Hoy (2015) provided a quantitative synthesis of the published literature investigating the effects of anodal tDCS, compared to sham, on WM, as assessed using the n-back, Sternberg and digit-span tasks. They also separated the results from tasks performed 'online' (during stimulation) and 'offline' (following stimulation) and investigated the effects of current density and stimulation duration.

Their findings show that crossover experimental designs were favoured by the majority of studies, which led us to using a crossover design. Moreover, by adopting a crossover design it reduces the influence of confounding covariates due to each crossover patient serving as their own control (Jones and Kenward, 2003). Subsequently, addressing the number of reports of high intra-and inter-individual response to tDCS, indicating that in some people the tDCS can be more effective than in others (Chew, Ho & Loo, 2015; Lopez-Alonso et al., 2014; Wiethoff, Hamada & Rothwell, 2014). Given the relatively small sample size, poor safety reporting and the lack of a priori information on the efficacy for a new treatment in individuals with HFA led us to adopting a phase II randomised clinical trial design to evaluate the efficacy and safety of tDCS on WM in individuals with HFA. Phase II trials are typically small and use targeted samples to obtain additional information regarding effectiveness and safety and randomized controlled trials (RCTs) are the most rigorous and robust research method of determining whether a cause–effect relation exists between an intervention and an outcome (Bhide, Shah, Acharya, 2018).

Moreover, Hill and colleges found no significant results for WM tasks performed online in the healthy cohort, whereas the neuropsychiatric cohort showed no significant improvement in offline

WM performance. Which lead us to adopt an online and offline montage (the electrodes placement, current intensity, duration of stimulation, ramp up and ramp down of the current is referred to as "montage") into our study in order to investigate this further. They also reported that accuracy scores were shown to be significantly improved in the higher current density group ($p = 0.005$), but not the lower current density group ($p = 0.48$); while longer ($p = 0.04$), but not shorter ($p = 0.58$), stimulation durations also led to significantly faster reaction times. This led us to using a 15-minute duration and intensity of 1.5 mA as it was the average of the all the studies that were examined. In terms of electrode placement, they found that the majority of the studies used the left DLPFC as the target site for anodal stimulation while the cathode was placed over the contralateral supraorbital region in all experiments, which we also utilised. Furthermore, we used a 30 second ramp-up and down as it is recommended to prevent electrical transients (Nitsche et al., 2008) and aids in having the sham stimulation indistinguishable from 'active' tDCS (Gandiga, Hummel & Cohen, 2006). Finally, a 48-hour wash-out was implemented as after-effect with 15 minutes of tDCS could last up to 1 hour or more (Nitsche et al., 2008) and to simultaneously "wash-out" the initial practice effect of the WM task (Falleti, Maruff, Collie and Darby, 2006). Moreover, we recruited only right handed males into the current study as research has shown the effects of tDCS could differ according to the handedness of stimulated subjects (Kasuga et al., 2015) and males and females have been reported to preform differently on WM tasks (see Hill, Laird and Robinson, 2014 for review) while taking into consideration a manageable and successful recruitment rate as the ASD male-to-female ratio is 3:1 (see Loomes, Hull and Mandy, 2017 for review). Furthermore, we excluded any individual over the age of 35 as research has demonstrated that WM starts to decline after 35 years of age (Hartshorne and Germine, 2016)

5.2.2 Ethical approval

The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and consistent with the principles of Good Clinical Practice. This study had two ethical approvals, one from the College of Science and Engineering, University of Glasgow obtained on 10th of January 2017 (reference number 300160040) and one from the West of Scotland Research Ethics committee (REC) 3 obtained on the 19th of January 2018 (reference number: 17/WS/0183. Appendix ii). Furthermore, the experiment was preregistered on ClinicalTrials.gov (reference number: NCT03255837).

5.2.3 Sample size

There is only one study investigating the effects of tDCS on WM in individuals with ASD (Van Steerburg et al., 2017). Therefore, there is limited data on which to model a sample size calculation and one output from this phase 2 study will be data that can be used in future sample size calculations for a full scale clinical trial.

The primary analysis will be carried out using a paired-samples t-test on the pre- and post-treatment accuracy scores in the HFA group. Using G power, and assuming a pre-treatment mean (SD) of 8.2 (2.6), a clinically important change of 1.8 units, and a conservative correlation of 0.3 between pre- and post-treatment scores, a total of 25 analysable participants with pre- and post-treatment scores were required. This gives 80% power of finding an effect size of 0.6 at the 5% significance level. To compare WMQ scored between HFA and TD participants an independent sample t-test will be carried out. Assuming an 80% power at the 5% significance level, and on the basis of the mean and standard deviation of previous research (ASD mean 34.5 (22.1) and TD mean 17.8 (11.5); Vallat-Azouvi, Pradat-Diehl and Azouvi, 2012), this gives a total of 19 participants required per group (total 38).

5.2.4 Study Population and recruitment

Recruitment is perhaps the most challenging part of a clinical research study and this phase II study will provide important information about the feasibility of recruiting to a full scale clinical trial. Inadequate recruitment is known to have a significant impact on the scientific and financial viability of RCTs. RCTs are widely accepted as the gold standard for the assessment of the safety and efficacy of healthcare interventions. Successful patient recruitment and retention in clinical trials is known to be one of the most difficult aspects to complete in RCTs (McDonald et al., 2006). It has been reported that difficulties with recruitment can disrupt the timetable for a research project, preoccupy staff, reduce the ability of a therapeutic study to detect treatment differences and, ultimately, result in a trial being abandoned (Ashery & McAuliffe, 1992). Increasing participation in clinical research has become a key area within the National Health Service (NHS) to facilitate evidence-based policy, improve health outcomes and reduce health inequality (Watson and Torgerson, 2006).

There are multiple factors that have shown to influence recruitment rates to RCTs, such as greater age, male gender, non-white race, urban residence, low educational status, unemployed or low occupational status, low family income, smokers, recent illness or poor present health, high use of medical care (Armstrong et al, 1992). There are also reports that locations such as large cities have a factor that influence recruitment, with possible suggestions for lower recruitment rates such as varied ethnic population (individuals who are traditionally more difficult to engage in medical research), higher population mobility (individuals potentially missing invitations or reminders to participate) and more university hospitals (creating *research fatigue* as individuals are repeatedly approached to participate in research) (Gilbert et al., 2012) Additionally, Marcus and Schütz (2005) observed that research volunteers were more extroverted, more open to experience and more narcissistic than non-volunteers, suggesting that personality traits could also be an influence to participation in research.

Adults with ASD can be a 'hard-to reach' population for researchers (Beadle-Brown et al., 2012). Howlin (2005) noted that the unique social-communicative profile associated with the autism spectrum is that some adults with ASD are reluctant to engage with new people and experiences or to disclose personal information that affects their willingness to participate in research. In addition, our study had a stringent inclusion and exclusion criteria, excluding individuals younger than 18 years of age and over the age of 35, who suffered from migraines (research by Sullivan and colleagues, (2014) has shown that the presence of migraines in ASD and sensory hyperactivity in the children are significantly linked), have ever suffered from epilepsy, febrile convulsions in infancy, had recurrent fainting spells or are on medications or psychoactive drugs that can lower seizure threshold (multiple studies have shown that up to 29% of individuals with ASD have epilepsy; Tuchman, Rapin and Shunnar, 1991; McDermott et al., 2005; Amiet et al., 2008; Bolton et al., 2011; Cuccaro et al., 2012; Woolfenden et al., 2012; Viscidi et al., 2013), have a family history of epilepsy (Sundelin et al., 2016 reported that family members of an individuals with epilepsy are also at an increased risk) and suffer from any major mood disorders (research showing that up to 38% of individuals with ASD have a comorbidity of depression and up to 21.4% have a comorbidity of bipolar disorder; Lainhart, 1999; Vannucchi et al., 2014). Therefore, not only did we have to contend with the recruitment issues faced elsewhere, but with additional set of issues associated with our stringent inclusion and exclusion criteria.

After two years (first year without NHS ethics), and contacting 116 individuals with HFA, we were able to recruit 25 participants with HFA into the study (21.55% recruitment rate). Recruitment of

individuals with HFA started in February 2017, an initial planning stage involving co-investigator (CM) identifying potential participants to be recruited to the study. HFA participants were recruited from service users of the Adult Autism Service of NHS Greater Glasgow and Clyde. A total of 25 typically developed controls were recruited from the students of the University of Glasgow and the general population. Eligible individuals meeting the inclusion/exclusion criteria were randomly allocated using a computerised program to allocate randomly participants to which stimulation condition they would receive first (anodal, cathodal, sham). The random allocation sequence and participant enrolment was done by the lead researcher.

Invitation to participate in the study was mailed to a participant by the medical secretary in January 2018. Three hundred and fifty information packs were sent out over three identification rounds. The information packs comprised an invitation to participate in the study, a letter from the potential participant's therapist, psychiatrist or psychologist, a participant information sheet, the WMQ and a FREEPOST envelope. In order to prevent identification of numerous potentially ineligible participants, co-investigator (CM) used the inclusion and exclusion criteria (although final assessment of eligibility into the study was made by the researcher (AH) after informed consent). It was explained to potential participants that on the back of the participant information sheet, a tear off slip was provided in which they could complete, to indicate they were interested in taking part in the study. Potential participants replied to the invitation to the study by FREEPOST using the self-addressed envelope provided, indicating whether they would like to meet the researcher to find out more about the study. If the potential participant was not interested in taking part in the full study, they were invited to complete the WMQ and return in the FREEPOST envelope.

Where an individual was interested in finding out more about a study the chief investigator (AH) then made first contact with the individual arranged to meet with them at a convenient time and location to the individual to discuss the study and answer any questions they had. Participants were invited to identify a place to meet. At the time of the first meeting with the potential participant, the researcher discussed what would be involved in participation in the research study. The researcher also read through the information sheet with the potential participant and the potential participant was invited to ask any questions. When the potential participant was satisfied that all their questions had been adequately answered, they were invited to choose whether or not they would like to participate.

The participant was given every opportunity to clarify points they did not understand and, if necessary ask for more information. The participant was given sufficient time to consider the information sheets provided and if necessary, schedule another meeting. If the individual was willing to participate they provided informed consent. It was emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. On completion of informed consent participants were screened for eligibility. Individuals who chose to take part in the research study were asked to complete a written consent form. The chief investigator and the participant signed and dated the consent form to confirm that consent has been obtained. The participant received one original consent form, the second original was kept with the chief investigator. Only after an individual had consented to participate would screening data be collected.

Typically developed controls were recruited from the students of the University of Glasgow and the general population by adverts detailing the purpose and duration of the experiment. Posters were posted around the university campus and on an online data base hosting psychological experiments. The majority of the typically developed controls had already been recruited through the previous ethics approved by the College of Science and Engineering (reference number 300160040) of the University of Glasgow on the 5th of January 2017, which follows the exact same ethical and experimental protocol.

Eligibility of participants was based on the following inclusion and exclusion criteria

Inclusion criteria*:*

1. Males
2. Aged 18+
3. Clinical diagnosis of ASD (for the HFA group only)
4. Met the ADOS criteria for ASD (for the HFA group only)
5. Right handed
6. Speaks English fluently
7. Normal vision or corrected to normal
8. Passing tDCS safety screening

***Exclusion criteria**:*

1. Participants younger than 18
2. Participants who do not understand verbal or written English (i.e. would be in need of translators)
3. Participants that have ever suffered from epilepsy, febrile convulsions in infancy or had recurrent fainting spells
4. Has a family history of epilepsy
5. Suffer from any major mood disorders
6. Has a Heart pacemaker, Cochlear implant, Medication pump, Surgical clips
7. Drank more than 3 units of alcohol in the last 24 hours
8. Suffered from migraines
9. Metal in the head, implanted brain medical devices.
10. Have undergone a neurosurgical procedure
11. Had more than one cup of coffee, or other sources of caffeine in the last hour
12. Taking any prescribed or over the counter medication that might affect tDCS
13. Medications or psychoactive drugs that can lower seizure threshold [imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, cocaine, (MDMA, ecstasy), phencyclidine (PCP, angel dust), ketamine, gamma-hydroxybutyrate (GHB), alcohol, theophylline].
14. Withdrawal from alcohol, barbiturates, benzodiazepines, meprobamate, chloral hydrate.

5.2.5 Informed consent

The chief investigator (AH) was responsible for ensuring informed consent was obtained before any protocol specific procedures are carried out. A participant information sheet was given to the potential participants were given the opportunity to ask questions and to clarify anything they did not understand. Before informed consent was obtained the decision of an individual to participate in

the research study was based on a clear understanding of what the study was about and what was involved. Participants were also given the opportunity to decline to take part in the research study and it was emphasised that the participant may withdraw their consent at any time and to decline to take part in any particular aspect any time and for any reason, without explaining why, and this will not affect their medical care or legal rights, this was also clearly outlined in the participant information sheet. The process of introducing the study to potential participants and carers took place at the Autism services, and seeking informed consent took place after the researcher and the participant meet the University of Glasgow, Department of Psychology. Ongoing consent was also checked and assessed throughout the study period.

5.2.6 Participants

A random sample of 50 male participants consisting of 25 individuals with HFA and 25 typically developed (TD) individuals, between the ages of 18-35 with a mean age of 24.33 (*SD*=3.80) took part in this study. All self-reported that they had normal or corrected vision, normal colour vision and passed the tDCS safety screening process. Participants gave informed consent as per APA regulations, the faculty of science and engineering at the University of Glasgow and NHS greater Glasgow and Clyde approved the study.

5.2.7 Materials

5.2.7.1 Materials used to screen and examine eligibility of participants

5.2.7.1.1 Autism Quotient (AQ)

The AQ has been cited over 1700 times, and it is used to test for traits of ASD which are said to lie on a continuum within the general population (Frith, 1991; Baron-Cohen, 1995). Therefore, TD participants (N=25) were asked to complete the Autism spectrum quotient (AQ) (Baron-Cohen et al., 2001) to ensure they scored within average scores of TD individuals and did not show any tendencies of autism. The AQ is a self-administered test for measuring the degree to which an adult with normal intelligence has the traits associated with the autistic spectrum. Individuals score in the range of 0-50; it comprises of 50 questions, made up of 10 questions assessing 5 different areas: *social skill; attention switching*; *attention to detail; communication; imagination.* Each item scores 1 point if the respondent records abnormal or autistic-like behaviour either mildly or strongly.

Individuals scoring 0-11 indicate no tendency of autistic traits, scoring 12-21 is the average score of TD individuals, 22-25 indicate slight autistic tendencies, 26-31 gives borderline indications of autism and scoring 32-50 indicates a strong likelihood of autism (Baron-Cohen et al., 2001). All TD participants scored in between 3-21, with a mean of 13.2. Once participants completed the AQ and scored within "no tendencies of autistic traits" and "average scores" (a score of < 22) they were assigned to the TD group, participants that did not meet the AQ cut-off where excluded.

5.2.7.1.2 Autism Diagnostic Observation Schedule - 2 as a measure of diagnostic reliability

One of the most widely used observation instruments for the assessment of autism and considered the "gold standard" of ASD observation instruments is the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, DiLavore, & Risi, 2008). The ADOS has been widely used in research and academic centers for approximately 15 years to classify individuals with an ASD diagnosis for research studies and to assist in making clinical diagnoses. How clinicians experience and view ASD is not established, multiple factors can influence how clinicians view or diagnose a disorder. Personal experience, education, and culture are all factors that may impact a diagnosis. Indeed, research on clinician's opinion on the reliability of psychiatric diagnosis in clinical settings has demonstrated that clinicians are reporting that psychiatric diagnoses are unreliable. When asked for the reasons behind the diagnostic unreliability, the largest component was attributed to clinician factors (63.5%) including clinicians experience, training and school of thought, bias toward certain diagnoses, style of interview, and lack of agreement on definitions of psychiatric symptoms were some of the factors reported (Aboraya, 2007). Therefore, the HFA participants with a clinical diagnosis (N=25) in this study underwent the ADOS to ensure we had a clinical and research reliable standardised test to confirm all of the participants were on the spectrum.

The ADOS is recommended in several Best Practice Guidelines as an appropriate standardized diagnostic observation tool (National Research Council, 2001; Wilkinson, 2016).
The ADOS consists of a series of structured and semi-structured tasks and interview-based questions, generally takes from 40 to 60 minutes to administer. The examiner observes and identifies segments of the subject's behaviour and assigns these to predetermined observational categories. Research-determined cut-offs identify the potential diagnosis of classic autistic disorder or related autism spectrum disorders, allowing a standardized assessment of autistic symptoms.

The ADOS-2 is a revision of the original ADOS and like its predecessor is a semi-structured, standardized observational assessment tool designed to assess autism spectrum disorders in children, adolescents, and adults (Lord, Rutter, DiLavore, Risi, Gotham, & Bishop, 2012). The second edition includes updated protocols, revised algorithms, a new Comparison Score, and a Toddler Module. Administration and coding procedures for the ADOS-2 are functionally the same as those for the ADOS.

In our study Module 4 of the ADOS-2 was used, which is designed for verbally fluent adolescents and adults who have the ability to use complex sentences and talk about things that are not immediately present, include questions about emotions and relationships as well as retelling a story from a book and demonstrating a routine activity. For each task, a hierarchy of "presses" or social structures is provided. Following the administration of the ADOS, behaviours are coded using a 0 to 3-point coding system, with a 0 indicating that the behaviour is appropriate in the way specified in the coding description and a 3 indicating that a behaviour is not appropriate and interferes in some way with the individuals functioning. Some items vary on their scaling, e.g. 0-2 in A5, B1, B2, B6, B8 and 0-3 in A1, A3, A4, A6, A7. Some items have 7, 8 or 9 in their scale, e.g. A2, A9, A10, B3, B10, and E1, however, these scores are converted to 0 during the coding process. A cut-off of 7-9 was used for the total score of communication and social interaction subtotal. All HFA participants scored between 7-9, with a mean of 7.92. Once participants completed the ADOS and scored within "Autism spectrum" (a score of >7 and <9) they were assigned to the HFA group. ADOS classifications are based on specific coded behaviours that are included in a scoring algorithm using the DSM-IV diagnostic criteria, resulting in a Communication score, a Reciprocal Social Interaction score, and a Total score (a sum of the Communication and Reciprocal Social Interactions scores). Algorithm scores are compared with cut-off scores to yield one of three classifications: autism, autism spectrum (ASD), or non-spectrum. ADOS items regarding play and stereotyped behaviours are also coded but are not included in the diagnostic algorithm due to the difficulty in accurately assessing these characteristics in a limited period of time (Lord et al., 2008).

Administering the ADOS-2 as a diagnostic reliability test is vital as establishing and maintaining reliability is crucial to maintaining consistency and comparability across research studies on ASD. Various studies have examined the reliability of the ADOS as it is used in clinical practice. For example, Mazefsky and Oswald (2006) examined the diagnostic utility and discriminative ability of the ADOS using a clinical population of 75 children referred to a specialty diagnostic clinic over a

3-year time span. They reported 77% agreement between ADOS classification and team diagnosis, with most discrepancies being in autism versus ASD. Another study also investigated the diagnostic validity of the ADOS in a clinical sample (Molloy, Murray, Akers, Mitchell, & Manning-Courtney, 2011). ADOS classifications were compared to final diagnoses given to 584 children referred for evaluation for a possible ASD in a children's medical center. Sensitivities were moderate to high on the algorithms, while specificities were substantially lower than reported in the original ADOS validity sample. In a large study conducted by Catherine Lord and colleagues (2012) where they investigated the relationships between behavioural phenotypes and clinical diagnoses of different autism spectrum disorders vary across 12 university-based sites. They found that the scores on standardized measures (ADOS and ADI-R) were similar across sites.

5.2.7.1.3 Working memory questionnaire as a measure of everyday working memory concerns

See chapter 3 for a detailed summary of the WMQ.

5.2.7.1.4 Wechsler Abbreviated Scale of Intelligence as a Measures of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) is an individually administered intelligence test designed for use with individuals aged from 6-89 years. The WASI provides a reliable measure of cognitive ability. The WASI consists of four subtests: Vocabulary, Block Design, Similarities, and Matrix Reasoning. These four subtests compose the Full Scale IQ and yield the Full Scale IQ score. The Vocabulary and Similarities subtests compose the Verbal Scale and yield the Verbal IQ, and the Block Design and Matrix Reasoning subtest compose the Performance Scale and yield the Performance IQ.

The Vocabulary subtest is a 42-item task similar to the Vocabulary subtest of the WISC-III and the WAIS-III, except that the WASI subtest includes low-end picture items. Items 1-4 of the Vocabulary subtest require the examinee to name pictures, which are displayed one at a time. Items 5-42 are orally and visually presented words that the examinee orally defines. Vocabulary is a measure of the individual's expressive vocabulary, verbal knowledge, and fund of information. Additionally, it is a good measure of crystallized intelligence and general intelligence, or g. It also

taps into other cognitive abilities, learning ability and concept and language development (Sattler, 1988).

The Block Design subtest consist of a set of 13 modelled or printed two-dimensional geometric patterns that the examinee replicates with a specified time limit using two-colour cubes. The subtest taps the abilities related to spatial visualization, visual-motor coordination, and abstract conceptualization. It is a measure of perceptual organization and general intelligence.
The Similarities subtest contains 4 picture items (items 1 -4) and 22 Verbal items. For each of items 1-4, the examinee is shown a picture of three common object on the top row and four response options on the bottom row. The examinee responds by pointing to the one response option that is similar to the three target objects. For the verbal item, a Pair of words is presented orally, and the examinee explains the similarity between the common objects or concepts that the two words represent. Similarities is a measure of verbal concept formation, abstract verbal reasoning ability and general intellectual ability

The Matrix Reasoning subtest consist of a series of 35 incomplete gridded patterns that the examinee completes by pointing to or stating the number of the correct response from five possible choices. Matrix Reasoning is a measure of nonverbal fluid reasoning and general intellectual ability. The WASI has proven to be an effective and reliable measure of IQ, the basis of its validity and reliability can be found in research, such as the study conducted by Hays, Reas and Shaw (2002) where the WASI appeared to be a valid screening measure of verbal, performance, and general intellectual ability for use with an inpatient psychiatric population, in addition to the study by Canivez et al. (2009) that demonstrated meaningful convergent validity coefficients and a latent factor structure consistent with the theoretical intellectual models the test was constructed to reflect. However, there are studies that suggested caution in the use of the WASI as it does not accurately estimates individuals IQ (Axelrod, 2002; McCrimmon and Smith, 2013), nonetheless, it was our decision to use the WASI due to the factor of it not having a working memory component, following on the note made by Poirier and colleagues (2011) that when participant groups are matched on verbal IQ as measured by the Wechsler scales, group differences on WM tasks may be underestimated due to the test on which participants are matched including a sub-test of short-term/working memory. Additionally, the WASI is generally accepted to be reliable for group comparisons.

5.2.7.2 Materials used during experimental procedure

5.2.7.2.1 Direct current stimulation

A direct current was delivered to the head by a battery-driven, constant current stimulator (NeuroConn GmbH, Germany) and transferred by a pair of electrodes (35 cm2) coated in conductive paste. To stimulate the DLPFC, the anode electrode was placed over F3 and the cathode electrode was placed over the contralateral supraorbital area (Fp2) in accord to the 10/20 international EEG system which has been confirmed as a relatively accurate method of localization by neuro-navigation techniques (Herwig et al. 2003). Similar montages have been used in previous studies assessing the role of the DLPFC in WM (e.g., Rossi et al. 2001; Fregni et al., 2005; Boggio et al., 2006; Ohn et al., 2008; Jo et al., 2009; Andrews et al., 2011).

All three protocols began and ended with a 30s ramp-up period. A constant current of 1.5 mA intensity was applied for 15 min during anodal and cathodal stimulation. For sham stimulation, the electrodes were placed in the same positions during the anodal and cathodal stimulation but was counterbalanced between participants and the current was maintained at 1.5 mA for 30s in the Sham protocol before being ramped-down, which has previously been reported as being perceptually indistinguishable from 'active' tDCS (Gandiga, Hummel & Cohen, 2006). Therefore, the subjects felt the initial itching sensation in the beginning but received no current for the rest of the stimulation period. This procedure allowed to blind subjects for the respective stimulation condition (Nitsche et al. 2003). This method of sham stimulation has also been used in other tDCS studies (Baggio et al. 2005; Siebner et al. 2004; Fregni et al. 2006).

5.2.8 Procedure

5.2.8.1 Initial phase before experimental procedure

This study was designed as a single-blind, counterbalanced, randomised, crossover experiment. The study took place at the University of Glasgow in Scotland, United Kingdom, from February 2016 to December 2018. Participants underwent three experimental conditions anodal, cathodal and sham stimulation. All participants completed the Wechsler Abbreviated Scale of Intelligence (WASI) and the WMQ (Vallat-Azouvi, Pradat-Diehl and Azouvi, 2012). ASD participants that did not pass the tDCS screening were invited to complete the WMQ only. Additionally, TD participants completed

the Autism Spectrum Quotient (AQ), participants were informed that the AQ is not a diagnostic tool for ASD. Individuals with HFA underwent the ADOS, the ADOS was administered on the ASD participant for research reliability on their existing diagnosis.

5.2.8.2 Experimental procedure

One session involved anodal stimulation over the DLPFC (F3) with the cathode placed over the contralateral supraorbital area. The next session involved the same protocol but the cathode electrode was placed over the DLPFC and the anode over the contralateral supraorbital area. The third and final session involved sham stimulation where the current was 'ramped-up' for 30 seconds and then ramped down to 0 milliamps over 30 seconds. All participants performed a practice 3-back working memory task until they felt they understood the task and were comfortable with it, participants were seated approximately 70 cm from the monitor, with easy access to the keyboard. Following the practice run, Participants performed the 3-back working memory task pre, during and post stimulation; tDCS was then applied at a current of 1.5 milliamps for 15 minutes. To avoid carryover effects, the order of stimulation was fully counterbalanced across subjects. In addition, each condition was separated by at least 48 hours to washout the effects of the previous run. To test whether the effects of tDCS on DLPFC is dependent on polarity (anodal versus cathodal stimulation), the same experimental design as in the main experiment was utilised, however, with inverted electrode polarity. All equipment were CE marked and being used for their intended purposes. The order of these three conditions was randomised and counterbalanced across participants (Fig 13). After the electrodes were removed, a questionnaire documented the presence and severity of 5 sensory experiences during the session (headache, tingling, itching, burning, pain. Score 1 = 'Not experienced at all', 5 = 'Experienced very strongly' (modified from Brunoni et al., 2011). Participants were invited to guess which of the 3 days had involved Sham tDCS at the end of their final session. The researcher (AH) placed electrodes on participant's scalp surface as part of the tDCS montage. The location of electrode placement followed the EEG 10/20 system for locating areas of the brain for stimulation; standard operating procedures followed.

5.2.8.3 Consent, debriefing and end of study procedure

The researcher met the participant and took them to a dedicated tDCS laboratory where the experiment took place. The researcher (AH) explained exactly what would happen during the stimulation and went through the tDCS safety questionnaire with them. If they were happy to

continue they were asked to sign a consent form. The study took 2.3 hours to complete, after which participants were given a debriefing about the study along with a debrief form (Fig 14 shows full study flow chart). Once the study completed, participants were compensated for their time (£25 amazon voucher) and asked if they would like to be contacted again for future studies. The participants that agreed and declare interest to have their personal information stored for future research purposes had their personal contact details with the CI, which stored their information on a database that can only be accessed by a username and password. Participants were informed that this is entirely voluntary and they can refuse without it effecting their compensation for completing the study.

Figure 13. Schematic diagram of the experimental procedure. Each participant took part in all three conditions (anodal/cathodal/sham stimulation). The three conditions were randomised and the order was counterbalanced across participants and testing days (48 h between each session). During each trial, 30 letters were presented (500 ms/letter), followed by a delay (1000 ms). Participants judged whether the letter appeared 3 steps back.

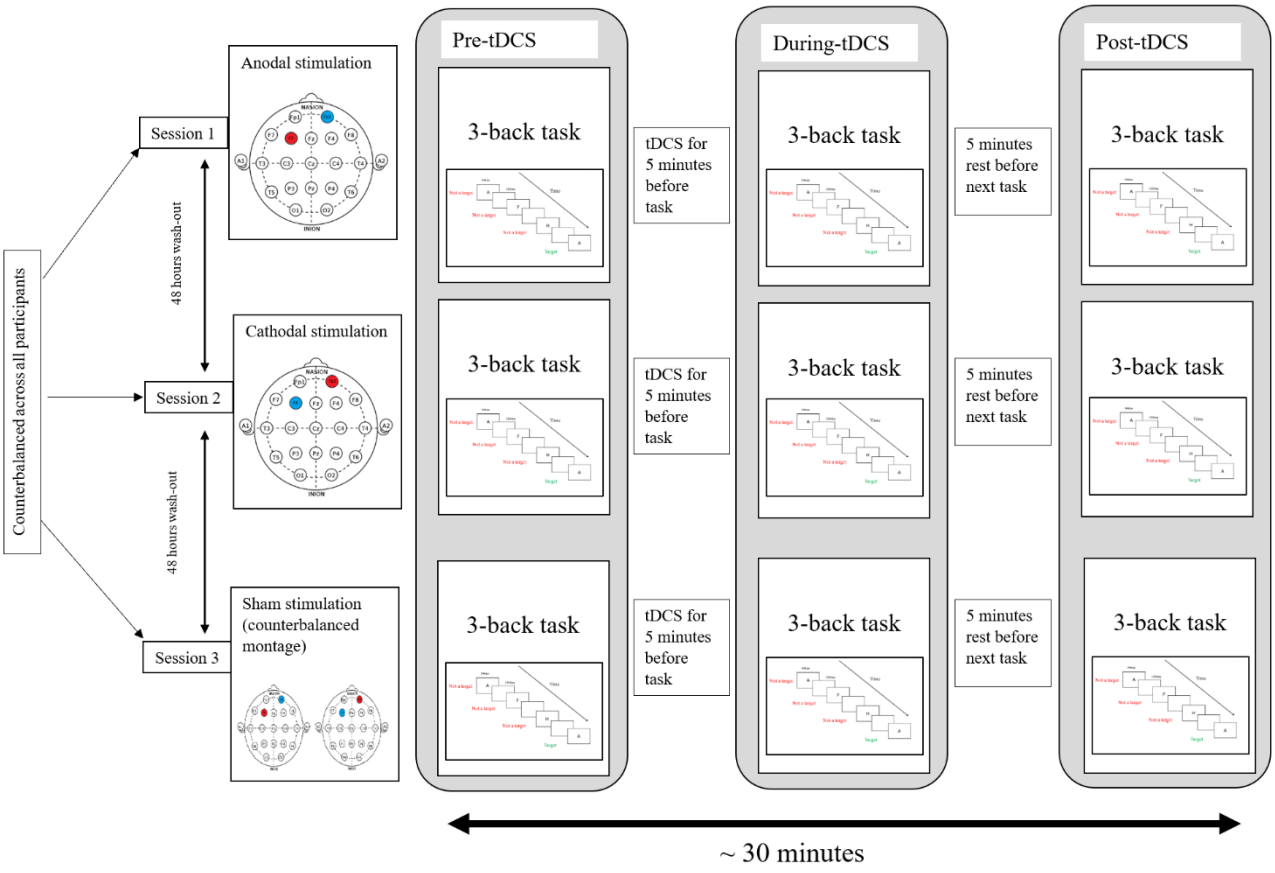


Figure 14. Study flow chart

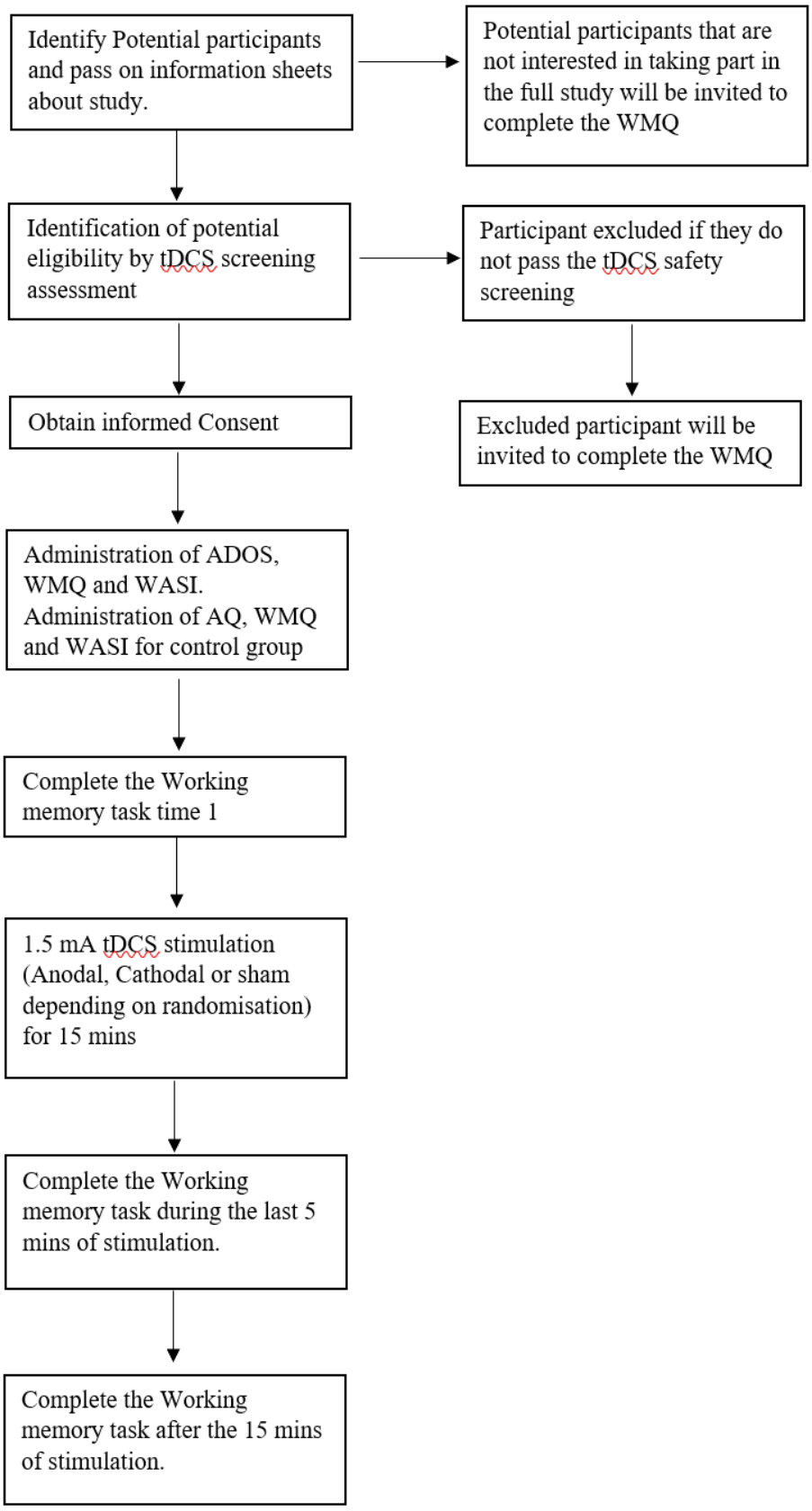
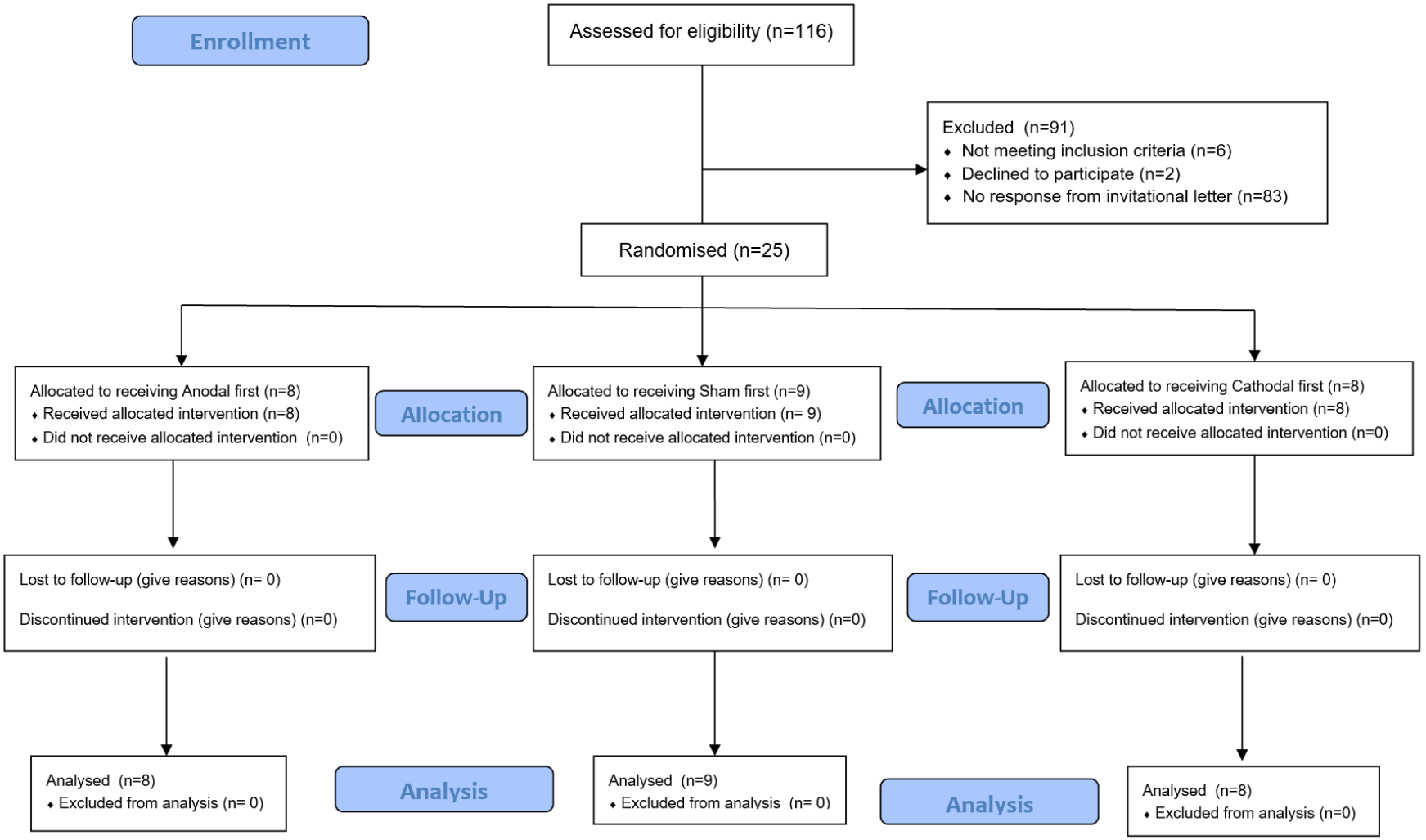


Figure 15. Consort flow diagram



5.2.9 Study outcomes

5.2.9.1 Primary outcomes

In order to test efficacy of tDCS on WM a 3-back task was utilized. Kirchner (1958) initially introduced the N-back task as a visual and spatial task with four load factors ('0-back' to"3-back") and Mackworth (1959) as a visual letter task with up to six load factors. In 1990 Gevins and colleges introduced the N-back to the field of neuroscience by using it as a ‘‘visuomotor memory task’’. N-back tasks are considered to be the gold standard for assessing WM capacity in cognitive psychology (Conway et al., 2005). The task involves multiple processes, such as the encoding of the incoming stimuli, the monitoring, maintenance, and updating of the material, as well as matching the current stimulus to the one that occurred N positions back in the sequence. Different cognitive processes have been reported to be involved during N-back task such as decision, selection, inhibition, and interference resolution (for a comprehensive task analysis, see Jonides et al., 1997, p. 471). The sequential nature of the task requires the simultaneous execution of all these processes, in particular the simultaneous storage and processing of the material, which leads to the classification of the N-back task as a WM measure (Jonides et al., 1997; Kane & Engle, 2002).

In N-back tasks, participants are presented with a continuous string of letters or images and are instructed to judge whether the item they are currently seeing matches a previous one that was presented N-items previously (e.g., Jonides et al., 1997; Gevins and Smith, 2000; Krause et al., 2000; Owen et al., 2005; Pesonen et al., 2007; Palomäki et al., 2012; Scharinger et al., 2015). Therefore, by increasing the N, the task becomes increasingly demanding on the WM. During a 1-back task, participants have to continuously update the stimuli maintained in WM and in the 2-back and 3-back, participants must shift the attention between stimuli for comparison and inhibit stimuli no longer needed to be maintained in WM as well as incorrect response trends for stimuli in the wrong sequence position. (Jonides et al., 1997; Chen et al., 2008).

Studies investigating the reliability of N-back performance have produced varying results ranging between r.02 and r.91, and in general, only higher task levels (2- and 3-back) seem to result in reliability estimates exceeding .80, presumably because of issues with ceiling performance in the lower levels (Friedman et al., 2006; Friedman et al., 2008; Hockey &

Geffen, 2004; Kane et al., 2007; Oberauer, 2005; Salthouse, Atkinson, & Berish, 2003; Shamosh et al., 2008; Shelton, Elliott, Hill, Calamia, & Gouvier, 2009; Van Leeuwen, Ven den Berg, Hoekstra, & Boomsma, 2007). Moreover, Jaeggi and colleagues (2010) investigated the reliability of performance on auditory and visual N-back tasks in three different samples. Reliability coefficients ranged from .09 to .08 in the two-back condition and .39 to .60 in the 3-back conditions.

In regard to construct validity, there are some studies that have correlated the N-back task with other measures of WM. What is noteworthy here is that these studies used a single measure of WM capacity such as a reading span task or an operation span task that reports rather weak intercorrelations, ranging between r=10 and r=24 (Colom, Abad, Quiroga, Shih, & Flores-Mendoza, 2008; Kane et al., 2007; Oberauer, 2005; Roberts & Gibson, 2002). Additionally, Shamosh et al. (2008) obtained a correlation with a 3-back task of r=55 by using a composite score of four complex span measures (operation span, reading span, symmetry span, and rotation span). For all these reasons, we decided to use a 3-back task as the measure of WM in our study.

In a 3-back WM task, the participant must perform multiple cognitive operations, including encoding of new stimuli, update and maintenance of past stimuli, and recognition and response of whether each new stimulus matches the 3-back stimulus. To evaluate changes in WM before, during and after tDCS, the chief investigator used the three-back letter WM similar to the one previously described (Baggio et al. 2005; Ohn et al. 2007). Participants were presented with a random set of ten letters (A-Z). The stimuli were generated using the Eprime v2.0 software (Schneider, W., Eschman, A., and Zuccolotto, A. (2012). Each letter was displayed on computer monitor for 30 milliseconds (ms). A different letter was displayed every 2 s. Black letters were presented on a white background and subtended 2.4 cm (when viewed at 50 cm and a 2.75 ° visual angle). Participants were required to respond (key press 1) if the presented letter was the same as the letter presented three stimuli previously (a target). If it was not a target, participants were required to respond by pressing the number 2 (not a target) (Fig. 12). In this test, a total of 30 correct responses were possible. Participants performed the task 3 times so a more reliable and accurate score was obtained. Accuracy (number of correct responses), error rate (number of incorrect responses), and reaction time (interval between target presentation and pressing 1 or 2) were determined.

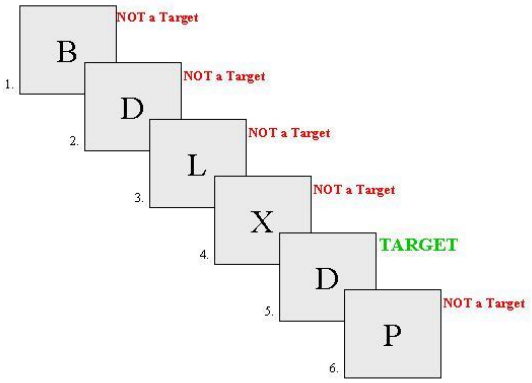


Figure 12. The sequence of the 3-back letter working memory task.

5.2.9.2 Safety outcome

To test safety and adverse effects of tDCS in individuals with HFA, a safety questionnaire was given to participants documenting the presence and severity of 5 sensory experiences during the session (headache, tingling, itching, burning, pain. Score 1 = 'Not experienced at all', 5 = 'Experienced very strongly' (modified from Brunoni et al., 2011). At the final session, participants were invited to guess which of the 3 days had involved Sham tDCS at the end of their final session.

5.2.10 Efficacy determinations

To determine the feasibility of a full-scale clinical trial efficacy of tDCS on WM in individuals with HFA was investigated. Accuracy, error rate and reaction time were evaluated before, during and after stimulation using a 3-back task. Improvement in performance was defined as a statistically significant increase in WM scores during or post anodal stimulation

from baseline, first time of preforming the 3-back task during anodal stimulation and any time participants/patients preformed the 3-back during cathodal and sham stimulation.

5.2.11 Safety Outcomes

In keeping with the overall objective of investigating the feasibility of a full scale clinical trial, determining the safety of tDCS is vital. Adverse side effects were evaluated after each stimulation session. tDCS was considered safe if 1) the participant/patient did not verbally report any discomfort or request for the stimulation to end at any point during the session or experiment, 2) no report of any adverse side effect from the participant/patient after each session and 3) no physical signs of heating effects/burning, irritation, or skin abrasion.

5.2.12 Statistics and data analysis

5.2.12.1 Primary efficacy analysis

Difference (pre-post) in accuracy scores with active anodal stimulation for HFA and TD group.

5.2.12.2 Secondary efficacy analysis

Difference in post-stimulation accuracy scores between sham and active groups for HFA and TD group.
Difference in post- stimulation accuracy scores between anodal and cathodal stimulation for HFA and TD group.
Difference in pre – stimulation, during- stimulation and post- stimulation accuracy scores for anodal, cathodal and sham stimulation for HFA and TD group.
Difference in WMQ scored between ASD and TD
Additionally, as tertiary analyses, ASD baseline and post stimulation scores will be compared to TD baseline and post stimulation scores.

5.2.12.3 Statistical analysis

The primary outcomes of this study were accuracy, error rate, and reaction time pre, during, and post stimulation. Accuracy (Ohn et al., 2008; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011), error rate (Fregni et al., 2005) and RT (Hoy et al., 2013; Teo, Hoy, Daskalakis, & Fitzgerald, 2011) are common measures of WM performance. Each session data was merged together with similar sessions (e.g. all of session 1 merged together) using Emerge, once the data was merged it was extracted and exported into SPSS. Analyses were performed using SPSS version 24 statistical software (Chicago, Illinois, USA). The differences between WM performances between each tDCS stimulation were analysed by paired sample t-tests. Effect sizes were calculated (using means, standard deviations and sample sizes) and expressed as Cohen's d (Cohen, 2013). Effect sizes were interpreted as small (d = 0.20), moderate (d = 0.50) and large (d = 0.80). Data were reported as means and standard deviations, and significance was accepted at $P < 0.05$. An ANOVA was conducted to check for stimulation effects and order effects. Descriptive statistics were used for participant demographics and all outcome measures. Reaction times (RT) below 100 and greater than 1500 ms were excluded from the analysis, RT less than 100 are considered anticipatory reactions and RT greater than 1500 were considered too slow for an accurate response. All trials that were inside this range were included in the analysis. Independent sample t-tests were conducted to compare both groups' baseline and post anodal stimulation performance on the task and compare the change in score from baseline to post stimulation. Moreover, Pearson correlation was performed to investigate if there was any relationship between WM scores at baseline and demographic variables (IQ, age, AQ and scores on the WMQ). An independent sample t-test was conducted to compare both groups' baseline and post anodal stimulation performance on the task and comparison of the change in score from baseline to post stimulation. Finally, a Wilcoxon signed-rank test and a Mann-Whitney U test were conducted to assess the degree to which sensory side-effects (tingling, itching, burning, headache and pain) were reported between each of the three stimulation conditions and compared the reported sensory side-effects between the two groups.

5.3 Results

The aims of this phase II study were;

1. Is to examine the feasibility of a full scale clinical trial on whether anodal tDCS leads to an improvement in WM accuracy scores when administered over the left DLPFC and compared to sham in adults with HFA, while investigating the balance between safety and potential efficacy.
2. To investigate if the observed effect of tDCS over the left DLPFC and working memory scores are dependent on polarity, anodal (positive) versus cathodal (negative) stimulation).

All participants that took part in the study attended and completed all three sessions of the experiment. No participant from either of the two groups withdrew from taking part or dropped out of the study. Overall adherence to the study was 100% in both groups. All the participants tolerated the experiment well and there was no complaint of pain or any uncomfortable symptoms during the stimulation. All participants confirmed, when explicitly asked, that they could not feel the difference between active and sham stimulation.

5.3.1 Participant characteristics

50 adults, 25 with HFA (Mean age: 25.81, range 18-35) and 25 TD (Mean age: 25.36, range 18-35) were randomised in to the study. All participants had an IQ score above 74, showing that the individuals with HFA are indeed highly functioning, and that there was no intellectual weakness in either of the groups. Participants were demographically comparable in terms of age ($t=0.322$, $df=49$, $p=0.75$) and IQ ($t=2.01$, $df=49$, $p=0.50$; see Table 11). However, WMQ scores was significantly higher in the HFA ($M= 53$, $SD= 20.85$) group compared to the TD ($M= 16.52$, $SD=8.75$) group ($t=8.1$, $df=49$, $p<0.001$, $d=2.31$) demonstrating that individuals with HFA are reporting greater everyday life problems related to deficits of WM compared to the TD group.

Table 11. Participant Characteristics and *P*-Values for Between-Group Comparisons

	HFA	TD	P-value
N	25	25	-
Age	25.81 (5.1)	25.36 (4.9)	0.749
IQ	109.19 (14.56)	115.96 (8.57)	0.50
WMQ	53 (20.85)	16.52 (8.75)	<0.0001
ADOS	7.92	-	-
AQ 50	-	13.84	-

HFA, high-functioning autism; TD, typically developed; IQ, intelligence quotient; WMQ, working memory questionnaire; ADOS, Autism Diagnostic Observation Schedule; AQ, Autism Quotient.

5.3.2 Working memory performance

One focus of the phase II study was to get an indication of the potential efficacy of tDCS on WM on individuals with HFA. Effects of tDCS on measures of accuracy, error rate, and RT were compared between the 3-back task separately for each session (session 1, session 2 and session 3) and each stimulation condition (anodal, cathodal and sham) using a paired sample t-test. Scores were also compared between pre, during, and post stimulation. We also compared baseline (the first time the performed the task regardless of stimulation condition) performance to post anodal stimulation to examine if there was an overall improvement in WM performance.

5.3.2.1 HFA group accuracy on task

There was no significant difference in accuracy identifying the target between the three stimulation conditions pre-stimulation ($p>0.05$). During stimulation, there was no statistical significant difference in accuracy between sham and cathodal ($p>0.05$). However, there was greater accuracy in anodal when compared to sham ($t=3.32$, $df=24$, $p=0.03$, $d=0.66$) and greater accuracy in anodal when compared to cathodal stimulation ($t=3.34$, $df=24$, $p=0.03$, $d= 0.67$). As predicted, HFA participants had significantly greater accuracy in identifying the target post anodal stimulation when compared to post sham stimulation ($t=3.64$, $df=24$, $p=0.001$, $d= 0.73$) and post cathodal stimulation ($t=3.99$, $df=24$, $p=0.001$, $d= 0.80$). There was no significant difference in scores between sham and cathodal stimulation ($p>0.05$) (Fig. 15). In order to test if the order effect was significant, a two-way ANOVA (stimulation type

versus order) was performed. This analysis revealed that there was no order effect (F=1.75, df=2,14, p=0.21), but only a stimulation effect (F=10.31, df=2,48; p<0.0001). This finding confirmed that the order of stimulation did not influence our results.

Within stimulation comparison showed that there was no significant difference between pre, during and post sham and cathodal stimulation (p>0.05). There was a significant difference between pre-anodal and during anodal stimulation (t=4.47, df=24, p<0.0001, d=0.89), pre anodal and post anodal (t=5.40, df=24, p<0.0001, d=1.1), and during and post anodal stimulation (t=3.28, df=24, p=0.003, d= 0.66). More importantly, the results demonstrate significantly greater scores in accuracy during anodal stimulation (t=2.67, df=24, p=0.013, d= 0.53) and post anodal stimulation compared to baseline (t=3.63, df=24, p=0.001, d= 0.73). The mean number of correct responses was 4.96 (1.83 SD) baseline, 5.35 (1.94 SD) post sham stimulation and 5.22 (2.29 SD) post cathodal stimulation, whereas the mean number of correct responses post anodal stimulation was 6.86 (1.59 SD). The mean difference between sham and anodal stimulation was 1.51, 1.64 between cathodal and anodal and 1.9 between baseline and post anodal stimulation.

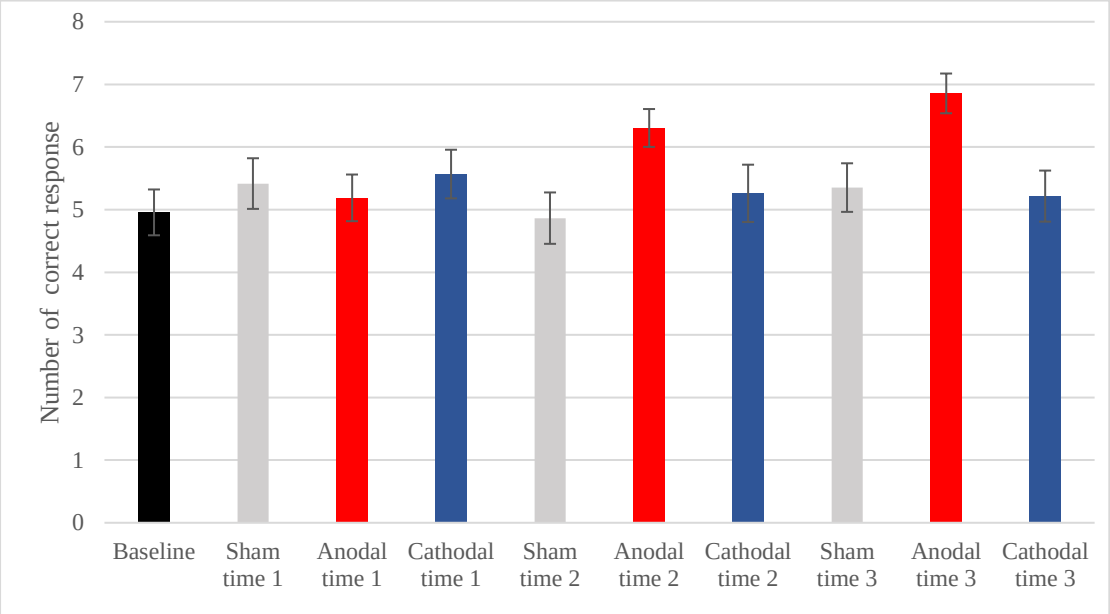


Figure 15 Number of correct responses of ASD group in identifying the target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the mean number of correct responses between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.2 *HFA group accuracy on task (no-target)*

Accuracy on the ability to identify the letter presented was not a target was also investigated. There was no significant difference in accuracy identifying the non-target between the three stimulation conditions at pre-stimulation ($p>0.05$). There was also no statistically significant difference in accuracy between sham and cathodal during stimulation ($p>0.05$). However, there was greater accuracy in anodal when compared to sham stimulation ($t=3.20$, $df=24$, $p=0.004$, $d= 0.64$) and anodal and cathodal stimulation ($t=3.35$, $df=24$, $p=0.003$, $d= 0.67$). The analysis revealed that participants had significantly greater accuracy in identifying the non-target post anodal stimulation when compared to post sham stimulation ($t=4.50$, $df=24$, $p<0.0001$, $d=0.90$) and post cathodal stimulation ($t=5.76$, $df=24$, $p<0.0001$, $d= 1.15$). There was no significant difference in scores between sham and cathodal stimulation ($p>0.05$) (Fig. 16). A two-way ANOVA was performed to test if there was an order effect. This analysis revealed that there was no order effect ($F=0.98$, $df=2,14$, $p=0.399$), but only a stimulation effect ($F=15.88$, $df=2,48$, $p<0.0001$).

Moreover, within stimulation comparison showed that there was no significant difference between pre, during and post sham and cathodal stimulation in identifying the non-target ($p>0.05$). Additionally, there was no significant difference between pre-anodal and during anodal stimulation ($p=0.105$), however, there was a significant greater accuracy between pre anodal and post anodal ($t=5.40$, $df=24$, $p<0.0001$, $d= 1.1$), and during and post anodal stimulation ($t=6.00$, $df=24$, $p<0.0001$, $d= 1.2$). The results also demonstrate significantly greater scores in accuracy during stimulation ($t=8.13$, $df=24$, $p<0.0001$, $d= 1.62$) and at post anodal stimulation compared to baseline ($t=9.84$, $df=24$, $p<0.0001$, $d= 1.97$). These results are presented in Table 12.

The mean number of correct responses was 10.52 (3.2 SD) baseline, 13.62 (3.97 SD) post sham stimulation and 13.87 (3.20SD) post cathodal stimulation, whereas the mean number of correct answers post anodal stimulation was 17.5 (1.46 SD), and the mean difference between sham and anodal stimulation was 3.88, 3.63 between cathodal and anodal and 6.98 between baseline and post anodal stimulation.

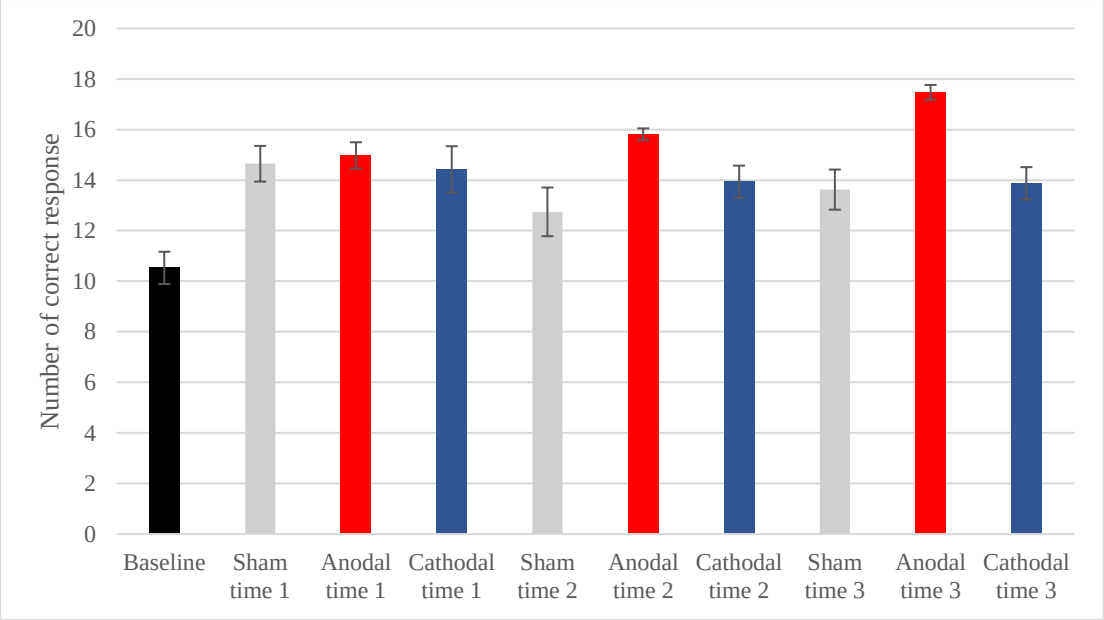


Figure 16 Number of correct responses of ASD group in identifying the letter was not a target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the mean number of correct responses between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.3 HFA group Error rate on task

Participants could make two types of errors when performing the 3-back task.
They can either omit the correct response or at the wrong time press the response key. We used only this last variable—designated as false alarms—to compute total errors as omissions are implicitly analysed under correct responses.

There was no significant difference in errors made between the three stimulation conditions at pre-stimulation ($p>0.05$). During stimulation, there was no statistically significant difference in errors made between sham and cathodal ($p>0.05$). However, there was a statistically fewer errors made in anodal when compared to sham stimulation ($t=3.19$, $df=24$, $p=0.004$, $d=0.64$) and anodal when compared to cathodal stimulation ($t=2.93$, $df=24$, $p=0.007$, $d=0.59$). Moreover, the analysis demonstrated that HFA participants had significantly fewer errors during post anodal stimulation when compared to post sham stimulation ($t=3.65$, $df=24$, $p=0.001$, $d=0.73$) and cathodal stimulation ($t=4.56$, $df=24$, $p<0.0001$, $d=0.91$) (Fig. 17). However, there was no significant difference in scores between sham and cathodal stimulation ($p>0.05$). As done previously, a two-way ANOVA was

performed in order to test if the order effect was significant. The findings show that there was no order effect ($F=1.91$, $df=2,14$, $p=0.184$), but only a stimulation effect ($F=9.68$, $df=2,48$; $p<0.0001$). Following our previous finding, this finding confirmed that the order of stimulation did not influence our results.

Within stimulation comparison showed that there was no significant difference between pre, during and post sham and cathodal stimulation ($p>0.05$). However, there was a significant difference between pre-anodal and during anodal stimulation ($t=5.55$, $df=24$, $p<0.0001$, $d=1.11$), pre anodal and post anodal ($t=6.01$, $df=24$, $p<0.0001$, $d=1.20$), and during and post anodal stimulation ($t=2.18$, $df=24$, $p=0.039$, $d=0.44$). There was also significantly less errors made during anodal stimulation ($t=3.38$, $df=24$, $p=0.002$, $d=0.68$) and post anodal stimulation when compared to baseline ($t=4.68$, $df=24$, $p<0.0001$, $d=0.94$). These results are presented in Table 12.

The mean number of errors made was 19.92 (7.26 SD) at baseline, 18.72 (7.64 SD) post sham stimulation and 19.56 (8.66 SD) post cathodal stimulation, whereas the mean number of errors made post anodal stimulation was 13.52 (6.2 SD). The mean difference between sham and anodal stimulation was 5.2, 6.04 between cathodal and anodal and 6.4 was the mean difference between baseline and post anodal stimulation.

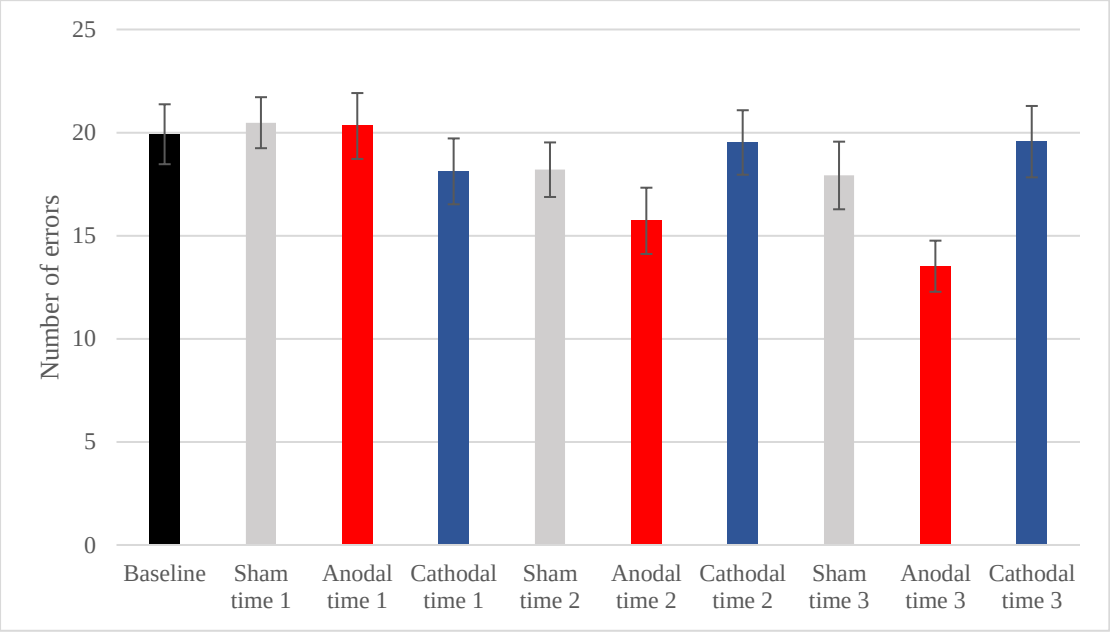


Figure 17 Number of errors of ASD group in identifying the target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the mean number of errors between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.4 HFA group Error rate on task (no-target)

Errors made on identifying letters presented were not a target was also investigated. There was no significant difference in error rate between the three stimulation conditions at pre-stimulation ($p>0.05$). During stimulation, there was also no statistically significant difference in accuracy between sham and cathodal ($p>0.05$). However, there was a significantly fewer errors made in anodal when compared to sham stimulation ($t=2.66$, $df=24$, $p=0.014$, $d=0.53$) and in anodal when compared to cathodal stimulation ($t=3.99$, $df=24$, $p=0.001$, $d=0.80$). Moreover, the analysis showed that HFA participants had significantly fewer errors in post anodal stimulation when compared to post sham stimulation ($t=4.10$, $df=24$, $p<0.0001$, $d=0.81$) and cathodal stimulation ($t=6.30$, $df=24$, $p<0.0001$, $d=1.26$) (Fig. 18). There was no significant difference in scores between sham and cathodal stimulation ($p>0.05$). As done previously, a two-way ANOVA was performed in order to test if the order effect was significant. The findings show that there was no order effect ($F=0.79$, $df=24,14$, $p=0.472$), but only a stimulation effect ($F=13.96$, $df=24,48$; $p<0.0001$).

Within stimulation comparison showed that there was no significant difference between pre, during and post sham and cathodal stimulation ($p>0.05$). However, there was also a significant difference between pre-anodal and during anodal stimulation ($t=3.12$, $df=24$, $p=0.005$, $d=0.62$), pre anodal and post anodal ($t=5.39$, $df=24$, $p<0.0001$, $d=1.08$), and during and post anodal stimulation ($t=3.32$, $df=24$, $p=0.003$, $d=0.66$). Consistent with our previous finding, there was significantly fewer errors made during anodal stimulation ($t=2.47$, $df=24$, $p=0.021$, $d=0.49$) and post anodal stimulation compared to baseline ($t=4.15$, $df=24$, $p<0.0001$, $d=0.83$). These results are presented in Table 12.

The mean number of errors made was 23.4 (12.25 SD) at baseline, 25.28 (15.37 SD) post sham stimulation and 23.72 (9.79 SD) post cathodal stimulation. Whereas the mean number of errors made post anodal stimulation was 15.32 (7.90 SD). The mean difference between sham and anodal stimulation was 9.96, 8.4 between cathodal and anodal and 8.08 was the mean difference between baseline and post anodal stimulation.

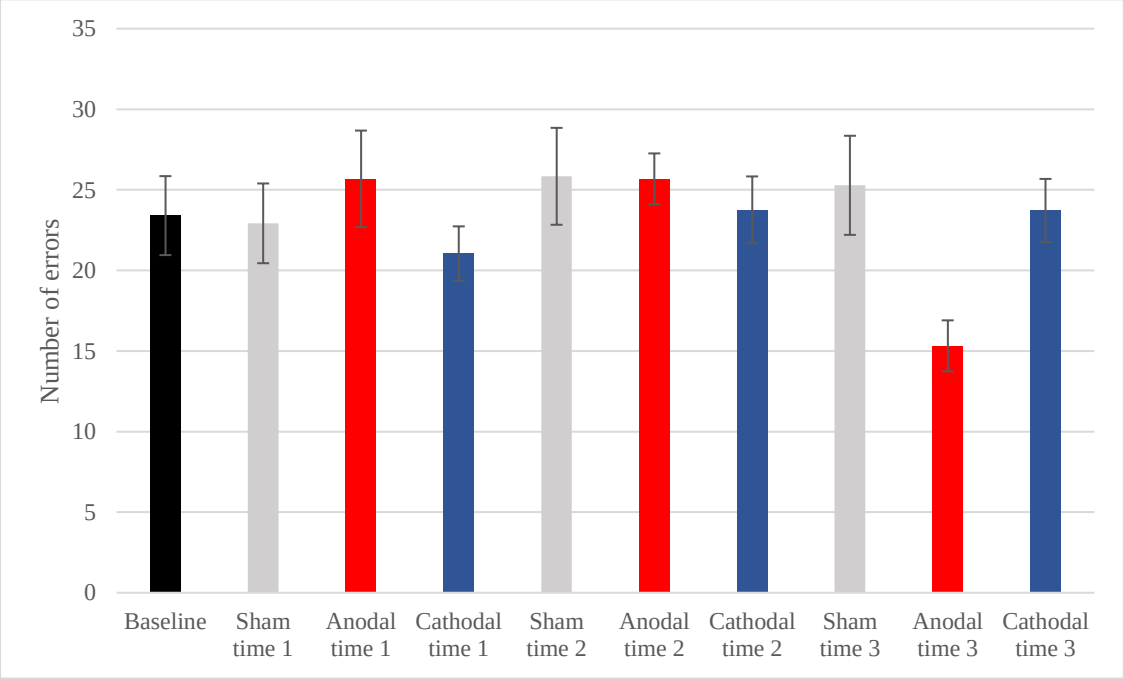


Figure 18 Number of errors of ASD group in identifying the letter was not a target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the mean number of errors between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.5 HFA group reaction time on task

There was no significant difference in RT between the three stimulation conditions at pre-stimulation ($p>0.05$). During stimulation, there was no significant difference in RT between sham and cathodal ($p>0.05$). However, there was a significantly faster RT in anodal when compared to sham stimulation ($t=3.17$, $df=24$, $p=0.004$, $d=0.63$) and in anodal when compared to cathodal stimulation ($t=3.38$, $df=24$, $p=0.002$, $d=0.68$). Moreover, HFA participants had significantly faster RT in identifying the target post anodal stimulation when compared to post sham stimulation ($t=3.23$, $df=24$, $p=0.004$, $d=0.65$) and post cathodal stimulation ($t=3.39$, $df=24$, $p=0.002$, $d=0.68$). There was no significant difference in scores between sham and cathodal stimulation ($p>0.05$) (Fig. 19). As conducted previously with the other outcomes, a two-way ANOVA was performed to test if there was an order effect. This analysis disclosed that there was no order effect ($F=0.81$, $df=2,14$, $p=0.466$), but only a stimulation effect ($F=6.24$, $df=2,48$; $p=0.004$).

Within stimulation comparison show that there was no significant difference between pre, during and post sham and cathodal stimulation ($p>0.05$). Yet there was a significant difference that shows participants had faster RT during anodal when compared to pre-anodal stimulation ($t=3.94$, $df=24$, $p=0.001$, $d=0.79$), post anodal when compared to pre anodal stimulation ($t=4.73$, $df=24$, $p<0.0001$, $d=0.95$), but no significant difference during and post anodal stimulation ($p=0.901$). There was also a significantly faster RT during anodal stimulation ($t=3.66$, $df=24$, $p=0.001$, $d=0.73$) and post anodal stimulation compared to baseline ($t=3.20$, $df=24$, $p=0.004$, $d=0.64$). These results are presented in Table 1.

The mean RT at baseline was 675.93 (134.56 SD) at baseline, 669.13 (220.56 SD) post sham stimulation and 614.22 (199.8 SD) post cathodal stimulation, whereas the mean RT post anodal stimulation was 556.18 (175.16 SD). The mean difference between sham and anodal stimulation was 112.95, 58.04 between cathodal and anodal and 119.75 was the mean difference between baseline and post anodal stimulation.

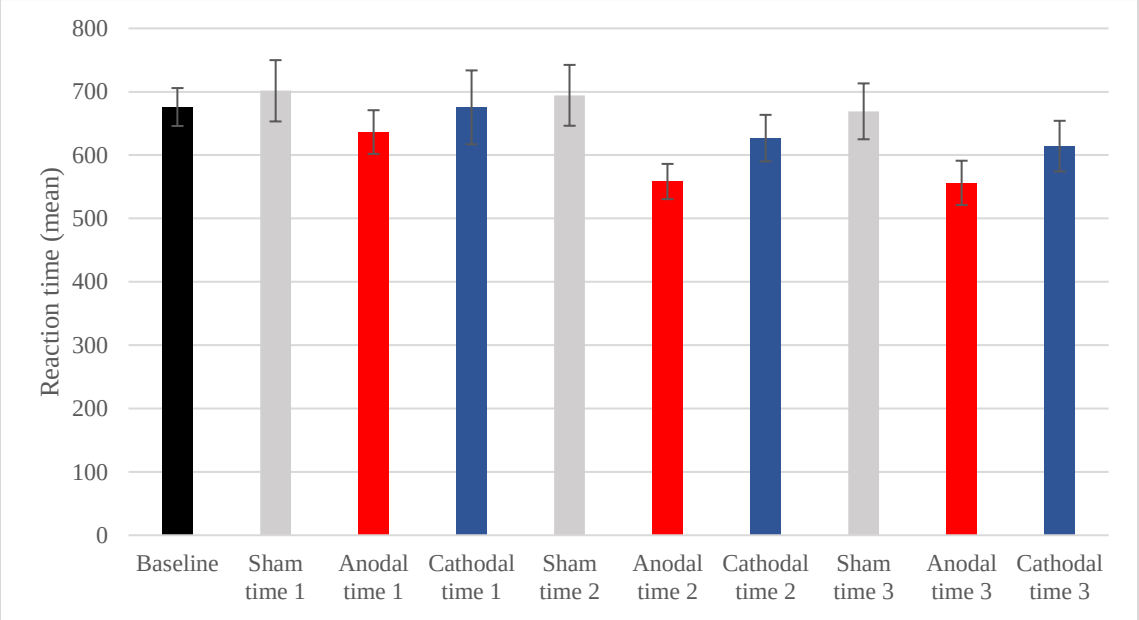


Figure 19 Mean response time (in milliseconds) of ASD group in identifying the target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the RT between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean)

5.3.2.6 HFA group reaction time on task (no-target)

RT on identifying letters presented not being a target was also investigated. There was no significant difference in RT between the three stimulation conditions at pre-stimulation ($p>0.05$). During stimulation there was no significant difference in RT between conditions ($p>0.05$). However, there was a significantly faster RT in anodal when compared to sham stimulation ($t=3.2$, $df=24$, $p=0.004$, $d=0.64$) and in anodal when compared to cathodal stimulation ($t=3.17$, $df=24$, $p=0.004$, $d=0.63$). Moreover, HFA participants had significantly faster RT in identifying the non-target post anodal stimulation when compared to post sham stimulation ($t=3.44$, $df=24$, $p=0.002$, $d=0.69$) and post cathodal stimulation ($t=3.3$, $df=24$, $p=0.003$, $d=0.66$). There was no significant difference in scores between sham and cathodal stimulation ($p>0.05$) (Fig. 20). As conducted previously with the other outcomes, a two-way ANOVA was performed to test if there was an order effect. This analysis disclosed that there was no order effect ($F=2.65$, $df=2,14$, $p=0.106$), but only a stimulation effect ($F=8.16$, $df=2,48$; $p=0.001$).

Within stimulation comparison show that there was no significant difference between pre, during and post sham and cathodal stimulation ($p>0.05$). Yet, there was a significant difference between pre-anodal and during anodal stimulation ($t=3.3$, $df=24$, $p=0.003$, $d=0.66$), pre-anodal and post anodal ($t=3.51$, $df=24$, $p=0.002$, $d=0.7$), but no significant difference between during and post anodal stimulation ($p=0.348$). There was significantly faster RT during anodal stimulation ($t=3.33$, $df=24$, $p=0.003$, $d=0.67$) and post anodal stimulation compared to baseline ($t=3.89$, $df=24$, $p=0.001$, $d=0.78$). These results are presented in Table 1.

The mean RT was 607.67 (164.52 SD) at baseline, 609.75 (169.80 SD) post sham stimulation and 611.45 (195.2 SD) post cathodal stimulation, whereas the mean RT post anodal stimulation was 467.1 (127.90 SD). The mean difference between sham and anodal stimulation was 142.65, 144.35 between cathodal and anodal and 140.57 was the mean difference between baseline and post anodal stimulation.

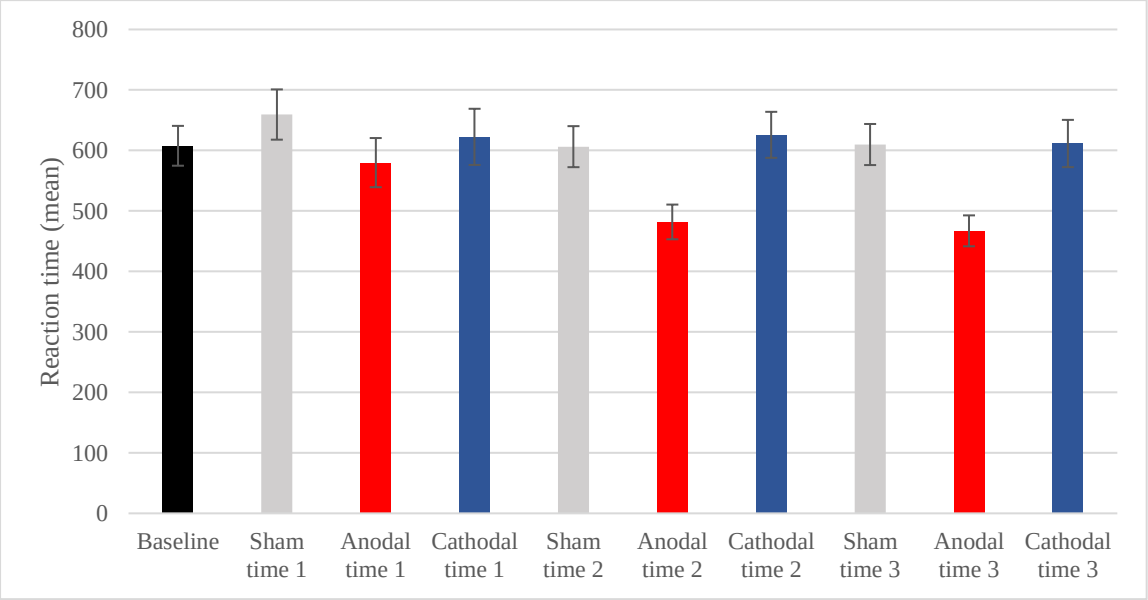


Figure 20 Mean response time (in milliseconds) of ASD group identifying the letter was not a target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the RT between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean)

Table 12 Mean scores (SD) of ASD group on the 3-back task scores across conditions on accuracy, error rate and reaction time in identity the target and not a target.

Outcome	Baseline	Sham pre-stimulation	Sham during stimulation	Sham post stimulation	Anodal pre-stimulation	Anodal during stimulation	Anodal post stimulation	Cathodal pre-stimulation	Cathodal during stimulation	Cathodal post stimulation
Accuracy on target	4.96 (1.83)	5.42 (2.02)	4.86 (2.05)	5.35 (1.94)	5.19 (1.86)	6.30 (1.51)	6.86 (1.59)	5.57 (1.94)	5.26 (2.29)	5.22 (2.03)
Accuracy on non-target	10.53 (3.2)	14.65 (3.53)	12.74 (4.81)	13.62 (3.97)	14.98 (2.6)	15.82 (1.51)	17.47 (1.46)	14.42 (4.59)	13.94 (3.19)	13.87 (3.2)
Error rate on target	19.92 (7.26)	20.48 (6.19)	19.52 (6.99)	18.72 (7.64)	20.32 (7.99)	15.44 (7.55)	13.52 (6.2)	18.12 (7.99)	19.52 (7.82)	19.56 (8.66)
Error rate on non-target	23.4 (12.25)	22.92 (13.37)	25.84 (15.04)	25.28 (15.37)	25.68 (14.99)	18.64 (7.91)	15.32 (7.9)	21.04 (8.46)	23.76 (10.36)	23.72 (9.79)
Reaction time on target	675.93 (134.56)	701.56 (241.89)	694.39 (240.15)	669.13 (220.56)	636.41 (172.5)	558.33 (138.94)	556.18 (175.16)	675.41 (294.64)	626.85 (183.68)	614.22 (199.8)
Reaction time on non-target	607.67 (164.52)	659.34 (207.76)	606.22 (169.52)	609.75 (169.79)	579.84 (203.26)	481.8 (143.44)	467.07 (127.86)	622.42 (232.2)	625.82 (190.05)	611.46 (195.19)

The primary outcome findings of this phase II clinical trial indicate that individuals with HFA had significant improvement in accuracy, fewer error and faster reaction time during and post anodal stimulation when compared to baseline, cathodal and sham performance. Indeed, these findings were observed when the participants had to identify whether the letter presented was a target or non-target.

5.3.2.7 TD group accuracy on task

There was no significant differences in accuracy between the three stimulation conditions at pre-stimulation, during stimulation and post stimulation ($p>0.05$). Moreover, there was no significant difference during and post anodal stimulation and baseline ($p>0.05$). Within stimulation comparison show that there was also no significant difference between pre, during and post sham, anodal and cathodal stimulation ($p>0.05$) (Fig.21). These results are presented in Table 13.

The mean number of correct responses at baseline was 6.67 (1.75 SD), post sham stimulation was 6.39 (1.96 SD) and 6.8 (1.43 SD) post cathodal stimulation, whereas the mean number of errors made post anodal stimulation was 6.62 (1.38SD), and the mean difference between sham and anodal stimulation was 0.23, 0.18 between cathodal and anodal and 0.05 was the mean difference between baseline and post anodal stimulation.

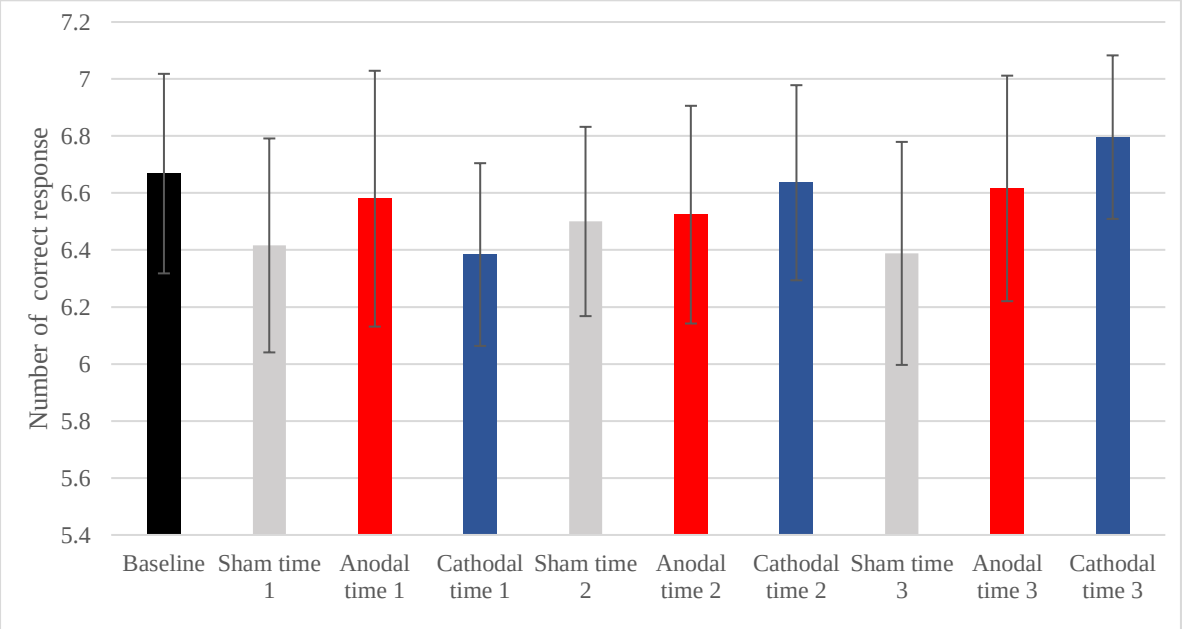


Figure 21 Number of correct responses in identifying the target during each stimulation condition (anodal, cathodal and sham). There was no significant difference in the mean number of correct responses between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.8 TD group accuracy on task (no-target)

Accuracy on the ability to identify the letter was not a target was also investigated. The analysis show there was no significant difference in accuracy between the three stimulation conditions at pre-stimulation, during stimulation and post stimulation ($p>0.05$). Also, there was no significant difference during and post anodal stimulation and baseline ($p>0.05$). Within stimulation comparison show that there was also no significant difference between pre, during and post sham, anodal and cathodal stimulation ($p>0.05$) (Fig. 22). These results are presented in Table 2.

The mean number of correct responses at baseline was 17.36 (1.97 SD), post sham stimulation was 15.82 (2.34 SD) and 16.14 (2.14 SD) post cathodal stimulation, whereas the mean number of errors made post anodal stimulation was 16.42 (2.2 SD), and the mean difference between sham and anodal stimulation was 0.6, 0.28 between cathodal and anodal and 0.94 was the mean difference between baseline and post anodal stimulation.

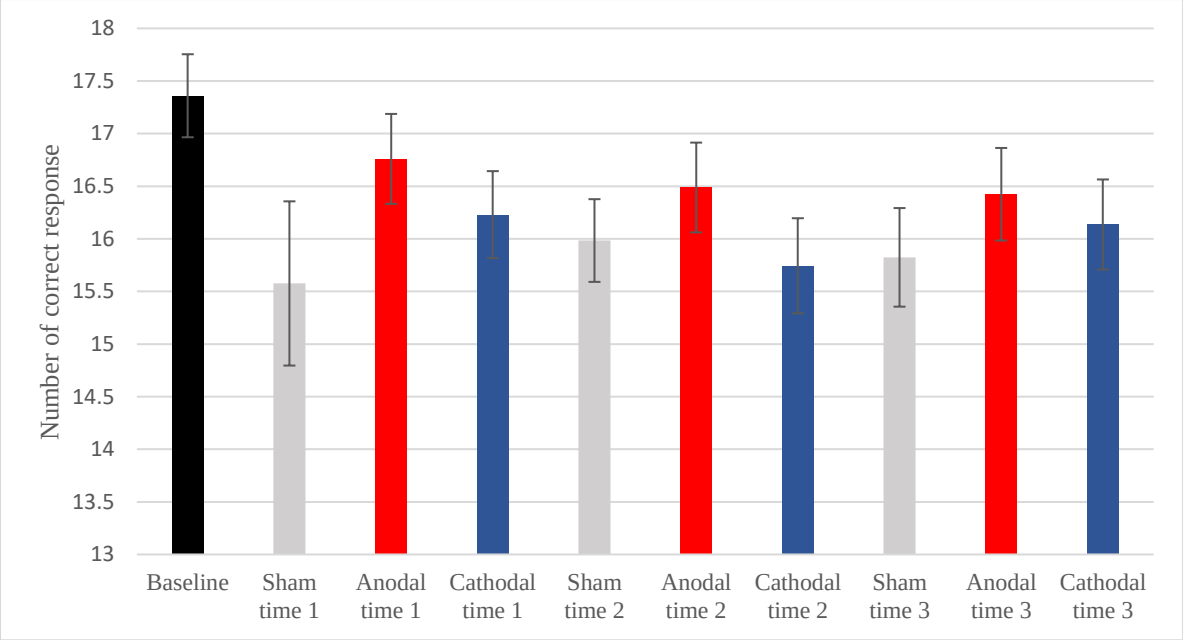


Figure 22 Number of correct responses in identifying the letter was not a target during each stimulation condition (anodal, cathodal and sham). There was no significant difference in the mean number of correct responses between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.9 TD group Error rate on task

There was no significant difference in the amount of errors made between the three stimulation conditions at pre-stimulation, during stimulation and post stimulation ($p>0.05$). Moreover, there was no significant difference during and post anodal stimulation and baseline ($p>0.05$). Within stimulation comparison show that there was also no significant difference between pre, during and post sham, anodal and cathodal stimulation ($p>0.05$) (Fig. 23). These results are presented in Table 13.

The mean number of errors made at baseline was 14 (9.57 SD), post sham stimulation was 12.92 (7.72 SD) and 11.76 (5.66 SD) post cathodal stimulation, whereas the mean number of errors made post anodal stimulation was 12.16 (7.63 SD), and the mean difference between sham and anodal stimulation was 0.76, 0.40 between cathodal and anodal and 1.86 was the mean difference between baseline and post anodal stimulation.

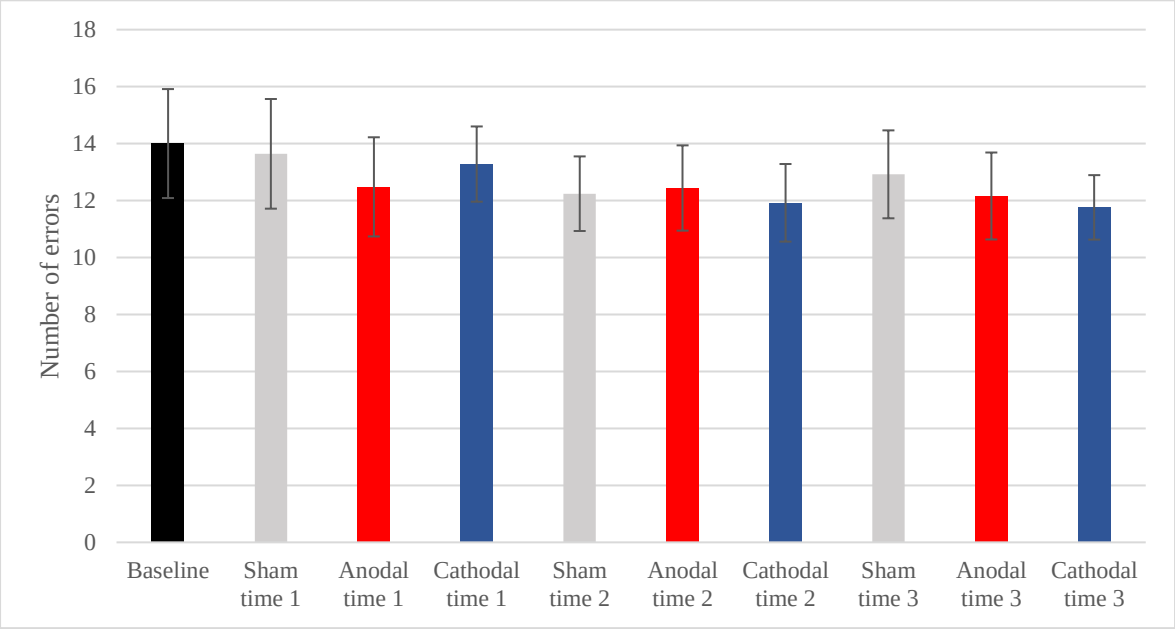


Figure 23 Number of errors in identifying the target during each stimulation condition (anodal, cathodal and sham). There was no significant difference in the mean number of errors between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.10 TD group Error rate on task (no-target)

Errors made on identifying letters were not a target was also investigated. There was no significant difference in the amount of errors made between the three stimulation conditions at pre-stimulation, during stimulation and post stimulation ($p>0.05$). Furthermore, there was no significant difference during and post anodal stimulation and baseline ($p>0.05$). Within stimulation comparison show that there was also no significant difference between pre, during and post sham, anodal and cathodal stimulation ($p>0.05$) (Fig. 24). These results are presented in Table 13.

The mean number of errors made at baseline was 10.84 (9.04 SD), post sham stimulation was 14.80 (9.35 SD) and 13.44 (8.09SD) post cathodal stimulation, whereas the mean number of errors made post anodal stimulation was 13.12 (8.29 SD), and the mean difference between sham and anodal stimulation was 1.68, 0.32 between cathodal and anodal and 2.28 was the mean difference between baseline and post anodal stimulation.

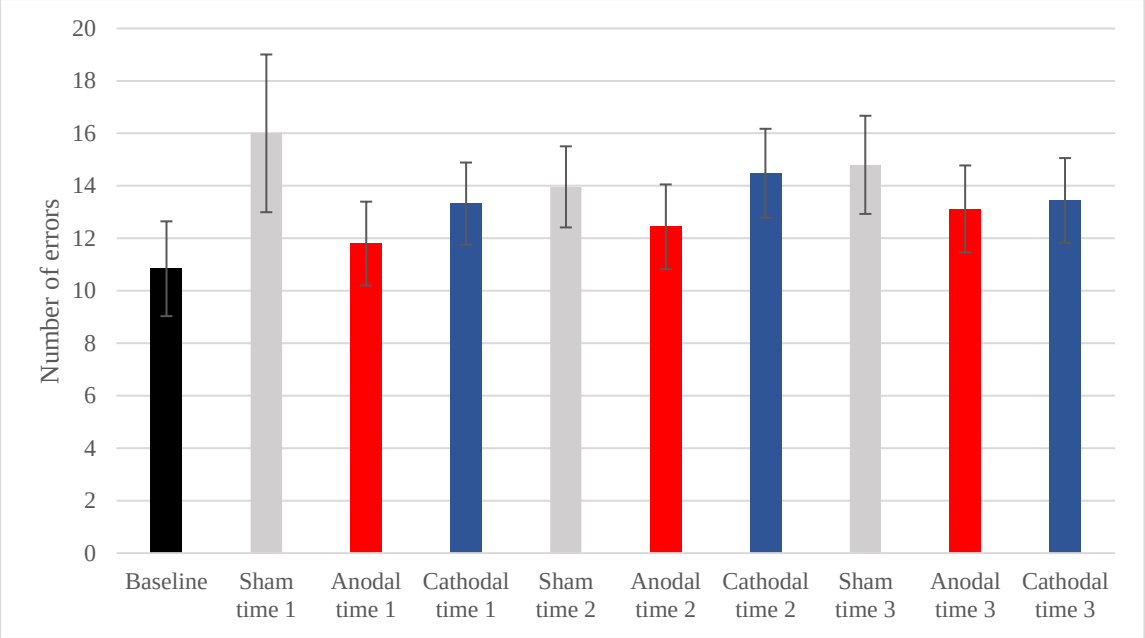


Figure 24 Number of errors in identifying the letter is not a target during each stimulation condition (anodal, cathodal and sham). There was no significant difference in the mean number of errors between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.11 TD group reaction time on task

There was no significant difference in RT identifying the target between the three stimulation conditions at pre-stimulation ($p>0.05$). There was no statistically significant difference in RT between sham and cathodal during stimulation ($p>0.05$). However, there was a significantly faster RT in anodal stimulation when compared to sham stimulation ($t=3.23$, $df=24$, $p=0.004$, $d=0.65$) and in anodal when compared to cathodal stimulation ($t=3.23$, $df=24$, $p=0.004$, $d=0.65$). Moreover, TD participants had significantly faster RT in identifying the target post anodal stimulation when compared to post sham stimulation ($t=3.36$, $df=24$, $p=0.003$, $d=0.67$) and post cathodal stimulation ($t=3.19$, $df=24$, $p=0.004$, $d=0.64$). However, there was no significant difference in scores between sham and cathodal stimulation ($p>0.05$) (Fig. 25). As preformed previously with the other outcomes, a two-way ANOVA was conducted to test if there was an order effect. This analysis disclosed that there was no order effect ($F=0.50$, $df=2,14$, $p=0.616$), but only a stimulation effect ($F=5.33$, $df=2,48$; $p=0.008$).

Within stimulation comparison showed that there was no significant difference between pre, during and post sham and cathodal stimulation ($p>0.05$). Yet, there was a faster RT between

during anodal stimulation when compared to pre-anodal stimulation (t=4.80, df=24, p<0.0001, d=0.96), pre anodal when compared to post anodal stimulation (t=5.00, df=24, p<0.0001, d=1), and during when compared to post anodal stimulation (t=2.81, df=24, p=0.010, d=0.56). More importantly, the results demonstrated significantly faster RT during anodal stimulation (t=7.04, df=24, p<0.0001, d=1.41) and post anodal stimulation compared to baseline (t=7.28, df=24, p<0.0001, d=1.46). These results are presented in Table 13.

The mean RT was 862.93 (308.1 SD) at baseline, 660.31 (252.84 SD) post sham stimulation and 663.03 (224.83 SD) post cathodal stimulation, whereas the mean number of correct answers post anodal stimulation was 498.62 (117.61 SD). The mean difference between sham and anodal stimulation was 161.69, 164.41 between cathodal and anodal and 364.31 was the mean difference between baseline and post anodal stimulation.

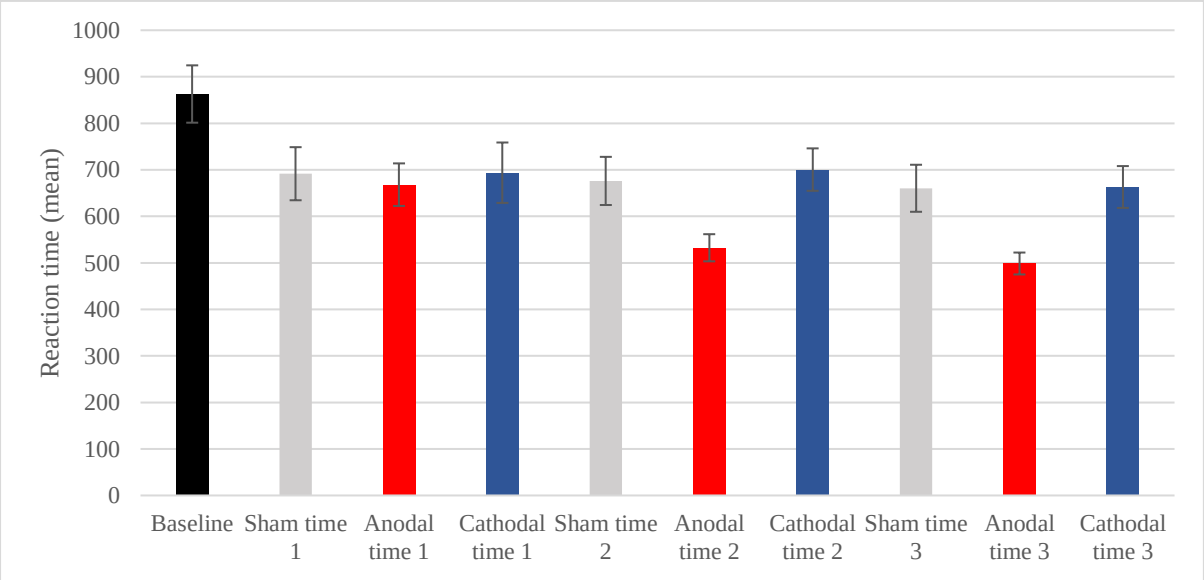


Figure 25 Mean response time (in milliseconds) of TD group in identifying the target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the RT between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean).

5.3.2.12 TD group reaction time on task (no-target)

RT on the ability to identify the letter was not a target was also investigated. There was no significant difference in accuracy identifying the target between the three stimulation conditions at pre-stimulation (p>0.05). There was no statistically significant difference in accuracy between sham and cathodal during stimulation (p>0.05). However, there was faster RT in anodal stimulation when compared to sham stimulation (t=3.36, df=24, p=0.003,

d=0.67) and anodal when compared to cathodal stimulation (t=3.21, df=24, p=0.004, d=0.64). Moreover, TD participants had significantly faster RT in identifying the non-target post anodal stimulation when compared to post sham stimulation (t=2.53, df=24, p=0.019, d=0.5) and post cathodal stimulation (t=3.41, df=24, p=0.002, d=0.68). There was no significant difference in scores between sham and cathodal stimulation (p>0.05) (Fig. 26). As preformed previously, a two-way ANOVA was conducted to test if there was an order effect. This analysis disclosed that there was no order effect (F=0.83, df=2,14, p=0.456), but only a stimulation effect (F=8.92, df=2,48; p=0.001).

Within stimulation comparison showed that there was no significant difference between pre, during and post sham and cathodal stimulation (p>0.05). There was a significantly faster RT during anodal stimulation when compared to pre-stimulation (t=3.26, df=24, p=0.003, d=0.65), faster RT post anodal stimulation when compared to pre-stimulation (t=3.43, df=24, p=0.002, d= 0.69), however, there was no difference in RT between during and post anodal stimulation (p=0.161). More importantly, the results demonstrate significantly faster RT during anodal stimulation (t=5.32, df=24, p<0.0001, d=1.06) and post anodal stimulation compared to baseline (t=5.39, df=24, p<0.0001, d=1.08). These results are presented in Table 13.

The mean RT was 771.79 (279.81 SD) at baseline, 619.74 (236.21 SD) post sham stimulation and 613.80 (184.94 SD) post cathodal stimulation, whereas the mean number of correct answers post anodal stimulation was 459.07 (116.11 SD). The mean difference between sham and anodal stimulation was 161.69, 164.41 between cathodal and anodal and 364.31 was the mean difference between baseline and post anodal stimulation.

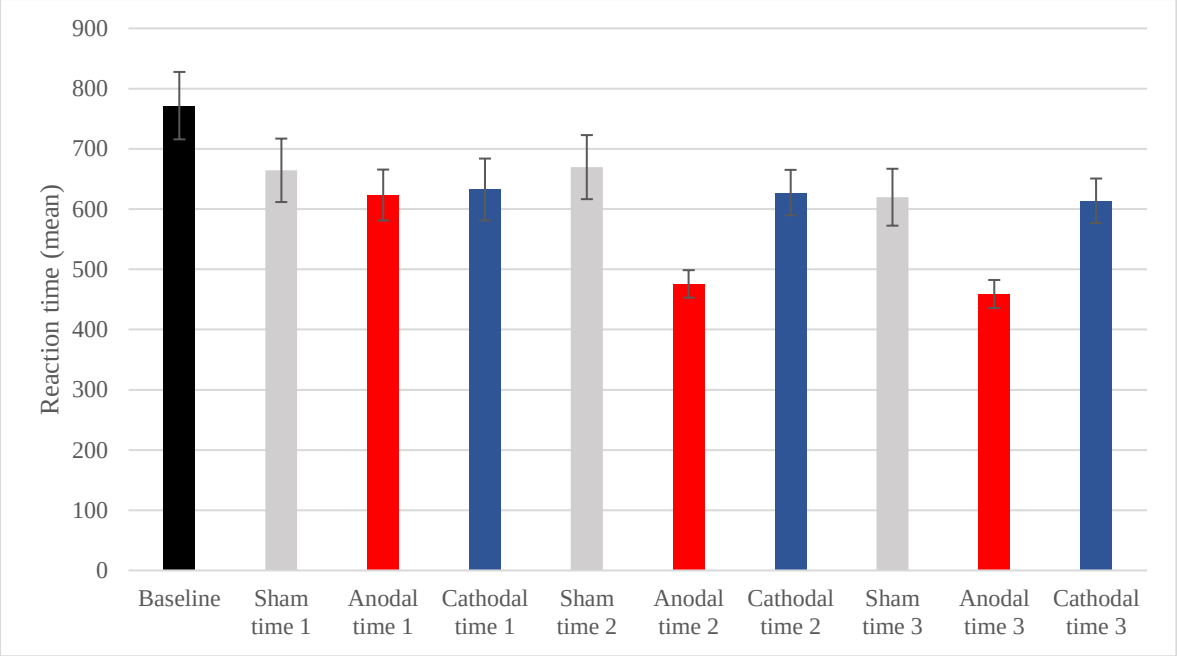


Figure 26 Mean response time (in milliseconds) of TD group in identifying the letter was not a target during each stimulation condition (anodal, cathodal and sham). There was a significant difference in the RT between sham, cathodal and anodal stimulation. Error bars indicate ±SEM (standard error of the mean)

Table 13 Mean scores (SD) of TD group on 3-back task scores across conditions on accuracy, error rate and reaction time in identity the target and not a target.

Outcome	Baseline	Sham pre-stimulation	Sham during stimulation	Sham post stimulation	Anodal pre-stimulation	Anodal during stimulation	Anodal post stimulation	Cathodal pre-stimulation	Cathodal during stimulation	Cathodal post stimulation
Accuracy on target	6.67 (1.75)	6.42 (1.88)	6.5 (1.66)	6.39 (1.96)	6.58 (2.24)	6.52 (1.91)	6.62 (1.98)	6.38 (1.6)	6.34 (1.71)	6.8 (1.43)
Accuracy on non-target	17.36 (1.97)	15.58 (3.9)	15.98 (1.97)	15.82 (2.34)	16.76 (2.14)	16.49 (2.13)	16.42 (2.2)	16.23 (2.07)	15.74 (2.26)	16.14 (2.14)
Error rate on target	14 (9.57)	13.64 (9.63)	12.24 (6.55)	12.92 (7.72)	12.48 (8.7)	12.44 (7.48)	12.16 (7.63)	13.28 (6.61)	11.92 (6.81)	11.76 (5.66)
Error rate on non-target	10.84 (9.04)	16 (15.03)	13.96 (7.28)	14.8 (9.35)	11.8 (7.98)	12.44 (8.07)	13.12 (8.29)	13.32 (7.84)	14.48 (8.47)	13.44 (8.09)
Reaction time on target	862.93 (308.09)	691.59 (285.24)	676.08 (258.71)	660.31 (252.84)	668.04 (228.65)	532.43 (145.74)	498.62 (117.61)	693.74 (324.66)	700.46 (228.20)	663.03 (224.83)
Reaction time on non-target	771.79 (279.81)	664.38 (263.41)	669.69 (265.81)	619.74 (236.21)	623.41 (211.11)	475.74 (114.39)	459.07 (116.11)	632.53 (256.81)	627.45 (188.46)	613.79 (184.94)

5.3.3 Between group observational comparison

The preliminary results of experiments were not designed to compare the two groups. However, we thought it would be important to compare both groups' baseline and post anodal stimulation performance on the task and compare the change in score from baseline to post stimulation. Baseline line comparison showed that HFA group had statistically significant lower accuracy ($t=3.38$, $df=48$, $p=0.001$, $d=0.98$), greater errors ($t=2.47$, $df=48$, $p=0.017$, $d=0.71$) and slower reaction times ($t=2.78$, $df=48$, $p=0.008$, $d=0.8$) in identifying the target compared to the TD group. Furthermore, HFA group had statistical lower scores in accuracy ($t=9.10$, $df=48$, $p<0.0001$, $d=2.62$), greater error rate ($t=4.13$, $df=48$, $p<0.0001$, $d=1.19$), and slower reaction time ($t=2.53$, $df=48$, $p=0.015$, $d=0.73$) in identifying the letter presented was not a target compared to the TD group (Fig. 27-29). In post anodal stimulation, the analysis showed that there was no significant difference between HFA and TD group in accuracy, error rate and reaction time in identifying the letter presented is a target ($p>0.05$). There was also no significant difference in error rate and reaction time in identifying the letter presented was not a target ($p>0.05$). However, there was a significant difference in accuracy ($t=4.10$, $df=48$, $p<0.0001$, $d=1.18$) showing that the TD group had greater scores of identifying the letter presented was not a target (Fig. 30-32), these results are presented in Table 14.

Furthermore, an independent sample t-test demonstrated that the HFA group had significantly greater changes in scores from baseline to post anodal stimulation when compared to the TD group in identifying target accuracy ($t=3.2$, $df=48$, $p=0.002$), in identifying not a target accuracy ($t=4.09$, $df=48$, $p<0.0001$), in identifying target error rate ($t=10.25$, $df=48$, $p<0.0001$), in identifying not a target error rate ($t=3.71$, $df=48$, $p=0.001$), in identifying target RT ($t=3.91$, $df=48$, $p<0.0001$), and in identifying not a target RT ($t=2.52$, $df=48$, $p=0.015$). These results are presented in Table 15.

Table 14 Means and standard deviation comparison of baseline and post anodal stimulation performance between HFA and TD groups.

Groups	Baseline accuracy target	Baseline accuracy not a target	Baseline error rate target	Baseline error rate not a target	Baseline reaction time target	Baseline reaction time not a target	Post anodal stimulation accuracy target	Post anodal stimulation accuracy not a target	Post anodal stimulation error rate target	Post anodal stimulation error rate not a target	Post anodal stimulation reaction time target	Post anodal stimulation reaction time not a target
HFA	4.96 (1.83)	10.53 (3.2)	19.92 (7.26)	23.4 (12.25)	675.93 (134.56)	607.67 (164.52)	6.86 (1.59)	17.47 (1.46)	13.52 (6.2)	15.32 (7.9)	556.18 (175.16)	467.07 (127.86)
TD	6.67 (1.75)	17.36 (1.97)	14 (9.57)	10.84 (9.04)	862.93 (308.09)	771.79 (279.81)	6.62 (1.98)	16.42 (2.2)	12.16 (7.63)	13.12 (8.29)	498.62 (117.61)	459.07 (116.11)

Table 15 Changes in score between baseline and post anodal stimulation.

Groups	Change in score target	Change in score not a target	Change in score error rate target	Change in score error rate not a target	Change in score reaction time target	Change in score reaction time not a target
HFA	1.9 (2.61)	3.17 (4.55)	19.92 (7.26)	-7.68 (10.11)	-119.75 (187.04)	-140.6 (180.64)
TD	-0.052 (1.58)	-0.94 (2.13)	-1.84 (7.74)	2.28 (8.82)	-364.31 (250.33)	-312.71 (290.16)

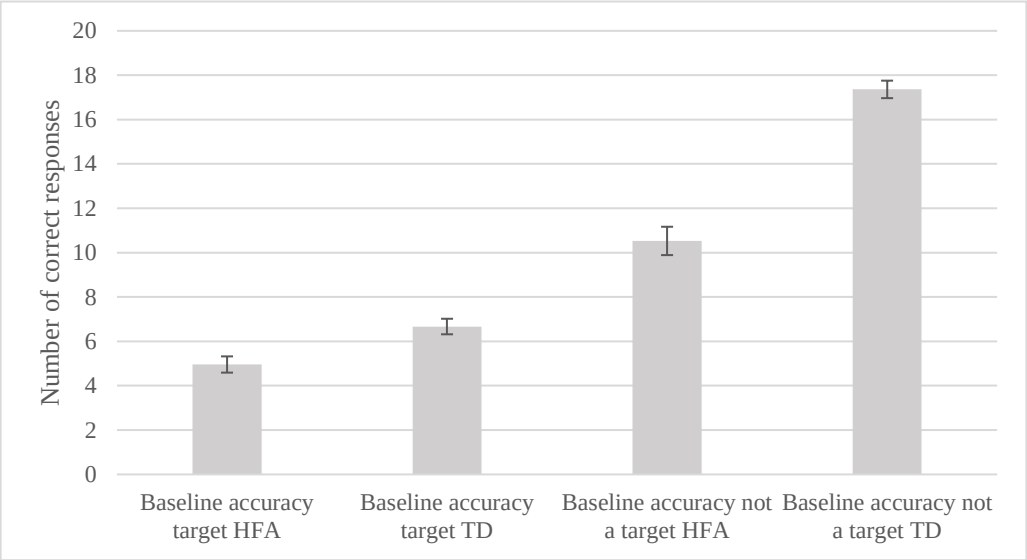


Figure 27 Number of correct responses on identifying the target at baseline. There was a significant difference in the mean number of correct responses between the HFA and TD group on baseline accuracy in identifying the letter was a target and non-target. Error bars indicate ±SEM (standard error of the mean).

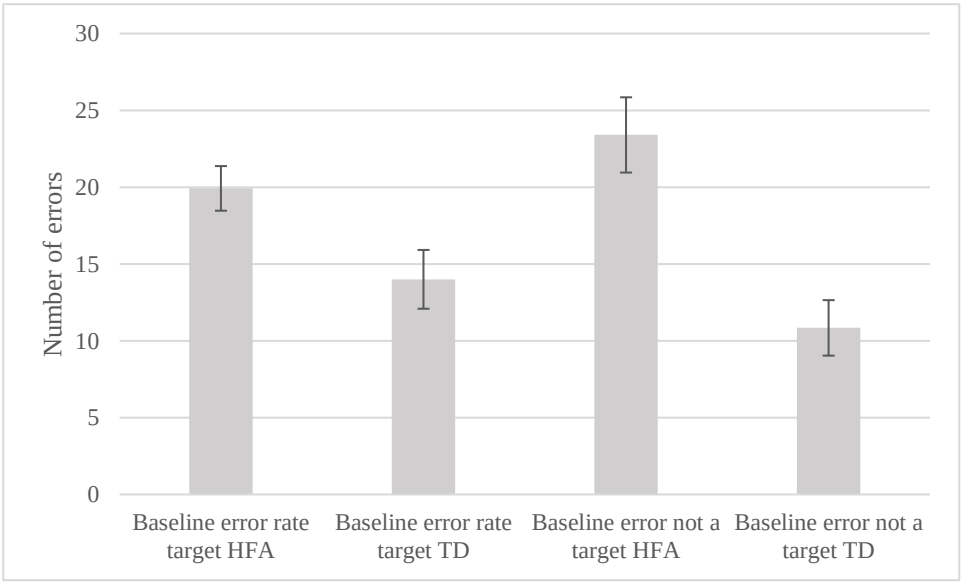


Figure 28 Number of errors made on identifying the target at baseline. There was a significant difference in the mean number of correct responses between the HFA and TD group on baseline errors made in identifying the letter was a target and non-target. Error bars indicate ±SEM (standard error of the mean).

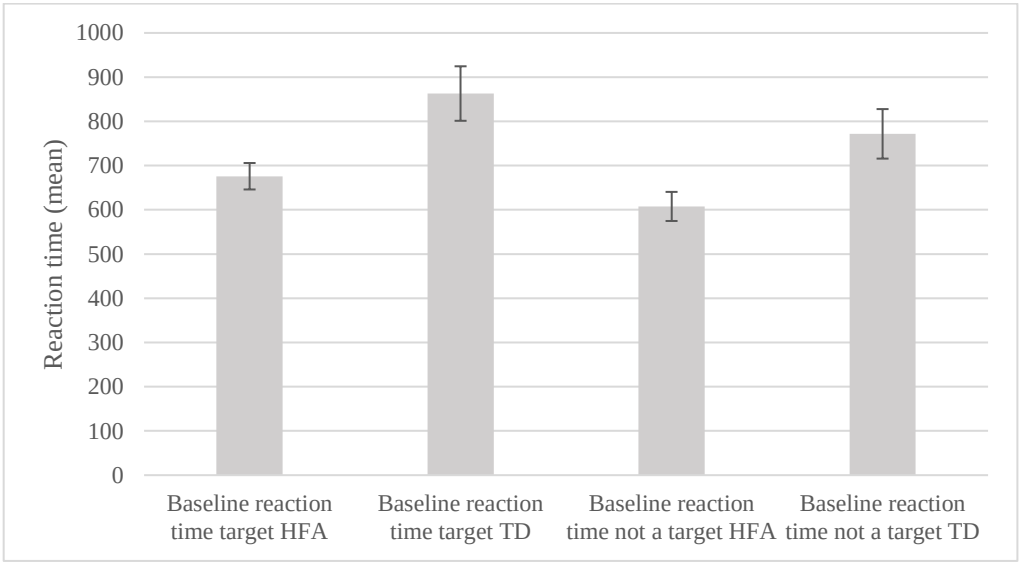


Figure 29 Number of reaction time on identifying the target at baseline. There was a significant difference in the mean number of correct responses between the HFA and TD group on baseline reaction time in identifying the letter was a target and non-target. Error bars indicate ±SEM (standard error of the mean).

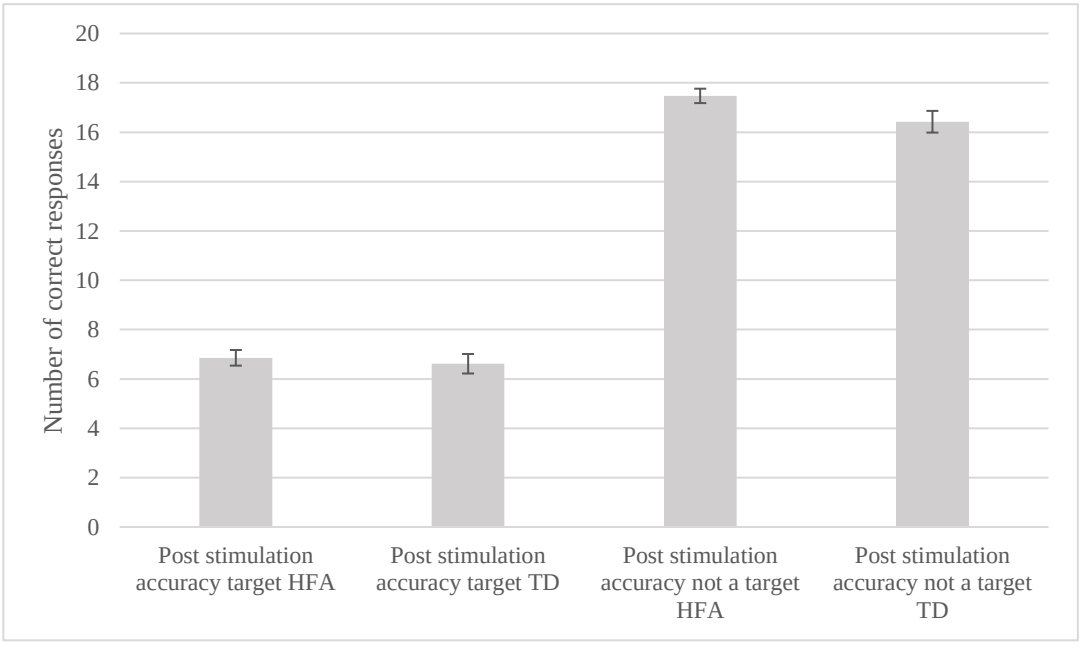


Figure 30 Number of correct responses on identifying the target post anodal stimulation. There was only a significant difference in the mean number of correct responses between the HFA and TD group post stimulation in identifying the letter was not a target. Error bars indicate ±SEM (standard error of the mean).

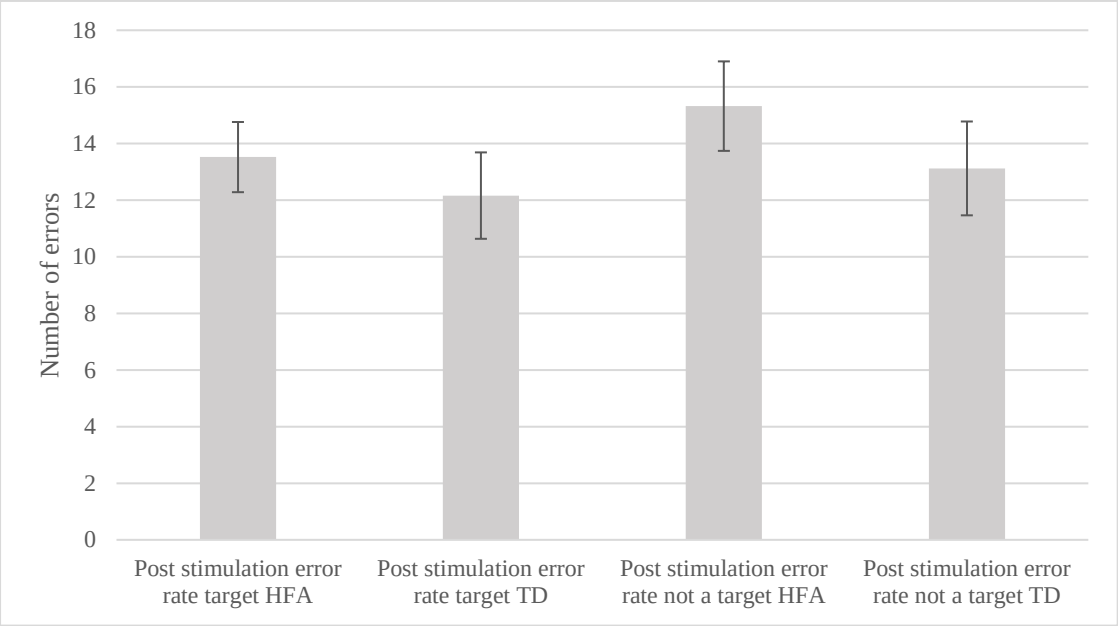


Figure 31 Number of errors made on identifying the target post anodal stimulation. There was no significant difference in the mean number of errors made between the HFA and TD group. Error bars indicate ±SEM (standard error of the mean).

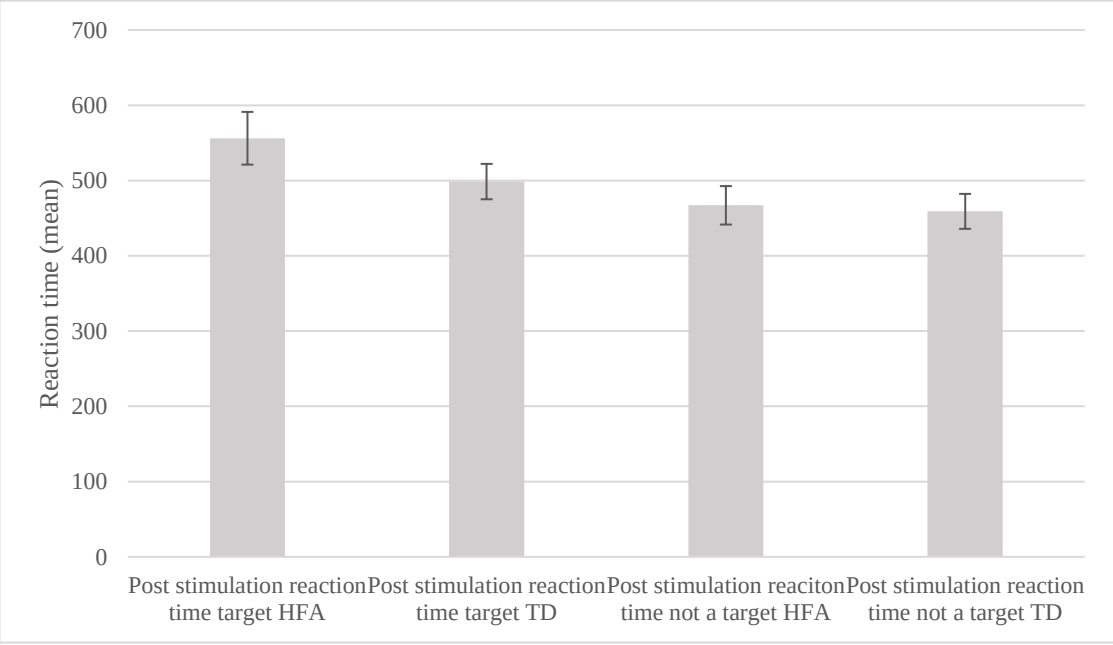


Figure 32 Reaction time (in milliseconds) on identifying the target post anodal stimulation. There was no significant difference in the mean reaction time between the HFA and TD group. Error bars indicate ±SEM (standard error of the mean).

These results demonstrate that individuals with HFA had significantly lower accuracy, greater number of errors and slower reaction time at baseline when compared to TD. However, after anodal stimulation, individuals with HFA preformed at the same level as TD individuals as there was no significant difference in accuracy, error rate or reaction time. This was evident despite if the participants had to identify whether the letter presented was a target or non-target, with the exception of accuracy in identifying the letter presented was non-target, where TD individuals performed better. The results also indicate that individuals with HFA had greater benefits from tDCS than the TD individuals as the HFA group had significantly greater changes in scores from baseline to post anodal stimulation when compared to the TD group.

5.3.4 Correlations

Relationships between WM scores at baseline and demographic variables were examined using Pearson correlation. The analysis demonstrates that there is no correlation in the HFA group between age and WM scores ($p=0.230$) as well as WM scores and scores on the WMQ ($p=0.808$). However, there was a moderate positive relationship between WM scores and IQ ($r=0.556$, $N=25$, $p=0.004$; Fig. 33). Moreover, there was no correlation between age and IQ, WMQ and IQ, and WMQ and age ($p>0.05$). A simple linear regression was carried out to test if IQ significantly predicted WM scores. The results of the regression indicated that the model explained 37.7% of the variance and that the model was significant, $F(1, 23) = 13.90$, $p=0.001$. Showing that IQ significantly predicted WMS.

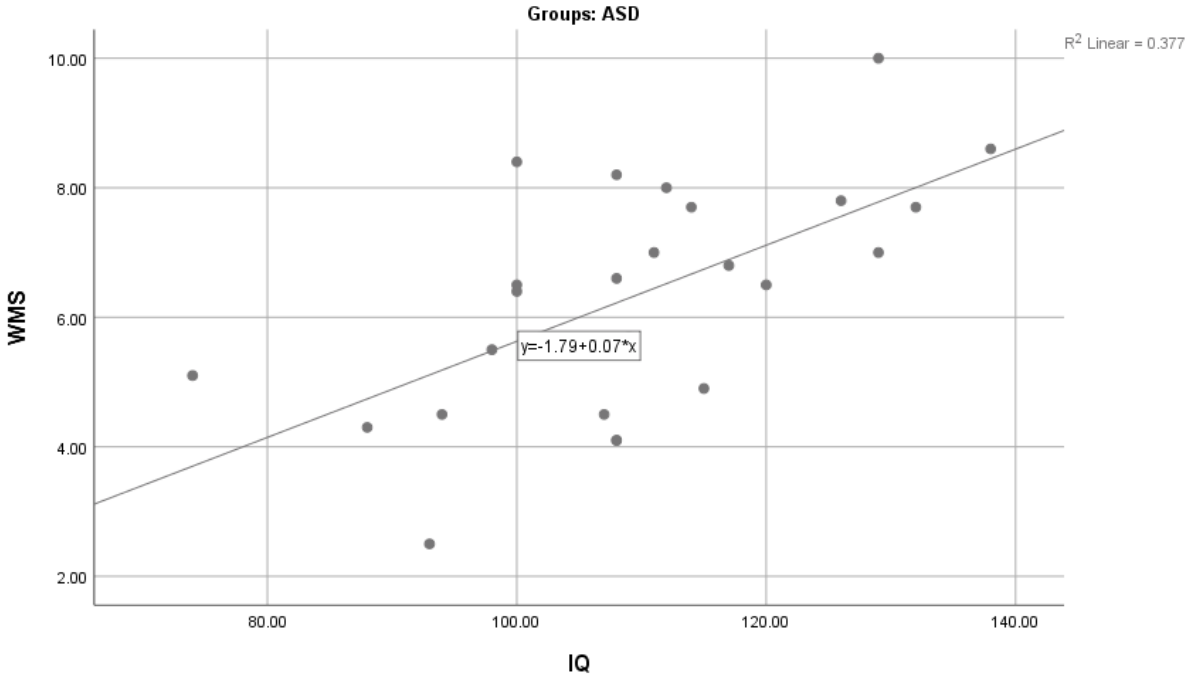


Figure 33 Shows the relationship between working memory scores and IQ.

In the TD group, the analysis showed that there was no relationship between WM scores, IQ and age ($p>0.05$). Furthermore, the analysis showed that there was no correlation between age and IQ, WMQ and AQ 50 scores, WM scores and AQ 50, as well as WMQ and IQ ($p>0.05$). However, there was a moderate strong positive relationship between the WMQ scores and age ($r=0.586$, $N=25$, $p=0.002$; Fig. 34). A simple linear regression was carried out to test if age significantly predicted scores on the WMQ. The results of the regression indicated that the model explained 34.3% of the variance and that the model was significant, $F(1, 23) = 12.03$, $p=0.002$. Showing that age significantly predicted scores on the WMQ.

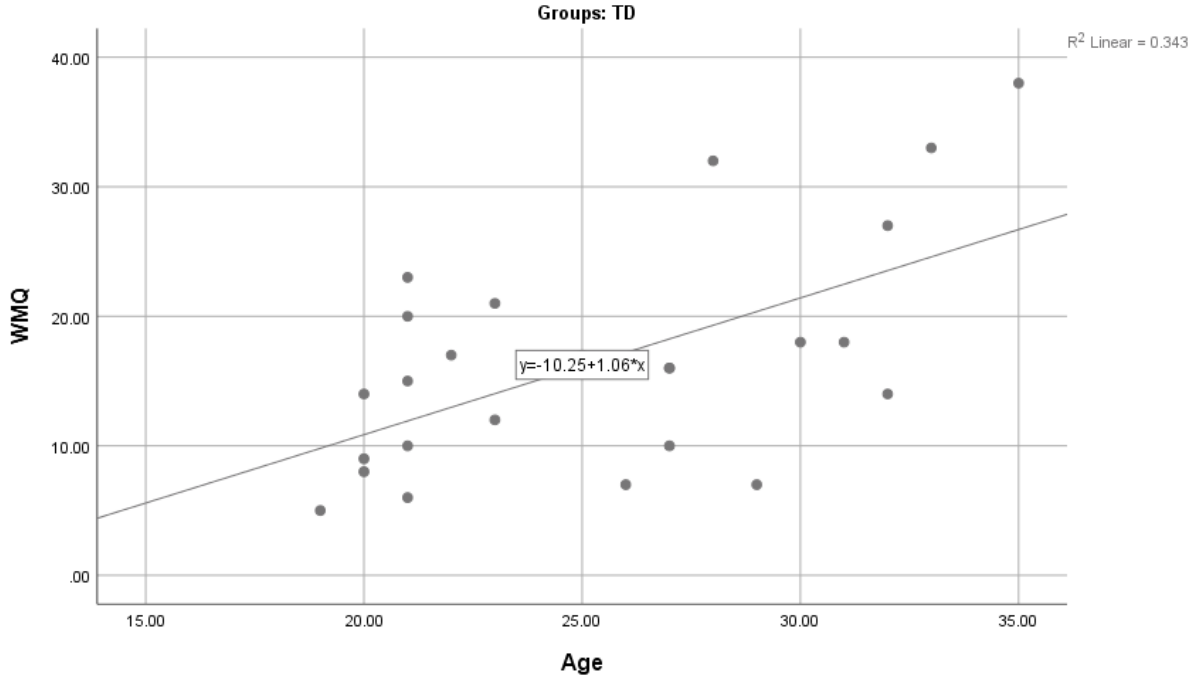


Figure 34 Shows the relationship between age and scores on the working memory questionnaire.

5.3.5 Side-effects questionnaire

Examining the balance between possible efficacy and safety is an important component of a phase 2 study design. To assess the degree to which sensory side-effects were reported we compared each sensory side-effect (tingling, itching, burning, headache and pain) between each of the three stimulation conditions using a Wilcoxon signed-rank test. Moreover, a Mann-Whitney U was performed to compare between both groups reported sensory side-effects.

In the HFA group, majority of the sensory side-effects were reported as ≤3 out of 5 in terms of severity, 84% reported tingling, 36% itching, 44% burning, 24% headache and 24% pain. Only a small percentage reported sensory side-effects as ≥4 out of 5, 4% reported tingling, 12% itching, 4% burning, 0% headache and 4% pain. In the TD group, 60% reported tingling, 52% itching, 36% burning, 12% headache, 16% pain of which were reported as ≤3 out of 5 in terms of severity. While 28% reported tingling, 12% itching, 8% burning, 0% headache, and 0% pain as a ≥4 out of 5 severity,

indicating that the tDCS was generally well tolerated in both HFA and TD groups (Fig. 35 and 36). These results are presented in Table 16 and 17.

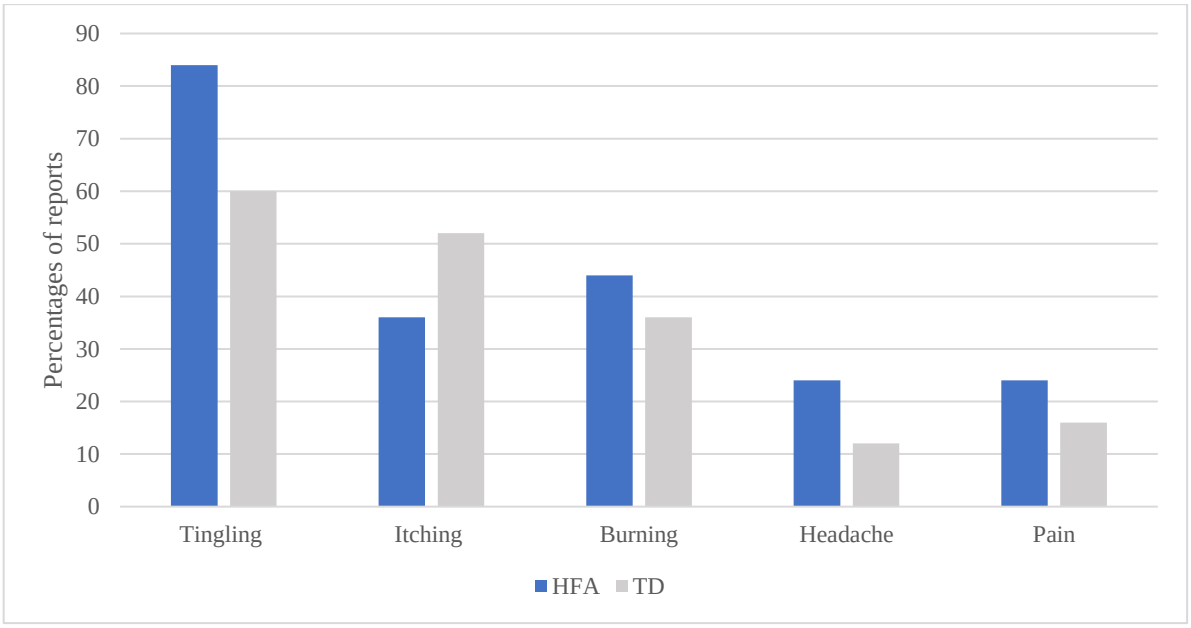


Figure 35 Percentages of sensory side-effects reported as ≤3 out of 5 during stimulation.

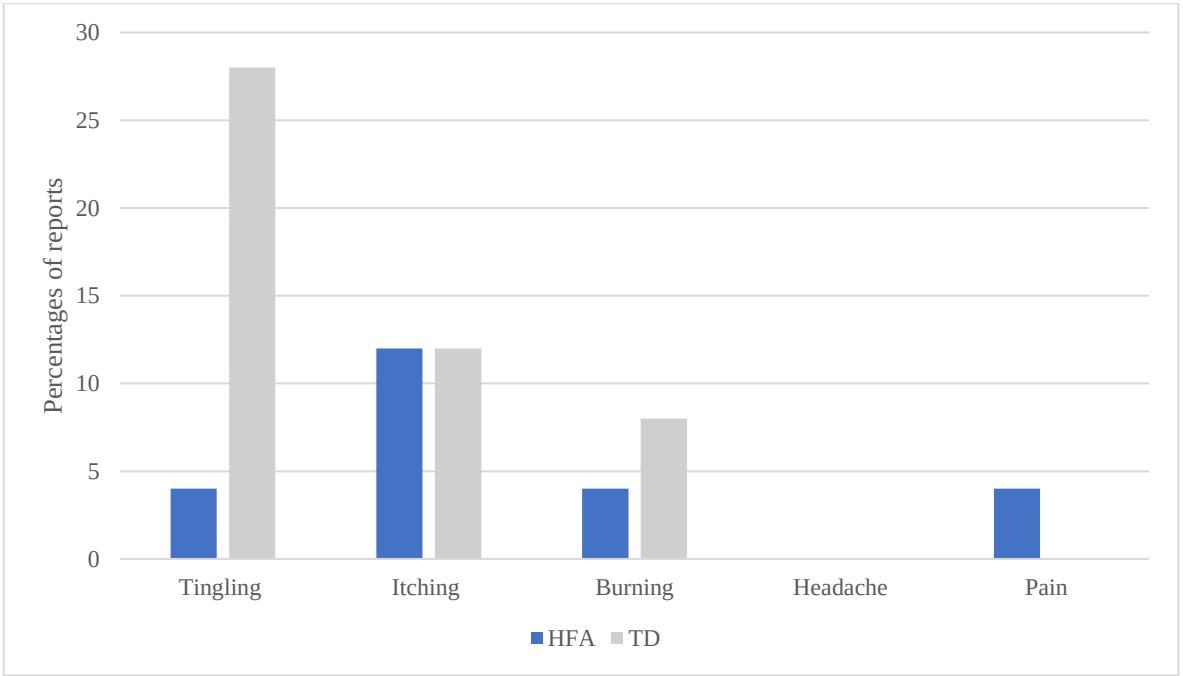


Figure 36 Percentages of sensory side-effects reported as ≥4 out of 5 during stimulation.

Table 16 Percentages of sensory side-effects reported as ≤3 out of 5 severity during active tDCS in HFA and TD group.

Groups	Tingling	Itching	Burning	Headache	Pain
HFA	84%	36%	44%	24%	24%
TD	60%	52%	36%	12%	16%

Table 17 Percentages of sensory side-effects reported as ≥4 out of 5 severity during active tDCS in HFA and TD group.

Groups	Tingling	Itching	Burning	Headache	Pain
HFA	4%	12%	4%	0%	4%
TD	28%	12%	8%	0%	0%

Interestingly, during sham stimulation, both groups reported side-effect session. The HFA group reported tingling 48%, itching 16%, burning 28%, headache 20% and pain 24% as ≤3 out of 5 in terms of severity. As well as tingling 16%, itching 4%, burning 4%, headache 0% and pain 0% as ≥4 out of 5 in terms of severity. In the TD group, 52% tingling, itching 28%, burning 12%, headache 4% and pain 4% as ≤3 out of 5 in terms of severity and 16% tingling, 4% itching, 0% burning, 0% headache, and 0% pain as ≥4 out of 5 in terms of severity. Of the 50 participants, none correctly guessed which of the 3 sessions involved Sham tDCS (Fig 37 and 38). These results are presented in Table 18 and 19.

Table 18 Percentages of sensory side-effects reported as ≤3 out of 5 severity during sham stimulation in HFA and TD group.

Groups	Tingling	Itching	Burning	Headache	Pain
HFA	48%	16%	28%	20%	24%
TD	52%	28%	12%	4%	4%

Table 19 Percentages of sensory side-effects reported as ≥4 out of 5 severity during sham stimulation in HFA and TD group.

Groups	Tingling	Itching	Burning	Headache	Pain
HFA	16%	4%	4%	0%	0%
TD	16%	4%	0%	0%	0%

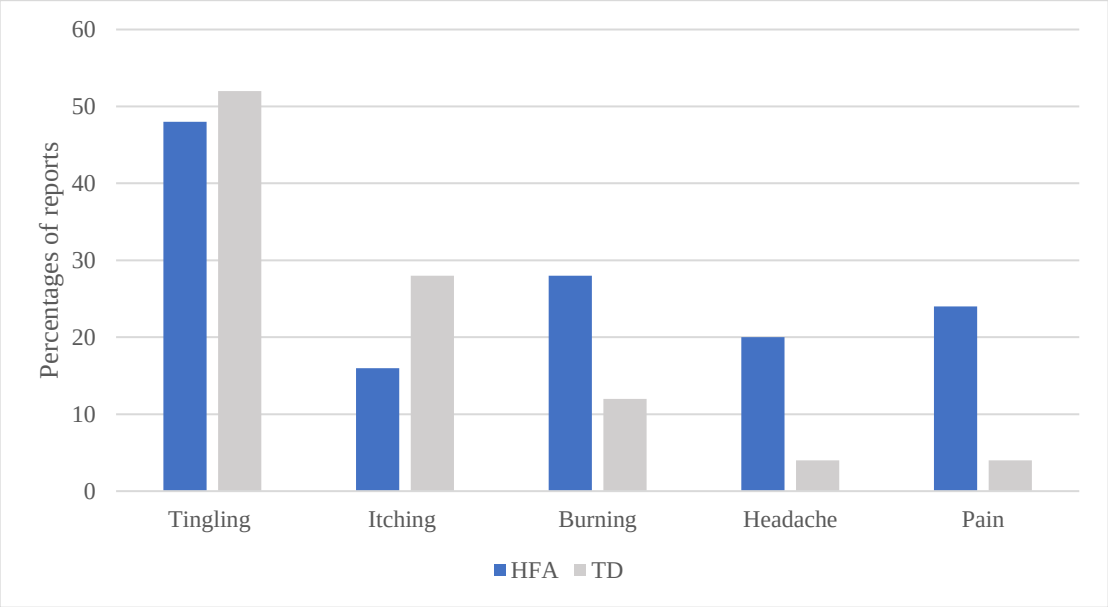


Figure 37 Percentages of sensory side-effects reported as ≤3 out of 5 during sham.

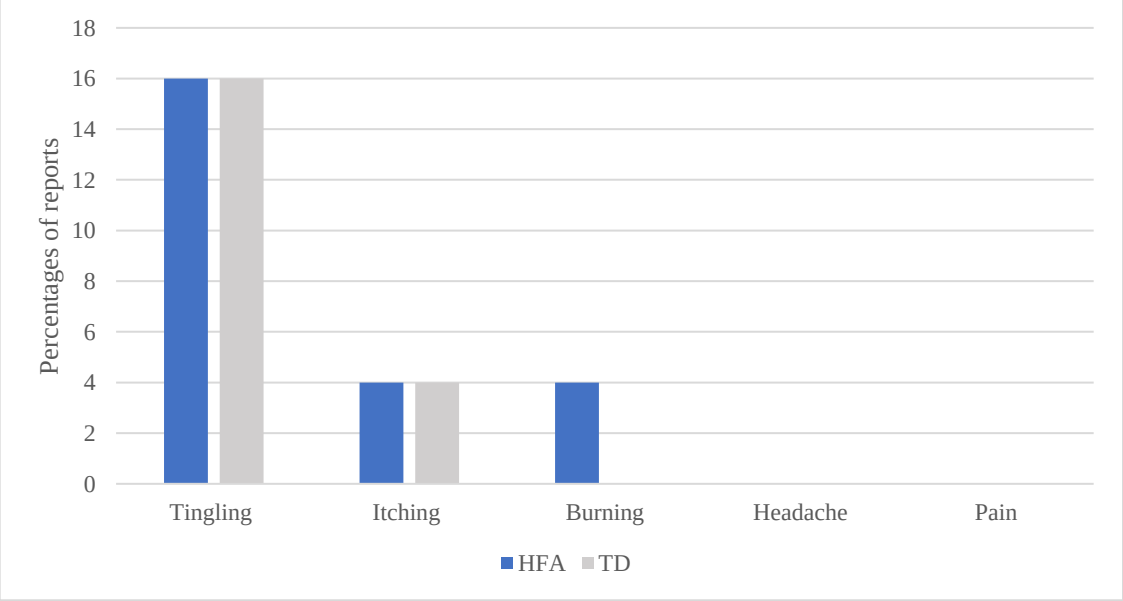


Figure 38 Percentages of sensory side-effects reported as ≥4 out of 5 during stimulation.

In the HFA group, a Wilcoxon signed-rank test showed no significant difference between majority of the sensory side-effects reported between stimulation conditions ($p>0.05$) apart from significantly more itching sensation during cathodal stimulation when compared to sham ($Z=2.1$, $p=0.036$, $d=0.87$) as well as significantly more tingling sensation during cathodal stimulation when compared to anodal stimulation ($Z=2.3$, $p=0.022$, $d=1.02$). In the TD group, a paired sample t-test showed no significant difference between the sensory side-effects reported between stimulation conditions ($p>0.05$). However, there was significantly more burning sensation during cathodal stimulation when compared to sham ($Z=2.64$, $p=0.008$, $d=1.31$), significantly more burning sensation during anodal stimulation when compared to sham ($Z=2.23$, $p=0.026$, $d=1.06$), significantly more itching sensation during anodal stimulation when compared to sham ($Z=2.16$, $p=0.031$, $d=0.97$).

A Mann-Whitney U test demonstrated no significant difference in sensory side effect severity reported between both groups in any of the stimulation conditions ($p>0.05$), apart from the HFA group reporting more pain sensation during sham ($U= 248.5$, $p=0.039$, $d=0.89$).
In addition, in an attempt to characterise parameters that led to a physical sensation of tDCS current, relationships between sensations and demographic variables were examined using Pearson correlation. These variables included measures of head size (inion to nasion) and age. While sleep deprivation has been suggested to change pain perception (Lautenbacher et al., 2006), it was not explored as majority of the participants did not report any sleep deprivation or variation in their sleeping patterns before stimulation. Moreover, the 7 participants (all individuals with HFA) that reported not getting enough sleep the night before did not report any pain side-effect during any of the stimulation conditions.

The analysis demonstrates that there is no correlation in the HFA group between age and any sensory side-effect ($p>0.05$). In the TD group, there was no correlation between age and majority of the sensory side-effect, apart from a moderate negative correlation between age and burning sensation ($r=-0.519$, $N=25$, $p=0.008$) showing that the younger the participants the higher report of burning sensation (Fig. 39). A simple linear regression was carried out to test if age significantly predicted scores on the WMQ. The results of the regression indicated that the model explained 27% of the variance and that the model was significant, $F(1, 24) = 8.5$, $p=0.008$. Furthermore, the analysis

demonstrates that there is no correlation in the HFA and the TD group between head size and any sensory side-effect ($p>0.05$).

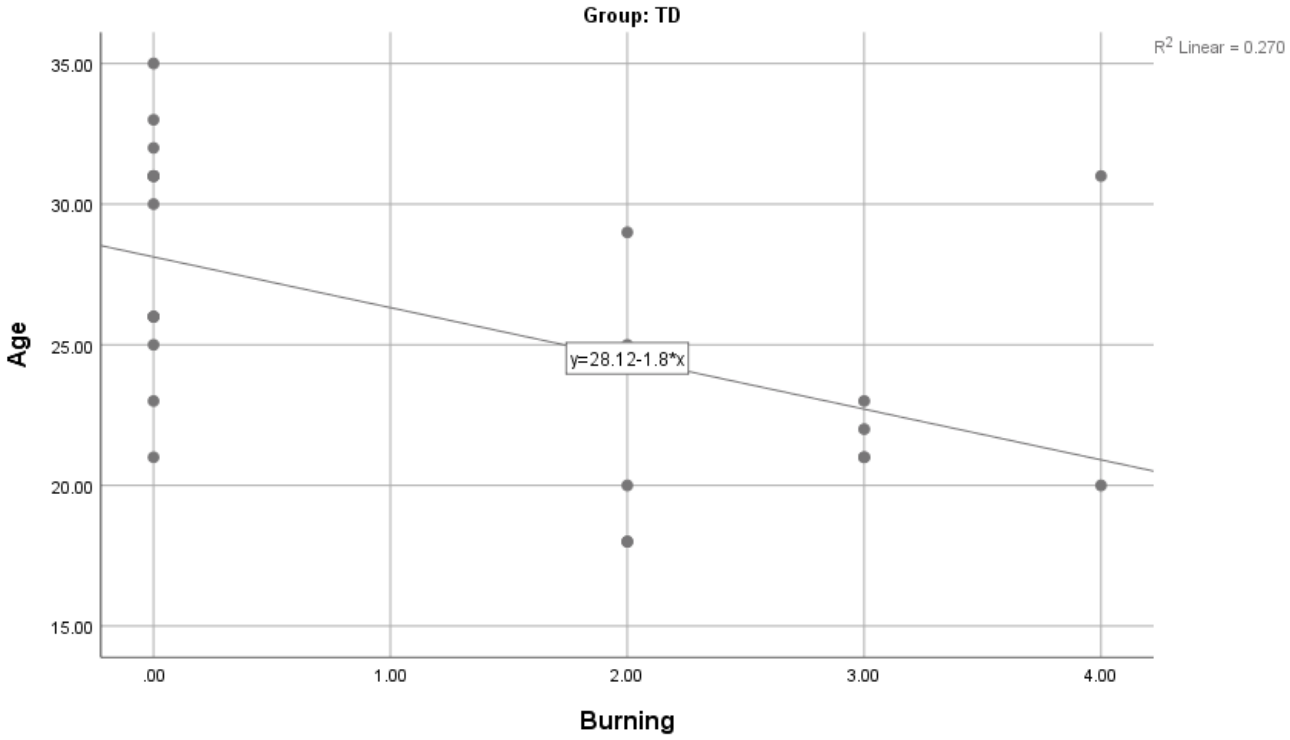


Figure 39 shows the relationship between age and burning sensation during stimulation in the TD group.

Furthermore, additional side-effects were reported after the anodal stimulation session. These reported side-effects are based on participants volunteering the information themselves without being specifically asked. Seven participants reported that they felt they had better attention for the rest of the day. Two parents and five partners reported that their son/partner were more sociable for the rest of the day and were generally in a better mood. One participant reported that he felt way better and focused and asked if he can keep receiving tDCS.

These result demonstrate that tDCS did not cause any adverse side effect, showing that 72% of all the participants reported a ≤3 out of 5 in terms of severity on the sensory side-effects regardless of the simulation condition, while 28% of the all participants reported a ≥4 out of 5 in terms of severity on the sensory side-effects. Interestingly, 76% of the HFA group reported a ≤3 out of 5 in terms of

severity on the sensory side-effects and 24% reported a ≥4 out of 5, while 68% of the TD group reported a ≤3 out of 5 in terms of severity on the sensory side-effects and 32% reported a ≥4 out of 5, demonstrating that TD individuals were more sensitive to the stimulation while individuals with ASD are reported to have increased pain sensitivity and increased touch sensitivity (Riquelme, Hatem and Montoya, 2016). Moreover, none of the participants verbally report any discomfort or request for the stimulation to end at any point during the session or experiment, reported any adverse side effect after each session or had any physical signs of heating effects/burning, irritation, or skin abrasion.

5.4 Discussion

This phase II clinical trial found that recruitment of individuals with HFA for tDCS studies is feasible, however only when having and using the appropriate resources. It would not have been possible for us to recruit the sum of participants we did had we not gone via the NHS, as stated in section 5.2.3, we were unable to recruit a single participant in the first year of this study, without NHS ethics. However, there is a possibility of using additional recruitment points in the future e.g, autism charities, support groups and schools.

Our findings from this phase II clinical trial demonstrated that 15 minutes of anodal tDCS at an intensity of 1.5 mA led to an improvement in WM performance scores when administered over the left DLPFC when compared to baseline, cathodal and sham stimulation of the same area in adults with HFA. This was revealed by greater correct responses, fewer errors and faster reaction times in identifying the target and non- target during and post anodal stimulation, showing that tDCS on WM was effective. While there was a significant difference in the HFA group, the TD group did not show any statistical difference on WM performance in accuracy and error rate on the task during and post anodal, cathodal and sham stimulation. However, there was significantly faster RT during and post anodal stimulation when compared to baseline, cathodal and sham stimulation. These findings were consistent with our hypothesis.

Baseline comparison between the two groups demonstrated that individuals with HFA were further impaired in WM when compared to the TD group, emphasising the importance of taking into account baseline task performance in the design of non-invasive brain stimulation protocols. Yet, there was no difference between the two groups post stimulation. As evident by the changes in scores, individuals

with HFA benefited more from the stimulation than the TD group. Furthermore, the findings revealed a relationship between the 3-back task and IQ (as measured with the WASI) in the HFA group, showing that individuals with higher IQ scores had greater scores on the 3-back task. There was also a relationship between age and the scores on the WMQ in the TD group. The results demonstrate that as participants in the TD group age increased they reported more issues with WM (as increased scores on the WMQ).

As per the reports of participants' sensory side-effects, tDCS was tolerable and did not cause discomfort or inconvenience to the participants. Participants could not differentiate between active or sham stimulation, as the analysis showed no significant difference between the sensory side-effects reported between stimulation conditions, although some participants reported greater sensory side-effect (tingling and burning) during active stimulation. The analysis investigating parameters that led to a physical sensation revealed that the younger the TD participants were the higher report of burning sensation during stimulation. Additional side-effects were reported after the anodal stimulation session such as better attention, more sociability, improved mood and greater focus. However, these reports should be interpreted with caution as the current experiment was not investigating these additional side-effects. The reports were not based on a standardised method, but rather the individuals volunteering the information themselves without being specifically asked.

5.4.1 Interpretation and comparison with previous studies

Our findings were consistent with a previous finding in regards to tDCS improving WM performance in individuals with ASD (Van Steenburgh et al., 2017) and consistent with previous findings that tDCS leads to improvements in WM (Andrews et al., 2011; Baggoi et al., 2005; Frengi et al., 2005; Lally et al., 2013; Ohn et al., 2008; Teo et al., 2011; Zaehle et al., 2011; for review: Hill, Fitzgerald and Hoy, 2015). There may be multiple explanations for the reported finding. One of the possible explanations of deficits in WM in individuals with ASD is that individuals with ASD show prefrontal hypoactivation during WM tasks (Luna et al., 2002; Koshino et al., 2008) and show reduced anterior-posterior connectivity (Cherkassy, Kana, Keller and Just. 2006; Kana, Keller and Minshew, 2007). Also, due to WM depending on PFC activity and communication between the DLPFC and posterior parietal resources (D'Esposito, Postle and Rypma, 2000; Cohen et al, 1997). Another explanation for the deficits is that individual with ASD are reported to using different brain regions during WM tasks

(Koshino et al., 2005; Luna et al., 2002; Silk et al., 2006). Another side effect of tDCS that could have led to improved task performance, is emotional control. Better emotional control could help participants combat frustration as WM task becomes more difficult (Feeser et al., 2014) also resisting the effects of stress (Bogdanov and Schwabe, 2016). Moreover, improved integration of the PFC with the rest of the WM network can also improve the ability to suppress irrelevant information and ignore interference (D'Esposito and Postle, 2015; Wu et al., 2014). Additionally, neuroimaging studies suggest that prefrontal anodal tDCS significantly enhances functional connectivity which in turn increase resources for more efficient cognitive processing (Keeser et al., 2011, Keeser et al., 2011) and processing speed (Gögler et al., 2017). Another possible explanation to the enhancement observed from tDCS is that tDCS may have increased glutamate levels (Clark, Coffman, Trumbo and Gasparovic, 2011) an amino-acid involved in WM, recognition memory, stimulus–response learning and memory, and higher cognitive functions (Robbins and Murphy, 2006). However, the observed improvement on the WM task in the current findings may be task specific and may not translate as an overall improvement in the construct of WM and thus a generalised WM improvement is not a guarantee.

The effects we found were among the largest in the literature for the individuals with HFA, meta-analyses of tDCS on WM have typically shown smaller effects of anodal stimulation at F3 in both healthy adults and clinical populations (Mancuso, Illieva, Hamilton and Farah, 2016; Hill, Fitzgerlad and Hoy, 2016). In our study, we found overall large effect sizes during accuracy, error rates and reaction time for individuals with HFA. Several factors could be attributed to the greater than typical effect sizes reported here. Baseline comparison between the two groups demonstrated that individuals with HFA were further impaired in WM when compared to the TD group, this might have provided more room for improvement than in TD adults. Possible dopamine depletion and its effects on working memory could be another explanation for the reported deficit as evidence suggests that ASD might be associated with dopaminergic dysfunctions (Scott-Van Zeeland et al., 2010; Ernst et al., 1997; Dichter et al., 2012). A neuroimaging study showed an increased release of dopamine in prefrontal and subcortical areas during a WM task (Aalto et al., 2005), showing that indeed, dopamine plays an important role in WM and that dopaminergic stimulation may be critical in maintaining the prefrontal cortex activity at a suitable level necessary for processes of WM. Therefore, it could be speculated that an increase in excitability and activity resulted in an increase in the dopamine release and in turn improved performance or the WM task. This is based on previous

transcranial magnetic stimulation studies that showed such effect after prefrontal cortical stimulation (Strafella, Paus, Barrett and Dagher, 2001; Keck et al., 2000).

The meta-analysis by Hill, Fitzgerald and Hoy (2016) found no significant results for WM tasks performed online in the healthy cohort, whereas the neuropsychiatric cohort showed no significant improvement in offline WM performance. However, our results revealed that in the HFA group, there was significantly greater performance on the WM task both during and post stimulation. While performance was slightly better post stimulation when compared to during stimulation, there was no significant difference between online stimulation and offline stimulation performance. In the TD group, we did not find a significant result in WM task performance during online and offline anodal stimulation. We only found faster RT, however, this found during online and offline anodal stimulation with RT slightly faster post stimulation but no significant difference between the two sessions.

Moreover, our findings are consistent with previous research, we found that the effect of tDCS depended on stimulation polarity (Nitsche and Paulus 2000; Nitsche et al., 2003), meaning that the WM improvement were only during anodal stimulation and not cathodal. This is due to anodal tDCS causing depolarization of the resting membrane potential, which increases spontaneous neuronal excitability and activity, while cathodal tDCS causing hyperpolarization of the resting membrane potential and thus decreases neuron excitability and activity (Nitsche et al., 2008). In addition, research has shown that anodal stimulation leads to increased blood flow to the brain whereas cathodal stimulation leads to decreased blood flow (Lang et al., 2005; Stagg, O'Shea, et al., 2009; Paquette, Sidel, Radinska, Soucy, & Thiel, 2011) and that anodal stimulation leads to a decrease in inhibitory (GABA) and increase in excitatory (glutamate) neurotransmitters, whereas cathodal stimulation leads to the opposite effect (Clark et al., 2011; Rango et al., 2008; Stagg et al., 2011, 2009). Our findings support the hypothesis that the DLPFC may be underactive or not fully utilised in individuals with ASD, as the depolarization of resting membrane potential caused by anodal tDCS suggests a possible correction to an underactive brain region that could impair WM. Indeed, research has shown that WM impairments specifically in ASD contributed to lack of focus and sustaining attention.

While the HFA group demonstrated improvement in WM performance post anodal tDCS, the TD group did not improve in performance in terms of accuracy or reduce error rate, however, there was significantly faster RT post stimulation, which is consistent with previous research (Wang, Wen and Li, 2018; Nikolin, Martin, Loo and Boonstra, 2018). A possible explanation for this observed effect is that since the TD groups' WM was not impaired, there was little room for improvement on performance, however, tDCS may have led to an increase in attention which lead to the significantly faster RT observed. Indeed, a study by Gladwin, Uyl, Frengi and Wiers, (2012) demonstrated that tDCS improved selective attention in the context of a Sternberg task and led to improved reaction time on the task.

Furthermore, our findings revealed a relationship between the 3-back task and IQ (as measured with the WASI) in the HFA group, showing that individuals with higher IQ scores had greater scores on the 3-back task. This is an important finding as there is widespread evidence that WM shares significant variance with fluid intelligence measures (Gf) (Ackerman, Beier, & Boyle, 2005; Kane, Hambrick, & Conway, 2005; Kyllonen & Christal, 1990; Oberauer, Schulze, Wilhelm, & Suss, 2005). Jaeggi, Buschkuehl, Jonides, and Perrig (2008) define fluid intelligence as the ability or power to reason and solve newly encountered problems without relying on previously acquired information or knowledge. In this case, fluid intelligence allows individuals to adapt their thinking to handle a new cognitive situation of problem. Jaeggi and colleagues indicate that fluid intelligence is critical for the performance of various cognitive tasks, which makes it an important determinant of learning achievement. As a result, fluid intelligence is highly relevant in educational and professional success especially in cases where individuals operate in complex and highly demanding contexts. Conceptualizing fluid intelligence as the human cognitive ability to comprehend complex relationships and address novel problems, Yuan, Steedle, Shavelson, Alonzo, and Oppezzo (2006) note that fluid intelligence is the nearest second-level factor in relation to general intelligence based on the concept of hierarchical model of intelligence. They further noted that the nature of fluid intelligence means that cognitive tests not reliant on previously acquired knowledge provide a good measure of fluid intelligence.

Given that WM allows individuals to maintain information actively in a readily accessible format, various researchers have investigated its relationship with wider intellectual ability measures, such as fluid intelligence and scholastic aptitude. Such research provides various viewpoints explaining the

relationship between the two constructs. For instance, Salthouse and Pink (2008) conducted a study involving 1,000 adults undertaking various cognitive and WM tasks that required the subjects to perform information storage and processing simultaneously. The study's design varied the set size (amount of information to be remembered) randomly across the trials, providing an opportunity to examine how WM and fluid intelligence relate across various levels of complexity. The findings of the study indicated that fluid intelligence had strong influences even in the simplest starting tasks of WM, suggesting that the two constructs are related independent of the quantity of information that needs to be maintained. In other words, the association of WM and fluid intelligence does not arise from higher fluid intelligence translating to preservation of more temporary information. Instead, they noted that the relationship between the two constructs may be a reflection of high levels of fluid intelligence enabling individuals to adapt quickly to novel tasks quickly and perform more effectively, even in contexts requiring minimal demands for storing and processing information simultaneously.

Moreover, it has been demonstrated that WM tasks and measures of Gf use similar neural networks (Duncan et al., 2000; Gray, Chabris, & Braver, 2003; Kane & Engle, 2002). There are a number of studies showing correlations between N-back performance and various intelligence measures (Friedman et al., 2006, 2008; Gevins & Smith, 2000; Salthouse, Pink, & Tucker-Drob, 2008; Shelton et al., 2009; Van Leeuwen et al., 2007; Waiter et al., 2009) the correlation coefficients range between r.19 and r.66, suggesting shared variance between N-back performance and Gf. Moreover, Gevins and Smith (2000) as well as Hockey and Geffen (2004) investigated whether individual intelligence differences predict performance in the N-back task which they found that indeed participants with high IQ scores performed faster in the N-back task, especially at higher task levels. Our finding supports previous studies where it was found that individuals with high WM performance have greater intelligence scores. Furthermore, our results demonstrated that as TD participants age increased they reported more WM issues. This is consistent and represented in previous findings, where WM declines with age (Pliatsikas et al., 2018) and where older individuals report worse WM than young adults (Bopp and Verhaeghen, 2009; Klencklen, Lavenex, Brander and Lavenex, 2017).

Participants were blinded as to what stimulation condition they were receiving as per the reports of the participants sensory side-effects of tDCS. Participants could not differentiate between conditions due to implementing the sham condition as described by Hummel and Cohen (2006), that ramping up

and down for 10 seconds, combined with a 30 second placebo stimulation which made real tDCS and the sham stimulation condition indistinguishable. The additional side-effects that were reported in regard to having better attention, increase in sociability, improved overall mood and focused after the anodal stimulation session should be interpreted with caution as the current experiment was not investigating these additional side-effects. The reports were not based on a standardised method but rather the individuals volunteering the information themselves without being specifically asked. A possible explanation is that tDCS may have stimulated other brain regions in the frontal lobe that improved other cognitive abilities apart from WM. Indeed, research has demonstrate that tDCS improved attention (Coffman, Clark and Parasuraman, 2014; Gladwin, Uyl, Frengi and Wiers, 2012), mood (Bueno et al., 2011) and social cognition (Santiesteban, Banissy, Catmur and Bird, 2012). These additional side-effects reported may be an interesting factor to investigate or enquire about in a standardised way in future research.

We compared our findings to the one study available on tDCS and WM in ASD by van Steenburgh et al. (2017). There are a number of similarities between the current study and the one conducted by van Steenburgh and colleagues. Both studies had individuals with HFA (this was assessed by IQ testing, and scoring over 70) diagnosed by a clinician and had their diagnosis confirmed with the ADOS. Moreover, all participants in both studies spoke English as their first language and had no record of neurological disease, psychiatric disorder, or active use of antipsychotic medications. From a methodological standpoint, both studies adopted a single-blind, crossover, randomised, counterbalanced design and investigated the offline and online effects of tDCS at 1.5 mA. During the sham condition, both studies utilised a 30 seconds duration stimulation. In addition, both studies allowed participants to practice the task before stimulation until they reached a plateau in performance, as well as investigated sensory side-effects with a questionnaire after stimulation.

However, while there are quite a few similarities, there are also some substantial differences. The first and biggest difference is that the study by van Steenburgh and colleagues had only 12 participants, between the ages of 20 and 66 (mean age 32.1) of which ten were males and two were females making it extremely underpowered for a within-subject comparison, which could lead to criticism that their observed significant effect may be inaccurate (Woods et al., 2016). Underpowered studies have been suggested to have a reduced chance of detecting a true effect, overestimate effect size and has low reproducibility of results, as well as an ethical dimensions issue, as unreliable research is

inefficient and wasteful (Button et al., 2013). In addition, the fact that they had older participants could have led to the observed baseline WM deficit, as it has been reported that WM deteriorates with age (Pliatsikas et al., 2018; Wang et al., 2011) and subsequently allowing for greater room for improvement. In our study, we had 25 male participants (based on a power calculation) in each group between the ages of 18 and 35 (mean age ~25 in both groups), controlling for WM decline, which has been reported to start after 35 years of age (Hartshorne and Germine, 2016) and allowing for a better representation of the male ASD population. Moreover, they study by van Steenburgh et al. collected information regarding participants years of schooling, however, they did not investigate if education played any role in the reported improvements.

Another significant difference is the duration of stimulation. In our study, we had a constant stimulation for 15 minutes per session, while van Steenburgh and colleagues had a 40 minutes stimulation per session. Although research has shown that greater stimulation duration lead to greater effects (see Hill, Fitzergald and Hoy, 2015 for review), the current study is one of the first studies investigating the effects of tDCS on WM and polarity in ASD, therefore, as a precaution, we did not implement a longer duration of stimulation. Nonetheless, research has already demonstrated that 15 minutes (and 10 minutes) of active stimulation over the left DLPFC led to an improvement in WM (Andrews et al., 2011; Berryhill and Jones, 2012; Fregni et al., 2005; Mulquiney, Hoy, Daskalakis and Fitzgerald, 2011; Oliveira et al., 2013; Zaehle et al., 2011). Moreover, van Steenburgh and colleagues implemented a ~seven day's washout between sessions with a minimum washout of 24 h, while in our study we had a 48-h washout minimum. This should not affect the outcome of either study in any way as both studies allowed sufficient time for the after effect of tDCS to washout (Nitsche et al., 2008). Another important difference between the two studies is that we investigated the effect of polarity (anodal vs cathodal) on WM, while van Steenburgh and colleagues only explored the effect of active stimulation vs sham.

Finally, we utilised a 3-back WM task while van Steenburgh and colleagues utilised a N-back task that increased from 1-back to 2-back to 3-back for each block. This could be problematic as participants may have been confused in regards which load they are currently in, even though a reminder message identified the current task load at the top of the screen. The reason a three-back WM task was used is because the degree of difficulty of a test is related to the likelihood to detect degradation or improvement in the brain function following tDCS (Mull and Seyal 2001; Freggni et

al., 2005). Using an easier task (such as lowering the N) as van Steenburgh and colleagues did might not have detected subtle behavioural effects due to ‘‘ceiling’’ effect, while a more difficult version (increasing the N) may have obscured performance due to the ‘‘floor’’ effect. This was also confirmed in their findings that higher-functioning participants showed ceiling effects. An important issue to consider with N-back tasks is practice effect, as the WM task was given repeatedly, and N-back tasks are prone to practice effect (see Au et al., 2015; Soveri et al., 2017 for reviews) which may lead to a practice curve that could affect the results. Of course, we addressed this concern by allowing the all participants to practice the test at the beginning until participants reported they were confident with the task and until they reached a performance plateau. The analysis revealed that there was no practice effect in either of the groups, as there was no difference in participants' performance at time 1 (pre-stimulation) on any of the three days.

Similar to van Steenburgh and colleagues, we found that active tDCS improved WM performance in individuals with HFA when investigating accuracy. In our study we also investigated error rate and reaction time, while van Steenburgh and colleagues only chose to investigate accuracy, this may not have a realistic representation of the subject being investigated as accuracy, error rate, and reaction time are all valid measures of WM and especially N-back tasks. Both studies had similar findings although in the current study, the electrodes were placed as per the more typical montage over F3 and Fp2, while the study by van Steenburgh and colleagues placed the electrodes over F3 and F4 using the 10–20 international electrode positioning system. However, both montages have been shown to improve WM (see Brunoni and Vanderhasselt, 2014; Hill, Fitzgerald and Hoy, 2015 for review). This may have contributed to the reason why in our study we found larger effect sizes than the study by van Steenburgh and colleges, where they found a Cohen's ds effect sizes of 0.52 for left anodal stimulation during stimulation and 0.33 post stimulation, while we found Cohen's ds effect size of 0.66 during stimulation and 0.73 post stimulation. Another factor that could have played a role, particularly in not finding a significant effect post stimulation is that van Steenburgh and colleagues had a 50-minute delay between the end of stimulation and the start of offline performances, which may have allowed for the effects of stimulation to diminish, while in our study participants performed the 3-back task immediately after the end of stimulation.

Although there is evidence that tDCS can have an impact on cognitive and behavioural outcome measures, research into the effect of tDCS has been rather inconsistent (for review: Jacobson,

Koslowsky, & Lavidor, 2012). The main reason for this discrepancy in the literature is namely due to variations in current density, electrode assembly and / or stimulate-to-task relationships can lead to different results. And since a standard tDCS protocol has not yet been developed, it is left to researchers to select their own values for each parameter leading to a largely disparate and incomparable literature.

Another criticism that tDCS research tends to receive is the inability to replicate findings in the literature. However, it is important to note, that tDCS research is not the only one facing concerns regarding reproducibility. For example, in 2015 a report from the Open Science Collaboration reported an inability to replicate over 60 experiments selected from the Psychological literature. Overall, 36% of the replications yielded significant findings compared to 97% of the original studies that had significant effects. Moreover, John Ioannidis (2005) showed that of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. In another study by John Ioannidis (2014), he reported that currently, many published research findings are false or exaggerated, and an estimated 85% of research resources are wasted. Furthermore, Begley and Ioanndis (2015) claimed that preclinical research is unable to replicate the majority of findings presented in high-profile journals, and that these estimates for irreproducibility based on these empirical observations range from 75% to 90%.

5.4.2 Strengths and limitations

There are a number of limitations to the current work that should be addressed in future research. Recruiting and investigating solely individuals with HFA creates problems with generalising the entire autism spectrum and findings may therefore not be observed in those with classic autism. Another limitation to our study is that we used a single-session of anodal tDCS to examine its effect on WM performance. A meta-analysis in 2015 by Horvath, Forte, and Carter (2015) suggests that single-session tDCS does not reliably benefit any cognitive. Our findings, however, do contradict these findings, showing that in fact a single session of tDCS did enhance WM performance. This again could be due to WM deficits in individuals with HFA providing more room for improvement and benefiting WM. Another limitation to the current study, is the comparison analysis between the

HFA and the TD group. These results should be interpreted with caution, as we did not have sufficient participants to conduct a valid statistical comparison, therefore, these results are more observational. Future research should consider these observed differences and investigate them fully in order to clarify this finding.

Blinding is a critical methodologic feature of RCTs (Karanicolas, Farrokhyar and Bhandari, 2010). In tDCS research and literature, blinding has received a great deal of attention. There are two main forms of blinding, single-blind (where only the participant is blinded) and double-blind (where the participant and the experimenter are blinded). Single-blind in tDCS research is normally referring to the stimulation sensation ratings reported by participants, as in can participants tell the difference between receiving active or sham stimulation. Therefore, participant sensorial experience is often considered a critical component of blinding. Double-blinding research when ideally performed, produces knowledge untainted by bias (Kaptchuk, 2001). By blinding data collectors and outcome adjudicators (sometimes the same individuals) ensure unbiased ascertainment of outcomes (Karanicolas, Farrokhyar and Bhandari, 2010). In terms of tDCS research, it has been suggested that double-blind experiments are usually ideal for experimental control (Thair, Holloway, Newport and Smith, 2017).

In our study, we only implemented a single-blind protocol as the lead researcher was the only person in the research team that was trained in the administration and operation of the tDCS device. Moreover, as this was an experiment part of a thesis of the lead researcher, it was inevitable that the lead researcher would also be the one conducting the analysis. However, we feel that this did not affect our results in anyway as research has shown that experimenters can still make guesses as to participant condition based on observations of sensations and erythema following stimulation. In a study that tracked experimenter blinding, findings suggest that the experimenter accuracy in determining participant stimulation condition is greater than chance, based largely on the presence of skin erythema (O'Connell et al., 2012). A potential solution to this issue is a dose of acetylsalicylate or topical application of ketoprofen that may reduce erythema (Durand, Fromy, Bouyé, Saumet, & Abraham, 2002; Guarienti et al., 2014). A practical solution is to not remove the electrode after stimulation and have the electrodes removed by another researcher that is not involved in data collection. But, of course, this solution is only achievable when the research is not conducted by one person. In our study, the same researcher who collected data was also responsible for the removal of

the electrodes. Finally, Coffman et al. (2012) reported no behavioural differences have been observed between single-blind and double-blind tDCS experiments, and thus experimenter influences may not be as significant as expected (Thair, Holloway, Newport and Smith, 2017). Although double-blind studies are favoured in the majority of cases due to scientific rigorousness, it may not be possible when it comes to tDCS research as studies have shown that during stimulation using a high current density (0.0571 mA/cm2), neither the practitioner nor participant was effectively blinded (O'Connell et al., 2012).

Furthermore, blinding was successful in our study based on reported sensation. Consistent with previous research (Kessler et al., 2012; Matzen et al. 2015), while there were reports of participants experiencing greater sensations when receiving active stimulation to sham stimulation, there was not a significant difference between stimulation conditions, supporting previous research that found no difference in sensation between anodal, cathodal, and sham tDCS (Gandiga, Hummel, & Cohen, 2006). In a meta-analysis conducted by Fertonani, Ferrari, and Miniussi, (2015) it was found that anodal (but not cathodal) tDCS produced an average discomfort rating roughly 25% higher than sham stimulation, however there was no statistical difference ($p=0.056$), which is consistent with our findings. Additionally, blinding was also successful based on inability of participants to correctly identify whether they had received active or sham stimulation (Russo, Wallace, Fitzgerald, & Cooper, 2013).

A common limitation in tDCS research is the lack of focality (Datta et al., 2009). Thus, other frontal areas of the brain aside from the DLPFC were likely effected by stimulation. Therefore, the lack of precise focality in the present study cannot rule out the possibility that perhaps areas adjacent to DLPFC may also have received increased activity. Using ring electrodes (Villamar et al., 2013) rather than the most commonly used rectangular electrodes sized between 25 and 35 cm^2 (5 × 5 cm and 5 × 7 cm) (Utz et al., 2010) has shown to enhanced focality due to the suppression of surrounding regions by the other electrodes, constraining any modulation (Datta et al., 2009), this is referred to as HD-tDCS.

Published tDCS research is largely underpowered due to small sample sizes (for discussions see: Brunoni et al., 2011; Berryhill et al., 2014; Horvath et al., 2014; Shiozawa et al., 2014).

Moreover, evidence suggests autistic traits are continuously distributed across the population (Wing, 1988; Constantino and Todd, 2003; Posserud, Lundervold and Gillberg, 2006), this could be problematic when having a TD group as research has showed that those with higher than typical levels often have performance patterns and even brain structure that are more similar to the clinical group than controls. (Grinter, Maybery, Van Beek, Pellicano, Badcock, et al., 2009a; Grinter, Van Beek, Maybery, & Badcock, 2009b; Stewart, Watson, Allcock, & Yaqoob, 2009; Sutherland & Crewther, 2010, von dem Hagen et al., 2011). However, we had the TD group preform the AQ, to account for autistic traits. Finally, the use of multiple statistical tests, there is an increased risk in this study for type I errors (i.e., identifying a significant effect in the sample when such an effect does not exist in the population). Replication of the current findings, ideally using larger samples of subjects if possible, is needed to determine their reliability and generalisability.

Nevertheless, our results are novel in several ways. To the best of our knowledge, this is the largest study to demonstrate that anodal tDCS over the DLPFC may have beneficial effects on WM in individuals with ASD. A strength of the current study is the sample size. Published tDCS research is largely underpowered due to small sample sizes (for discussions see: Brunoni et al., 2011; Berryhill et al., 2014; Horvath et al., 2014; Shiozawa et al., 2014). This has also been found true for clinical trials (Califf et al., 2012) and more specifically ASD research (Thrum and Swedo, 2012). We addressed this by basing our sample size on a power calculation (see Method section of Chapter 5), assuring we has a large enough sample to achieve a meaningful result. Moreover, we controlled for age and IQ assuring that there was no significant difference between participants age and IQ as research has shown that both age (Hartshorne and Germine, 2016) and IQ (Salthouse and Pink, 2008) play a role in WM.

Another strength to the current study was the rigours design and protocol adopted in the study. By referring to the systematic review and meta-analysis by Hill, Fitzergald and Hoy (2015), we ensured that our study design met a high standard by adopting a crossover design, testing the online and offline effects of tDCS, having a moderately high current density, moderately long duration time, comparing anodal stimulation to cathodal and sham, and utilising F3 and Fp2 electrode placement. Furthermore, by referring to the literature, we implemented a 30 second ramp-up and down, a 48-hour wash-out period for tDCS and practice effect of the WM task, and recruiting only right-handed male participants between the ages of 18 and 35 (See Study design of the method section for a

detailed summary). The work presented here makes a number of novel contributions to the present WM, ASD and ASD intervention literature which can be used to develop future studies centred on the most effective way to enhance the quality of life for individuals with ASD. This work also contributes to the tDCS literature by extending previous work in the domain of WM, these findings have an important implication for the researchers, clinicians as well as the patients. Our finding supports the possibility that tDCS could be used as a remediation technique.

5.4.3 Future research

The findings of this study raise a number of interesting questions and opportunities for further research in a similar vein. Perhaps the most obvious question that follows is where to go from here? Some further research can be done using this research as a foundation With the encouraging results of this phase II clinical trial, a logical step is to further assess the safety and efficacy of tDCS in a phase III study to systematically investigate tDCS application on WM impairments in individuals with HFA and evaluate the effectiveness of the new intervention and, thereby, its value in clinical practice, which is a prerequisite for the development of pivotal phase III efforts in the field of NIBS.

It would be useful to replicate this study in a full large-scale clinical trial, by recruiting more participants, including female participants, and implementing a follow-up (e.g. 6 months) in order to determine the duration of task improvements and observe if WM improvement induced by tDCS are lasting and if they are transferable to real-world skill.

Moreover, if the findings from a phase III study were positive it may be useful to test ASD individuals at the lower end of the spectrum could be important, since this research focused on highly-functioning individuals. However, this could be problematic as being at the lower end of the spectrum means that individuals already have intellectual weaknesses and thus the WM performance could be attributed to either WM deficits or intellectual weakness. Looking at younger or older participants can be important as this study was done on individuals between the ages of 18-35, majority at the university level. In addition, seeing the effect of multiple, longer periods of stimulation and/or higher currents of tDCS would improve performance in ASD, as tDCS research has shown that the effects of a single tDCS session last no longer than an hour (Nitsche et al., 2008). However, there is research reporting long-term improvement (lasting up to 12-months) after one

anodal and one cathodal tDCS sessions (Berryhill and Jones, 2012). In addition, future research can examine the functional networks and local activations engaged in WM processing which will improve our understanding of the effects of tDCS by analysis of patterns of brain activation accompanying the changes in cognitive performance. Further neuroimaging studies would help answer these questions and, importantly, help map the extent and role of WM in individuals with ASD. This would ultimately lead to successful approaches to improving WM in individuals ASD using non-invasive brain stimulation. Moreover, while the EEG 10/20 system is commonly used, adopting MRI-guided neuronavigation may be more accurate than the 10:20 EEG system and would improve locating the cortical areas of interest, which in turn improve the overall all outcome of tDCS. Furthermore, future research should focus on parametric variation (e.g. – current density, stimulation time, electrode location, etc.) in order to have a standardised protocol which can be utilised and in turn address the current variability seen in the literature. Until a standardised protocol is developed variability will most likely continue which in turn will obscure any true effect of tDCS.

Many biological and lifestyle factors could influence the effect of tDCS. The literature has suggested that hair thickness and amount of sweat produced on the skin surface below the electrode pad (Horvath et al., 2014), head size and tissue thickness (Bikson et al., 2012), skull thickness (Datta et al., 2012), subcutaneous fat levels along with CSF density, cortical fluid density, cortical surface topography and individual morphologies of cortical gyri and sulci (Opitz et al., 2015), initial state of the cortex before stimulation (Filmer et al., 2014; Krause and Cohen Kadosh, 2014), neurotransmitter levels (especially GABA) (Krause and Cohen Kadosh, 2014), stages of the menstrual cycle (Inghilleri et al., 2004; de Tommaso et al., 2014) age (Fujiyama et al.,2014; Li et al., 2015), intake of neuroaffective substances (e.g., nicotine) (Grundey et al., 2012), educational level (Berryhill and Jones, 2012), personality (Peña-Gómez et al., 2011), sex (Fumagalli et al., 2010), time of day (Marshall et al., 2004), level of thirst (Müller et al., 2002), medication (McLaren, Nissim and Woods, 2018), sleep (Lautenbacher et al., 2006), genetics (Egan et al., 2001; Chen et al., 2004 ; Hasan et al., 2013), and even expectations (Rabipour, Wu, Davidson and Iacoboni, 2018) could influence cortical excitability and modulatory response, all of which could easily be controlled and accounted for or matched as closely as possible between, or within, experimental groups. Future research should also use some type of side-effect questionnaire in order to better understand the adverse effect of tDCS, as this is currently lacking in tDCS research.

fMRI can be used to examine how tDCS influences brain networks with high spatial resolution and investigate the direct modulatory network changes after or during tDCS as well as also help to identify brain regions involved in a tasks (Thair, Holloway, Newport and Smith, 2017). EEG can be combined with tDCS to uncover a greater understanding of cortical excitability before and after tDCS (Schestatsky et al., 2013), as integrating tDCS and fMRI may have a large financial cost, and does have many practical and safety complications.

The most promising result of this study is that individuals with ASD benefited the most from tDCS. Therefore, it is likely that individuals with disorders that comorbid with ASD or symptoms overlap with ASD, such as ADHD, learning disabilities, fragile x syndrome, mood disorders, anxiety, OCD, Tourette syndrome, down syndrome and schizophrenia, may benefit from tDCS. Furthermore, research would need to be extended to show whether such improvement would lead to improvements of real-life functions. This will all aid in taking this topic forward in the literature and closer towards having a standardised protocol to implement as an intervention for WM deficits.

Moreover, the need for Patient & Public Involvement (PPI) and Patient Reported Outcome Measures (PROMs) warrants consideration. By having PPI it can ensure that the research questions are relevant and that the priorities reflect the needs of those affected. It can also help to ensure that the research is conducted in a way that is sensitive to the needs and preferences of the participant and that the research is designed and delivered with the patients in mind which can improve patients experience and influencing trial recruitment and retention. PROMs would allow us to know if the participant/patient is satisfied with the treatment, if treatment has improved a patient's health, symptoms and well-being. If this experiment would move to a full scale clinical trial, it would improve the rigour of the study by involving individuals with ASD in the design of the trial and measure secondary outcomes of the trail such as if the findings of the study are indeed is relevant to everyday life and if the findings improved participant's/patient's health, symptoms, well-being and quality of life.

Finally, tDCS researchers must now work towards performing robust, large-scale replication studies in order to develop standardised protocols. It is important that attempts to replicate this study take into account the aforementioned recommendations, even if the expected outcomes suffer. Sometimes negative results on expected indicators can be related to a positive effect for the participants and for

the general population as a whole. If replicated, such a finding could have important implications for the use of tDCS as a remediation technique toward enhancing WM across a number of neurologic and psychiatric conditions.

5.4.4 Conclusions

In conclusion, the present findings of the phase II clinical trial revealed that anodal tDCS administered over the left DLPFC enhanced WM in terms of the recognition accuracy in individuals with HFA, demonstrating the efficacy of tDCS on WM. As evident by the effect size the findings of this study may be beneficial for people with ASD, since individuals with ASD are associated with WM deficiencies. Moreover, there was no reported noticeable side effects associated with tDCS throughout the experimental procedure, demonstrating the safety of tDCS on individuals with HFA. As we were able to recruit 25 individuals with HFA out of 116 screened/invited, which indicates that conducting tDCS studies on individuals with HFA is feasible while having appropriate resources. Up to date, there is no specific treatment for ASD, so focusing on symptom treatment is the best we can do. In severe cases with memory and attention deficit, pharmacologic therapies are recommended, such as antidepressants and antipsychotics (Oswald et al., 2007). However, the outcomes are still unsatisfying, and these medications may cause adverse effects such as nausea, drowsiness, dry mouth, agitation, behavioural activation, and sleep problem (Oswald et al., 2007). Therefore, there is an urgent need for more effective treatment options. Even though there is no ‘cure’ for ASD, Mazurek (2012) reported “varying degree of improvement is possible” with early intervention. Early intervention has a substantial subsequent impact on prognosis: the earlier the diagnosis, and intervention, the better the prognosis (Fernell et al., 2013). tDCS might therefore be a potential therapeutic clinical tool through which to alleviate one of the many symptoms of ASD.

6 General discussion

As evident from this Ph.D. thesis, individuals with ASD report and demonstrate significant WM deficiencies in all aspects, theory and in applied setting. WM deficiencies have been shown to have a negative impact on the quality of life in individuals with ASD, as it not only associated with playing an important role in cognition and a central role in executive function (Hill, 2014), but also it has been demonstrated to contribute to social problems in people with ASD (Gilotty et al., 2002) as it is necessary to keep social information constantly changing in WM for social flexibility (Meyer et al., 2012). WM also encodes emotions observed on faces (Phillips et al., 2008), regulates emotional responses (Schmeichel et al., 2008) and breaks from restrictive or repetitive behaviours (Lopez, Lincoln and Ozonoff, 2005). The treatment of WM deficits could therefore improve some of the core cognitive and behavioural deficits characterising ASD. Cognitive impairments are an important area to investigate when it comes to ASD as cognitive impairment substantially interferes with everyday functioning and creates significant challenges for patients, their families and friends, and clinicians who provide their health care. Early recognition allows for diagnosis, support and appropriate treatment. However, as mentioned in Chapter 5, behavioural methods to remedy WM has had limited effects (Shipstead, Redick and Engle, 2012), and attempted behavioural interventions have suffered from high attrition rates (de Vries, Prinz, Schmid and Geurts, 2015). More importantly, it remains unclear whether improvements that may occur from behavioural remediation would generalise to other tasks or abilities (Ship stead, Redick and Engle, 2012). Moreover, unsatisfying results in treating WM impairments have also be shown from pharmacological approaches, from them not having an effect on improving WM (Wong and Stevens, 2012) to them also causing severe adverse effects (Oswald et al., 2007). This has lead us to conducting the main experiment of this thesis, as an alternative, simpler and faster approach to improving WM deficits is much needed.

The intentions of this thesis was to fulfil current gaps in the research by exploring the literature and finding if there is evidence to support that individuals with ASD suffer from WM impairments, as the literature has been inconsistent. Furthermore, we wanted to investigate if individuals with ASD report WM related difficulties in everyday life. The primary intention of this thesis was to design and conduct a randomised controlled trial looking at the effectiveness of tDCS on WM impairment in individuals with HFA and TD controls. A consistent strength in this thesis is in the rigours and

stringent approach in developing the experiments conducted in this thesis. These studies were conducted based on using the gold standards in meta-analyses and RCT in order to achieve valid and reliable findings and provide an accurate representation of the subject. This chapter will provide a summary of the main findings of the studies conducted for this thesis, as well as conclude with the wider theoretical and clinical implications of these studies, together with a discussion of potential future direction of research that might answer the questions that have been generated by this thesis.

6.1 Summary of main findings

6.1.1 A meta-analysis of working memory in individuals with autism spectrum disorders

In Chapter 3, the objective was to explore whether individuals with ASD experience significant impairments in WM and whether there are specific domains of working memory that are impaired. The current literature has been rather inconsistent in regards to whether individuals with ASD have evident WM deficits, therefore a systematic review and meta-analysis were conducted. The systematic review and meta-analysis showed that individuals with HFA across age groups demonstrated significant WM impairment in both phonological and visuospatial domains. The systematic review and meta-analysis focused on investigating the issue by exploring both WM domains, phonological and visuospatial, while considering different methodology of testing WM and found that WM deficits in ASD were evident across diverse methods of measurement. Moreover, we examined different WM performance outcomes such as accuracy and error rate, which allowed us to have a clear conclusion on the results of whether there are significant impairments in individuals with ASD. Age and IQ were investigated as moderators, and did not explain the variation between studies, suggesting that age did not play a factor in the reported deficits and that WM deficit is not simply attributable to IQ deficits. Our findings were supported by previous research showing that indeed WM is significantly impaired in individuals with ASD. We also did a direct comparison between our study and the only other meta-analysis published on the same issue (Wang et al., 2017). While we had similar findings, our study had a more rigours and stringent methodology and analysis process. Therefore, due to the uncertainty of the findings found by Wang and colleagues (see Chapter 3 for

details), it was recommend to interpret their findings with caution and that our findings have a better representation of the literature.

6.1.2 Assessing everyday life problems related to deficits of working memory in autism spectrum disorder

In Chapter 4, the aim was to investigate whether individuals with ASD experience significant everyday WM related difficulties. Research has shown that WM is crucial in everyday life, however, it has yet to investigate if the WM deficiencies are translated to difficulties with everyday life. This is the first ever study investigating difficulties in everyday life in individuals with ASD using the WMQ. A total of 111 males with ASD between the ages of 18 and 35 were presented with the WMQ. The findings from the study demonstrating relatively large and significant WM related difficulties in everyday life, which is consistent with previous research literature indicating that individuals with ASD experience WM deficiencies. These findings were consistent with our hypothesis that individuals with HFA will report high scores on the WMQ. Results from this study were compared with the study by Vallat-Azouvi and colleagues which developed the questionnaire and investigated the WMQ on individuals with brain injury, as it was the only other study that used the WMQ. It was evident from our findings that individuals with HFA report greater everyday difficulties related to WM than individuals with brain injury. Pearson correlation found no relationship between age and scores on the WMQ, while the study by Vallat-Azouvi and colleagues found that age did have a relationship on the scores of the WMQ (i.e. as participants got older, their scores on the questionnaire increased). Overall, this study confirms the strong relationship between individuals with ASD and WM deficiencies related difficulties. Furthermore, this study provides additional evidence that individuals with ASD report and demonstrate WM impairment apart from theory which is based on using cognitive tasks, but also in applied setting of WM difficulties in everyday life.

6.1.3 A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in adults with high-functioning autism

The aim of Chapter 5 was to conduct a phase II clinical trial and examine the feasibility of a full scale clinical trial on whether anodal whether tDCS led to an improvement in WM performance when administered over the left DLPFC and compared to sham in 25 adult males with HFA and 25 TD controls with no significant difference in their age and IQ, while investigating the balance between safety and potential efficacy. We also explored if the observed effect of tDCS over the left DLPFC on WM scores is dependent on polarity anodal (positive) versus cathodal (negative) stimulation. This is the first ever study of a randomised controlled trial on the effect of anodal tDCS versus cathodal and sham stimulation in adults with HFA and TD adults. In this study we were able to overcome the barriers of recruiting adults with HFA and have a sufficient amount of participants that met our power calculation, this is a critical point as most clinical research and specifically ASD research tends to be underpowered (see Method section of Chapter 5 for details). The main finding of this phase II clinical trial is that anodal tDCS for 15 minutes at an intensity of 1.5 mA led to an improvement in WM performance scores when administered over the left DLPFC when compared to baseline, cathodal and sham stimulation of the same area in adults with HFA. The TD group did not show any statistical difference on WM performance in accuracy and error rate on the task during and post anodal, cathodal and sham stimulation. However, there was significantly faster RT during and post anodal stimulation when compared to baseline, cathodal and sham stimulation. These findings were consistent with our hypothesis that anodal tDCS over the left DLPFC would elicit an improvement in WM in individuals with HFA. Moreover, studies have reported that only online tDCS result in significant enhancements (see Hill, Fitzgerlad and Hoy, 2016 for review). However, our findings showed improvement in WM performance in online and offline tDCS, without there being a significant difference between the two conditions.

6.1.4 Potential clinical implications of tDCS

tDCS has multiple potential clinical implications that support the reasons behind conducting clinical research on it and the possibility of adapting it to clinical applications. tDCS has a theoretical clinical

basis as a substitutive treatment for pharmacotherapy such as patients with poor drug tolerability or those with adverse pharmacological interactions (Brunoni et al., 2011). For example pregnant women with unipolar depression, due to a lack of satisfactory pharmacological alternatives for this condition (Zhang, Liu, Sun and Zheng, 2010). This shows the potential benefits for individuals with ASD and WM deficiencies as pharmacological and behavioural approaches have been unreliable. Furthermore, tDCS can be used as an augmentative treatment as tDCS boost the effects of other treatments in addition to its neurophysiological effects on membrane resting threshold that likely underlie its synergistic effects (Brunoni et al., 2011). This shows a potential for implementing WMT and tDCS or pharmacological approaches and tDCS simultaneity as a potential treatment for WM impairments. Indeed, in 2013, a larger study was conducted involving 120 unipolar depressed patients, which compared tDCS versus a pharmacological treatment (sertraline) and versus tDCS plus sertraline. The results showed a greater reduction in Montgomery–Asberg Depression Rating Scale scores in patients receiving the combined intervention (tDCS + sertraline) versus those receiving sertraline alone, tDCS alone or placebo (Brunoni et al., 2013). tDCS is also inexpensive, easy to use and has favourable tolerability profile in contrast to TMS which makes it easier to adapt worldwide (Lefaucheur et al., 2017).

Indeed, tDCS has shown to have promising therapeutic alternatives for patients with MDD (Bennabi and Haffen, 2018) and beneficial effects in the treatment of psychiatric conditions such has schizophrenia and substance use disorder (Mondino et al., 2014) as well as neurological diseases (Kuo, Paulus and Nitsche, 2014). Studies have shown that tDCS had similar effects to psychopharmacological methods, such as antidepressants. Rigonatti et al. (2008) compared the effect of fluoxetine 20mg/day and ten tDCS sessions (2 mA, 20 min) in 42 depressed patients, and noted a similar improvement in depressive symptoms following brain stimulation and pharmacological treatment, with an earlier antidepressant action in the tDCS group. Following a phase III clinical trial, it would be evident if tDCS may be a potential therapeutic intervention as a phase III trial would compare the effects tDCS on WM impairments with the best currently available treatment such as WM training and psychopharmacological approaches. To move forward with the trial, it needs to be demonstrated that tDCS is at least as safe and effective as existing treatment options.

Another important clinical implication of tDCS is that it has shown to have significant improvements to cognitive impairments, which up to date has no actual treatment. Cognitive impairment have not

been a focus of psychiatric conditions and are not part of the diagnostic criteria, however, cognitive deficits are becoming an important focus for psychiatric research in major psychiatric disorders, as psychiatrically disordered patients have been found to have cognitive impairments in comparison to a control population (Weiser et al., 2004). Therefore, having a clinical focus on the cognitive impairments of adults with psychiatric disorders could be potentially very beneficial as it may solve some of the difficulties reported and observed by individuals with psychiatric disorders. Psychiatric disorders are associated with significant mental healthcare costs, in the US the annual cost of medical treatment of psychiatric disorders exceeds 47 billion dollars per year (Olin and Rhoades, 2005) and cognitive impairments is a significant factor associated with the increased mental healthcare costs in patients with severe psychiatric illness (Mackin, Delucchi, Bennett and Areán, 2011). More specifically, multiple cognitive atypicalities and deficits appear to be a characteristic of ASD (Brunsdon et al., 2015) and the behavioural symptoms of ASD are thought to reflect underlying cognitive deficits/differences (see Brunsdon & Happe, 2014 for review). These cognitive impairments may also contribute to the economic cost of ASD healthcare as the lifetime economic cost of providing support to an individual with ASD is approximately $1.4 million in the USA and £0.92 million in the UK (Buescher, Cidav, Knapp, Mandell, 2014). Therefore, identifying interventions to cognitive impairments can lead to improved treatment outcomes and reduced mental healthcare costs for individuals with severe psychiatric illnesses and more precisely ASD. This specific area is where tDCS can possibly shine.

6.1.5 Future research and recommendations

A great deal of the foundational research needed to make this issue recognised has already been conducted in this thesis; however more research, assessment and replication of the primary findings regarding tDCS needs to be conducted. Nevertheless, this thesis is an initial attempt to utilising tDCS as a potential therapeutic tool for WM deficits. Therefore, a phase III clinical trial is needed as phase III clinical trials compare the safety and effectiveness of the new treatment against the current standard treatment, thus, phase III is a vital part of treatment development. Aside from testing safety and efficacy variables again, other aspects of the treatment may be investigated in a phase III clinical trial such as further exploration of the current intensity-duration relationship, receiving stimulation more often, the stimulation effects in larger populations, how the treatment affects people's quality of

life and its efficacy on individuals at different positions of the autism spectrum or when used in combination with other agents.

One priority for research is the development of a standardised protocol for tDCS to be used. As noted in Chapter 5, research has yet to come up with a standardised protocol and thus researchers are left to come up with their own montages, which in turn makes it difficult to eventually implement tDCS as an intervention. However, an understanding of what montages to adopt, such as duration, intensity, amount of sessions and electrode placement would make it easier to implement tDCS as an intervention with future research to be conducted on the effectiveness of these developed montages. As new tDCS montages are implemented, researchers will need to examine the effectiveness of these montages in order to have greater understanding of what structural changes occur. The development of montages should not be conducted exclusively by researchers in laboratory settings. It would be more fruitful if such investigations were conducted, at least in part, in actual clinical contexts by collaborative teams of researchers and clinicians. Such collaborations would help enhance both the quality and utility of the knowledge produced by the research which will aid researchers and clinicians to modify their practice in ways that will enable them to incorporate such assessments effectively, as research suggests that it is difficult for professionals to utilise new, decontextualized, explicit knowledge in their daily work practice (Hacker, 2003; Wierdsma, 2004; O'Connor and Kotze, 2008). Research often does not directly affect clinical practice, and research results do not automatically translate into improved patient care and treatment (Rangachari, Rissing and Rethemeyer, 2013). The question is how to bridge research and clinical practice? The use of research results in daily clinical life is vital in order to bridge the continuing gap between healthcare research and practice (Cochrane et al., 2007, Novins, Green, Legha and Aarons, 2013).

Much of the current tDCS research is conducted on TD individuals, so the clinical population is not that well represented and trying to use tDCS as an intervention could therefore be challenging. For example there currently are (including our study) only two studies looking at the effects of tDCS on WM in ASD. Thus, there is a need to explore the utility and feasibility of the effects of tDCS on ASD to be better understood through empirical studies. Furthermore, there is a vital need for research on ways to make tDCS usable by clinicians, rather than exclusively by researchers. Many of the currently available research require complex understanding of tDCS and its mechanism of action that only individuals with experience can fully utilise. If tDCS is to be applied more widely,

understandable montages will need to be developed to enable widespread use. Just as medications, clinicians would not prescribe them if they are not familiar their chemical components and their effects.

Research should be conducted to explore how tDCS can be made practical for use in clinics and at home. Additionally, research is needed on the feasibility of implementing tDCS as an intervention. The implantation of tDCS as an intervention for WM depends on substantial changes not only in clinics, but also in the research context in which assessments are conducted. Evidence suggests that the implementation of research results in clinical practice sometimes takes more than a decade and that it is often difficult to sustain innovations over time (Dilling et al., 2013; Ploeg et al., 2014). This is critical not only for patients who do not receive the best available treatment and care, but also for healthcare organisations and society, who fail to benefit from the potential financial value gains and returns on investment (Donaldson, Rutledge and Ashley, 2004). Once an intervention is well understood, its effectiveness as a therapeutic tool must be explored and documented. We strongly believes that the findings in this thesis represent promising directions for further development, and where available, has presented empirical support for the effectiveness of tDCS as potential treatment.

Up to date, ASD research typically has almost no impact on the wellbeing and quality of life of adults with ASD, as most research is based on laboratory based task relating to theoretical concepts. As WM plays an important role in everyday life and has a significant impact on quality of life, the findings from this study can have a significant impact on the wellbeing and quality of life in individuals with ASD. WM deficiencies in ASD have not been receiving the attention that it should, and has not been fully acknowledged by the scientific community. Therefore, we recommend future studies investigating ASD and executive functions or cognitive abilities and clinicians to take into consideration that WM seems to be rather a significant and possibly a core issue in ASD. Clinicians should also keep in mind that some of their patients complains regards difficulties in everyday life could be related to WM deficits.

Moreover, the findings from this thesis suggest a move away from the focus on the typical characteristics of ASD considered to be core features and towards focusing on cognitive impairments, more specifically WM, as they seem to be impairment throughout the spectrum and across life span. Working memory is a highly heritable yet complex cognitive trait with heritability estimates of up to

49% (Ando et al., 2001). Hence, research has shown deficits in certain WM modalities have also been found in unaffected relatives of schizophrenia (Park et al., 1995; Myles-Worsley and Park, 2002; Horan et al., 2008) and bipolar (Arts et al., 2008) patients. Furthermore, WM alterations are thought to be predictive of later onset of schizophrenia (Cornblatt et al., 1999; Niendam et al., 2003) and found in the offspring of schizophrenia patients (Diwadkar et al., 2011). Base on the literature, as research has shown schizophrenia (Burdick et al., 2005), bipolar disorder (Blackwood et al., 2001), and autism (Kilpinen et al., 2008) are linked to genetic variation in DISC1 (which plays important role for neurodevelopment; Ishizuka et al., 2006) and our findings could point toward that WM deficits could be valuable endophenotype candidates for ASD and could affect relatives on ASD individuals as research has suggested the existence of an endophenotype of ASD identifiable through the analysis of unaffected relatives, typically parents or siblings of autistic individuals ASD (Nydn et al., 2011; Spencer et al., 2012). Therefore, due to the heterogeneity between individuals with ASD the identification of endophenotypes may help further the understanding of the etiology and pathogenesis of a complex, genetically rooted disorder, such as ASD and a step towards biologically based classification of psychiatric illness based on WM deficits.

6.1.5.1 Future research direction of studies from the thesis

I believe that the work presented in this thesis raises a number of opportunities for future research. It would be beneficial to run a similar experiment to the one conducted in Chapter 3, while controlling for gender, ethnicity, and when possible categorising similar WM task with each other. Having such information would give us a clearer and more accurate picture of the issue of WM in ASD as a whole and allows us to better understand WM deficits in ASD. Moreover, it would be valuable if future meta-analyses attempt to combine all outcomes of WM tasks (such as accuracy, error rate and RT) into one index. However, it should be noted that in order to achieve that, research has to report all outcomes that could be measured accurately and in detail. If certain outcomes are not reported for any reason, such as the task not having a certain outcome to report (i.e. RT), or outcomes have an opposite relationship (i.e. as accuracy increase, error rate decrease), then when possible, research should explain the tasks utilised in detail in order to have a clear understanding of the task. To my current knowledge, there is no published meta-analysis looking at such details of WM in ASD.

As mentioned previously, there has been very little research investigating if WM deficits as reported by cognitive task translate into difficulties in everyday life. Running a similar experiment to the one conducted in Chapter 4 would be of great importance. However, additional steps could be taken in order to make the findings more rigors and accurate. For example, a big portion of the questionnaire was completed online which is subject to criticism, as online questionnaire have be subjected to response bias (Rosenman, Tennekoon and Hill, 2011), so having the questionnaire done in person or orally, as having the researcher ask the questions from the questionnaire to the participants which could simultaneously eliminate any misunderstandings from the questions. Another possible implementation is to have a partner or parent/carer present during the completion of the questionnaire or answer the questionnaire themselves in regards to the participant which would may remove any potential bias where the respondent wants to 'look good'. Furthermore, investigating females would also have significant contributions. Investigating individuals with LFA could be rather interesting, however, this could be problematic as being at the lower end of the spectrum means that individuals already have intellectual weaknesses and thus the issues reported on the questionnaire could be attributed to either WM deficits or intellectual weakness. Looking at difference age groups could also be important as WM related difficulties in everyday life could be something individuals report from young age. Finally, it is vital to confirm that the ASD participants have a clinical diagnosis which is reinforced with the ADOS for research reliability.

In Chapter 5, we adopted and utilised a rigorous, well researched, design. Thus, this might mislead people into thinking that there may be no improvements or updates that could be performed. However, this is far from the truth, it would be interesting to investigate the effects of a stronger stimulation intensity than the one used in our study, and a longer duration of stimulation to see if this leads to greater improvements in WM performance. Multiple groups could also be implemented, for example, one group could receive multiple stimulation sessions, another group could have tDCS administered using the F3 and F4 bilateral montage (adopted in the Van Steenburgh et al. study), while the main group remains using the typical F3, Fp2 montage. Furthermore, a follow-up at 6 months and 12 months would be interesting to observe how long these effects last. A female group and a LFA group could contribute to a complete representation of ASD, however, having a LFA group could be problematic as there is a correlation between WM and intelligence (Fukuda, Vogel, Mayr, and Awh, 2010; Salthouse and Pink, 2008; Unsworth, Brewer, and Spillers, 2009), so the LFA group may perform poorly on the WM task due intellectual weakness. Moreover, it would be beneficial to

divide the groups by sex as males and females have been reported to preform differently on WM tasks (see Hill, Laird and Robinson, 2014 for review). Education level is also another aspect to consider as research has shown that education levels have an effect on WM performance (de Souza-Talarico, Caramelli, Nitrini and Chaves, 2007). This is also true for ethnicity, as research has shown ethnicity and race have an effect on neuropsychological and cognitive testing (Baird, Ford and Podell, 2007; Díaz-Venegas, Downer, Langa and Wong, 2016). Additionally, by having enough participants, a formal statistical analysis could be conducted to see the differences between an ASD and a TD group. Either way, it is vital to control for all of the factors mentioned in Chapter 5. Also, due to the promising results of this phase II clinical trial, plans towards the development of a phase III clinical trial may be warranted in order to evaluate the overall risks and benefits of tDCS in individuals with ASD.

Furthermore, an important issue that needs to be addressed is feasibility, as the required 25 participants were only recruited after contacting/screening 116 individuals with ASD (21.55%). This recruitment rate could be a limiting factor for future studies, however, this may be a universal issue when it comes to ASD research as mentioned in section 5.2.4, ASD individuals are a ‘hard-to-reach’ population. The use of tDCS may also be a contributing factor, as tDCS use in clinical trial on individuals with ASD is a new and not a fully explored field. Future research on the feasibility of recruiting individuals with ASD to NIBS studies is vital.

6.1.6 Conclusion

Overall, this thesis has contributed to closing the gap in research regarding ASD and WM and has aided our understanding on the severity of subject. To achieve this understanding, as well as providing an update on the current evidence, robust systematic review and meta-analysis techniques were employed. Our findings demonstrated that individuals with ASD do in fact have WM deficiencies and these impairments are observed in both phonological and visuospatial domains. Furthermore, this thesis also demonstrated that these deficiencies relate to difficulties in everyday life. Lastly, the principal findings of the phase II clinical trial in this thesis offer promise in the treatment of WM deficits using tDCS, providing evidence that a phase III clinical trial is feasible and justified future direction.

7 Appendix

Appendix i: Systematic review and meta-analysis search strategy

Full search strategy of Medline database

Medline

No.	Search terms	Records
1	autis*.tw.	24594
2	asperg*.tw.	38742
3	pervasive development* disorder*.tw.	1694
4	kanner*.tw.	174
5	childhood schizophrenia.tw.	251
6	exp child development disorders, pervasive/	23512
7	Developmental Disabilities/	16182
8	(PDD or PDDs or HFA or ASD or ASDs).tw.	13093
9	Rett*.tw.	3165
10	(language adj3 delay*).tw.	1589
11	(communicat* adj3 disorder*).tw.	1795
12	(speech adj3 disorder*).tw.	2758
13	1 and 12	94672
14	working memory.tw.	18230
15	WM.tw.	6167
16	working memory capacity.tw.	881
17	WMC.tw.	248
18	working memory span.tw.	175
19	short-term memory.tw.	6215
20	short-term memory span.tw.	59
21	reading span.tw.	139
22	listening span.tw.	39
23	digit span.tw.	2017
24	word span.tw.	73
25	letter span.tw.	18
26	spatial working memory.tw.	2141
27	Verbal working memory.tw.	948
28	Verbal WM.tw.	154
29	n-back working memory task.tw.	106
30	N-back.tw.	873
31	episodic memory.tw.	4502
32	14 and 31	33625
33	13 and 32	492

Appendix ii: CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	85
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	N/A
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	85-91/99-101
	2b	Specific objectives or research questions for pilot trial	102
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	102/103
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	108/109
	4b	Settings and locations where the data were collected	115/116
	4c	How participants were identified and consented	107, 109-110
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	117-119, figure 13
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	122/123
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	105
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	107
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	107
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	107
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	115
	11b	If relevant, description of the similarity of interventions	115
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	124
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	119
	13b	For each group, losses and exclusions after randomisation, together with reasons	119
Recruitment	14a	Dates defining the periods of recruitment and follow-up	107
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	126 table 11
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	119
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	126,127,129, 133,137,139, 141,142,145

Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	146-159
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	154-159, table 16-19, figure 35-39
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	169-173
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	173-173
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	161-169
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	173-1760
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	104
Protocol	24	Where the pilot trial protocol can be accessed, if available	Clinicaltrials.gov
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	N/A
	26	Ethical approval or approval by research review committee, confirmed with reference number	104

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendix iii: Ethical Approval

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Mr Abdullah Habib PhD student University of Glasgow
Institute of Health and Wellbeing 1st Floor Admin Building Gartnavel Royal Hospital University of Glasgow
1055 Great Western Road
Glasgow G120XH

West of Scotland REC 3
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
(former Royal Hospital for Sick Children Yorkhill)
Dalnair Street
Glasgow G3 8SJ
www.nhsggc.org.uk

Date 1st September 2017
Your Ref
Our Ref
Direct line 0141 232 1805
E-mail WOSREC3@ggc.scot.nhs.uk

Dear Mr Habib

Study Title: **A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism.**
REC reference: **17/WS/0183**
IRAS project ID: **226148**

The Research Ethics Committee reviewed the above application at the meeting held on 24 August 2017. Thank you for attending to discuss the application.

Provisional opinion

Authority to consider your response and to confirm the Committee's final opinion has been delegated to a meeting of the Sub-committee of the REC.

Further information or clarification required

Social or scientific value; scientific design and conduct of the study

The Committee made the following observations around the study design and methodology, the sample size and analysis:

A60
The sample size calculation appears to be incorrect as it seems to be based on a comparison between the ASD and TD study groups. These are independent groups and therefore the sample size calculation should be based on a two sample t-test and not a paired t-test. The comparison should really be of the change in pre-post stimulation working memory accuracy scores between

the two groups rather than a straight comparison of the post stimulation values which appeared to be what the Researcher seems to be planning to do.

A62
Multiple paired t-tests would be required to compare the primary outcome measure between baseline, during stimulation and post-stimulation. The Committee wondered how you were going to be able to adjust for multiple comparisons.

The study design appears complex and will result in a large amount of data. To adequately analyse the data and answer all the research questions would require the use of mixed effects models. The Committee agreed that you should involve a Statistician.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee noted that A50 it stated that the study would be registered on a public database and would like details of this.

Recruitment
The Committee agreed that the exclusion criteria should be changed to include people with major mood disorders. The Protocol should be updated to reflect this change.

Changes required to the Participant Information Sheet (PIS)
As discussed at the meeting it would be helpful if service user feedback was obtained regarding the content of the PIS.

In the first paragraph second sentence 'what this terms mean' should be 'what this term means'.

At the sentence starting 'Before – the comma should be removed after before.

At 'Why are we doing this' the first word should be 'Previous' and not 'Pervious' .

At 'Can I ask questions about the research project' details of someone independent should be added. This must be someone who knows about the study, can answer questions or give advice but should not be involved in any way.

At 'What if something goes wrong & I want to complain' '&' should be changed to 'and'. Details of how to access the NHS Complaints system should be added.

Suitability of Supporting Information
A28 states that there would be no posters or advertisements for recruitment yet A29 paragraph 6 states controls will be recruited using posters and advertisements. The Committee would like to see copies of these documents.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact the REC Manager, contact details at the beginning of this letter.

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the

changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 01 October 2017.

Summary of the discussion at the meeting

Recruitment arrangements and access to health information, and fair participant selection

The Committee asked whether there was a need for a capacity check prior to recruitment to the study.

You advised that those being recruited were highly functioning patients with autism. You would make sure that they did not have learning disabilities or any IQ issues that could impact on capacity.

The Committee noted that controls had already been recruited to the study.

You *advised that less than half the controls had already been recruited. Initially the study was supposed to be done through the University Ethics Committee but it was then decided to involve the NHS.*

The Committee asked who the controls were.

You advised that these were in the main University students who had applied to take part through adverts.

The Committee asked why it was only males that would be recruited to the study.

You advised that it was mostly males who had autism.

Informed consent process and the adequacy and completeness of participant information

The Committee asked whether consent would be taken each time.

You advised that consent would only be taken at the beginning.

The Committee noted that an independent person would witness consent and asked who this was.

You *advised that it would depend on where you would meet with the participant. One person would take consent and the other would just observe the consent process. This was done as a matter of course with studies where vulnerable people were being recruited.*

The Committee asked whether there had been service user involvement with the PIS as it was difficult to read.

You confirmed that they would be happy to do this.

Other general comments

The Committee noted there was reference to scanning in the application and asked what this referred to.*You advised that this was a typo and should be ignored.*

The Committee wondered what the clinical point of the intervention was if the wash out period was just 48 hours.

You advised that this was a vulnerable population and this intervention had not been done before so the time and strength of the current would be minimal.

The Committee asked whether the device was being used within its CE marking.

You advised that the device was used specifically for brain stimulation for experimental use which was within its CE marking.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters [GP letter]	1	10 July 2017
Other [ADOS Sample]		
Other [ADOS]	1	10 July 2017
Other [AQ]	1	10 July 2017
Other [Debriefing]	1	10 July 2017
Other [Side effect questionnaire]	1	10 July 2017
Other [Safety screening]	1	10 July 2017
Other [WASI]	1	10 July 2017
Other [Second supervisor CV]		
Participant consent form [Consent form]	1	10 July 2017
Participant information sheet (PIS) [PIS]	1	10 July 2017
REC Application Form [REC_Form_02082017]		02 August 2017
Research protocol or project proposal [Protocol]	1	10 July 2017
Summary CV for Chief Investigator (CI) [CV Habib]		10 July 2017
Summary CV for supervisor (student research) [CV Melville]		10 July 2017

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

17/WS/0183	**Please quote this number on all correspondence**

Yours sincerely

Liz Jamieson
REC Manager
On behalf of Dr Adam Burnel, Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments.

Copy to: Ms Emma-Jane Gault

West of Scotland REC 3

Attendance at Committee meeting on 24 August 2017 Committee

Members:

Name	*Profession*	*Present*	*Notes*
Miss Taryn Anderson	Remote Area Nurse	No	
Dr Sarah J E Barry	Consultant Biostatistician	Yes	
Dr Adam Burnel	Consultant Psychiatrist - Chair	Yes	
Mr John Cassels	Environment Protection Officer	No	
Ms Suzanne Clark	Retired - Lay	No	
Dr Anne-Louise Cunnington	Consultant Geriatrician and Alternate Vice Chair	Yes	
Mrs Monica Ann Dickson	Retired - Lay Plus Member	Yes	
Ms Susan Fleming	Public Health Researcher	Yes	
Dr Anja Guttinger	Consultant in Sexual & Reproductive Health	No	
Mrs Lorna Hammond	Senior Clinical Pharmacist	Yes	
Dr Stuart Milligan	Lecturer in Cancer and Palliative Care University of the West of Scotland.	No	
Dr Stephen Noble	Consultant Anaesthetist	No	
Mr Ben Parkinson	Lecturer in Nursing	Yes	
Mr Robert Paterson	Retired Lecturer - Lay Plus Member	Yes	
Mrs Helen Ross	Lay Plus Member	Yes	
Mrs Rosie Rutherford	Volunteer - Lay Plus Member and Vice Chair	No	
Dr Alasdair Wilson	General Practitioner	No	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Sophie Bagnall	Assistant Co-ordinator
Mrs Liz Jamieson	REC Manager

Written comments received from:

Name	*Position*
Dr Stephen Noble	Consultant Anaesthetist
Dr Alasdair Wilson	General Practitioner

WoSRES
West of Scotland Research Ethics Service

Mr Abdullah Habib PhD student University of Glasgow
Institute of Health and Wellbeing, 1st Floor Admin Building Gartnavel Royal Hospital
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West of Scotland Research Ethics Service West Glasgow Ambulatory Care Hospital
(former Royal Hospital for Sick Children Yorkhill) Dalnair Street
Glasgow G3 8SJ
www.nhsggc.org.uk

Date 5th October 2017 Your Ref
Our Ref
Direct line 0141 232 1805
E-mail WOSREC3@ggc.scot.nhs.uk

Dear Mr Habib

Study Title: **A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism.**
REC reference number: **17/WS/0183**
IRAS project ID **226148**

Thank you for responding to the Committee's request for further information on the above research,and enclosing the following revised documents:

Document	*Version*	*Date*
Other [Recruitment poster]		
Other [Letter to REC]		
Participant information sheet (PIS) [Participant information sheet]	1.1	29 September 2017
Research protocol or project proposal [Protocol]	1.1	29 September 2017

The further information and revised documentation has been considered on behalf of the Committee by a Sub-Committee of the REC.

The Committee was satisfied with most of the responses to the points in the Provisional Opinion letter. However, the Committee would be grateful for a more complete response on the following points:

The Sub Committee was unable to replicate the sample size calculation based on the information provided. There are various issues with the calculation as it stands:

The sample size calculation appears to be based on a comparison of the post-stimulation scores between the ASD and TD groups, which does not address the primary objective of the study. In order to address the primary objective, the primary outcome needs to be changed from baseline to post-tDCS.

The primary objective does not mention the TD group, so it is difficult to see how the you are planning to use their data in the analysis. If the TD group is not part of the primary objective/outcome, then they are not relevant in the sample size calculation.

The primary objective mentions a comparison between tDCS and sham but this is not included in the sample size calculation.

In order to replicate the sample size calculation, the following information is required for a two group comparison (whether that be ASD vs TD or tDCS vs sham):

1. Anticipated mean change from baseline in working memory accuracy score in group
2. Anticipated mean change from baseline in working memory accuracy score in group
3. SD of change in working memory accuracy score in each group
4. Power, significance level (already provided).

The Committee strongly recommends that the researchers enlist the help of a statistician to carry out their sample size calculation and the Robertson Centre for Biostatistics Advisory Service would be able to help in this regard.

Any further revised document submitted should be given a revised version number and date.

The 60 day clock for issue of a final ethical opinion on this application will re-start when the Committee has received a response on the outstanding points.

17/WS/0183	**Please quote this number on all correspondence**

Yours sincerely

Liz Jamieson
REC Manager

Copy to: Ms Emma-Jane Gault, University of Glasgow

W oSR ES
West of Scotland Research Ethics Service

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Greater Glasgow and Clyde

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G3 8SJ
(Formerly Yorkhill Childrens Hospital)

Date 18 October 2017
Direct line 0141 232 1807
E-mail WoSREC3@ggc.scot.nhs.uk

Dear Mr Habib

Study title: **A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism.**
REC reference: **17/WS/0183**
IRAS project ID: **226148**

Thank you for your submission received on 16 October 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see

"Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters [GP letter]	1	10 July 2017
Other [ADOS Sample]		
Other [ADOS]	1	10 July 2017
Other [AQ]	1	10 July 2017
Other [Debriefing]	1	10 July 2017
Other [Side effect questionnaire]	1	10 July 2017
Other [Safety screening]	1	10 July 2017
Other [WASI]	1	10 July 2017
Other [Second supervisor CV]		
Other [Recruitment poster]		
Other [Letter to REC]		
Other [Stats Rec letter]		
Participant consent form [Consent form]	1	10 July 2017
Participant information sheet (PIS) [Participant information sheet]	1.1	29 September 2017
REC Application Form [REC_Form_02082017]		02 August 2017
Research protocol or project proposal [Protocol]	1.2	13 October 2017
Summary CV for Chief Investigator (CI) [CV Habib]		10 July 2017
Summary CV for supervisor (student research) [CV Melville]		10 July 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality- assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/WS/0183	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

On behalf of
Dr Adam Burnel
Chair

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Ms Emma-Jane Gault*
West of Scotland REC 3

Attendance at Sub-Committee of the REC meeting Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Sarah J E Barry	Consultant Biostatistician	Yes	
Dr Adam Burnel	Consultant Psychiatrist - Chair	Yes	Chair of Meeting
Mrs Rosie Rutherford	Volunteer - Lay Plus Member and Vice Chair	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Abibat Adewumi-Ogunjobi	REC Manager

WoSRES
West of Scotland Research Ethics Service

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Mr Abdullah Habib PhD
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Research Ethics
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Glasgow G3
8SJ
(Formerly Yorkhill Childrens Hospital)

Date 20 October 2017
Direct line 0141 232 1807
E-mail WoSREC3@ggc.scot.nhs.uk

Dear Mr Habib

Study title: **A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism.**
REC reference: **17/WS/0183**
Amendment number: **REC Ref AM01**
Amendment date: **20 October 2017**
IRAS project ID: **226148**

Thank you for your letter (e-mail) of 20 October 2017, notifying the Committee of the above amendment. The amendment relates to an updated consent form to reflect the new document date and version number in the PIS previously missed.

The Committee does not consider this to be a “substantial amendment“ as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Notice of Non Substantial Amendment [E-mail]	REC Ref AM01	20 October 2017
Participant consent form	1.1	29 September 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

17/WS/0183:	**Please quote this number on all correspondence**

Yours sincerely

Abibat Adewumi-Ogunjobi
REC Manager

Copy to: *Ms Emma-Jane Gault*

W oSR ES
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Mr Abdullah Habib
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8SJ
(Formerly Yorkhill Childrens Hospital)

Date 10 April 2018
Direct line 0141 232 1807
E-mail WoSREC3@ggc.scot.nhs.uk

Dear Mr Habib

Study title: **A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism.**
REC reference: **17/WS/0183**
Amendment number: **AM02 24/03/2018 (REC Ref AM02-1)**
Amendment date: **29 March 2018**
IRAS project ID: **226148**

Thank you for submitting the above amendment, which was received on 03 April 2018. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 02 February 2018 refers). This is a modified amendment which relates to the introduction of a working memory questionnaire.

The modified amendment was reviewed by the Sub-Committee in correspondence. A list of the members who took part in the review is attached.

Ethical opinion

The Subcommittee noted the response with regards to the 3 points raised in the unfavourable opinion letter. They noted that the sample size calculations are now correct, however, the choice of primary analysis was strange. The response stated that an RCB statistician had been consulted. With this in mind, the name of the statistician was requested verbally on 06 April 2018 via telephone. A discussion ensued privately with the statisticians and Subcommittee. The Subcommittee eventually agreed that although the statistical analysis could be better no further requests will be made. With regards to the update to the text in the PIS, another change was requested for clarity and to avoid any confusion. This was reported back to you in writing on 09 April 2018 as thus:

This was re-reviewed again by a Subcommittee of the REC and they required a change within the PIS for clarity. As such please change the text “If once you have completed the questionnaire and have any concerns, feel that you would like to discuss any question that came up during the questionnaire, want to ask any question regarding the questionnaire itself or the significance of the questionnaire, please feel free to contact us.” to “Once you have completed the questionnaire, if you have any concerns or feel that you would like to discuss any questions that came up during the questionnaire, or you want to ask any

questions regarding the questionnaire itself or the significance of the questionnaire, please contact us."

If this proviso is met, then the Subcommittee is prepared to issue a favourable opinion of the amendment.

The request was made and hence deemed acceptable for approval.

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

Document	*Version*	*Date*
Covering letter on headed paper [Letter to REC]		
Non-validated questionnaire [WMQ Info Pack - No Patient ID]	1	19 November 2017
Non-validated questionnaire [WMQ - Patient ID]	1	19 November 2017
Notice of Modified Amendment	AM02 24/03/2018 (REC Ref AM02-1)	29 March 2018
Participant consent form	1.4	09 April 2018
Participant consent form [WMQ Consent]	1.2	09 April 2018
Participant information sheet (PIS)	1.4	09 April 2018
Research protocol or project proposal	1.4	14 March 2018

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/WS/0183:	**Please quote this number on all correspondence**

Yours sincerely

On behalf of
Mrs Rosie Rutherford
Chair

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Emma-Jane Gault, University of Glasgow*

West of Scotland REC 3

Attendance at Sub-Committee of the REC meeting in April 2018 Committee

Members:

Name	*Profession*	*Present*	*Notes*
Dr Alex McConnachie	Assistant Director of Biostatistics	Yes	
Mrs Rosie Rutherford	Volunteer - Lay Plus Member and Chair	Yes	Chair of Meeting

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Abibat Adewumi-Ogunjobi	REC Manager

Coordinator/Administrator: JMcGarry/ RSyed
Telephone Number: 0141 232 1817
E-Mail: ray.syed@ggc.scot.nhs.uk
Website: www.nhsggc.org.uk/r&d

Research & Development
West Glasgow ACH
Dalnair Street
Glasgow G3 8SW

22 November 2017

Abdullah Habib

Dept of Psychology
Gartnavel Royal Hospital
1055 Great Western Road
G12 0XH

Dear Mr Habib,

Letter of Access for Research

This letter confirms your right of access to conduct research through **NHS Greater Glasgow and Clyde** for the purpose and on the terms and conditions set out below. This right of access commences on **01/11/2017** and ends on **01/11/2020** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **NHS Greater Glasgow and Clyde** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **NHS Greater Glasgow and Clyde** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **NHS Greater Glasgow and Clyde**, you will remain accountable to your employer **The University of Glasgow** but you are required to follow the reasonable instructions of **Professor Craig Melville** in this NHS organisation or those given on his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **NHS Greater Glasgow and Clyde** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **NHS Greater Glasgow and Clyde** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **NHS Greater Glasgow and Clyde** premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment

and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and the health board's HR department prior to commencing your research role at the Health board.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

NHS Greater Glasgow and Clyde will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Joanne McGarry

Research Co-ordinator

cc: **Debra Stuart, UoG HR.**

Arthur J. Gallagher

3rd Floor Spectrum Building
55 Blythswood Street
Glasgow
G2 7AT
Tel: 0141 285 3300
Fax: 0870 191 6766
www.ajginternational.com

TO WHOM IT MAY CONCERN

23rd November 2016

Dear Sirs

We are the Risk and Insurance Managers for the client below and have pleasure in confirming details of their insurance arrangements as follows:-

Insured

Name(s)	**University of Glasgow**
Postal Address	**University Avenue, Glasgow, G12 8QQ**
Our Ref	**20522973**
Business Description	**University**

Clinical Trials Liability

Insurer Newline Syndicate 1218 at Lloyds(NWL 1218)

Policy No. SYB16898588A

Expiry Date 31 July 2017

Limit of Indemnity

Section 1 Public Liability	£15,000,000 any one occurrence
Section 2 Products Liability/completed Operations	£15,000,000 aggregate
Section 3 Legal Liability for Human Clinical Trials	£15,000,000 aggregate
Section 4 No Fault Compensation for Human Clinical Trials	£15,000,000 aggregate

Sections 2,3 and 4 total combined aggregate limit £15,000,000(Legal costs in addition)

Cover is subject to the full terms, conditions and exclusions of the policy.

This document is issued to you as a matter of information only and the issuance of this document does not: -

i) create any contractual relationship between Arthur J. Gallagher Insurance Brokers Limited and the recipient
ii) make the person or organisation to whom it has been issued an additional assured, nor does it modify in any manner the contract of Insurance between the Assured and the Underwriters.

Any amendments, change or extension of such contract can only be effected by specific endorsement attached thereto with the consent of the Assured and the Underwriters.

We accept no responsibility whatsoever for any inadvertent or negligent act, error or omission on our part in preparing this information or for any loss, damage, expense hereby occasioned to the recipient of this letter

Should the insurance cover be cancelled assigned or changed in any way during the period of insurance neither we nor insurers accept any obligation to notify any recipient.

Yours faithfully

Alex Sawers
Client Servicing Director
Direct dial: 0141 285 3342
Email: Alex_Sawers@ajg.com

Appendix iv: Consent form

Research Institute of Health and Wellbeing 1st Floor, Admin Building
Gartnavel Royal Hospital University of Glasgow 1055 Great Western Rd,
Glasgow, G12 0XH

Subject ID:

A single blind, randomized controlled trial of anodal transcranial direct- current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism.

Consent Form

This form asks if I will take part in a research study.

I understand that the researchers will keep my information confidential and safe at the University of Glasgow and that representatives of the study Sponsor, NHS Greater Glasgow and Clyde, may look at it for audit purposes.

Please initial the BOX if you agree with what it says

I confirm that I have read and understand the Participant Information Sheet (Version 1.5 05/09/2018) for the above study. I understand what my role will be in this research, and all my questions have been answered to my satisfaction ☐

I have asked all the questions I want to. I am also free to ask any questions at any time before and during the study ☐

I know it is OK to say 'no' to taking part in the study. I don't have to take part.
I don't have to say why. If I say 'no', I know it will not affect my future health care, or support, in any way. ☐

If I decide to take part in the study, I know I can change my mind and say 'no' later on, without my medical care or legal rights being affected ☐

I know that the research team will write about the study results. However, the results will not include my name. No one will be able to identify me from the results	☐
I agree that my GP will be notified of my participation in this research.	☐
I agree to take part in the above study	☐

Name of Participant	Date	Signature
----------	----------	----------

Name of Researcher	Date	Signature
----------	----------	----------

1 copy to the patient, 1 copy to the researcher

Appendix iv: Letter to participant's GP

*Direct Line:*07454877103

E-mail: A.Habib.1@research.glasgow.ac.uk

11 April 2019

Dear Dr

Re: Participant's name, address and D.O.B.

The person named above has chosen to take part in a research study entitled,

A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High- Functioning Autism

This study is being run by the University of Glasgow. The person will be undergoing non-invasive brain stimulation (Transcranial Direct Current Stimulation) while completing a computer based cognitive task investigating working memory .

If you would like further information about the study please contact us.

Thank you for taking the time to read this letter.

Yours sincerely

Abdullah Habib
Chief investigator
Mental Health and Wellbeing, University of Glasgow

Researcher
Abdullah Habib
Research Institute of Mental Health & Wellbeing
University of Glasgow
Admin Building, Gartnavel Royal Hospital, 1055
Great Western Road,
Glasgow, G12 0XH.
Telephone: 07454877103
Email: A.Habib.1@research.gla.ac.uk

Research Team
Dr. Craig Melville, Senior Lecturer in Learning Disabilities, University of Glasgow.
Telephone: 0141 211 3878
Email: Craig.Melville@glasgow.ac.uk

Professor Frank Pollick, Professor of Psychology and Associate Academic in the Institute of Health & Wellbeing, University of Glasgow.
Telephone: 0141 330 3945
Email: Frank.Pollick@glasgow.ac.uk

Appendix v: Study invitation information sheet and resources

PARTICIPANT INFORMATION SHEET

A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High- Functioning Autism

We would like to invite you to participate in a research study. It is very important that you understand what being involved in the study will mean for you. Please take time to read this information sheet. Before you decide whether you want to take part, you will have a chance to have all your questions answered by the researcher. You can take as much time as you need before making a decision as to whether or not to take part in the study. Please remember that you can withdraw from the study at any time without giving a reason.

Why are we doing this?

This study involves the use of transcranial direct current stimulation (tDCS). Previous research has shown that tDCS leads to an increase in working memory. Working memory is the ability to maintain and modify everyday information. Working memory is required in a variety of environments from remembering instructions, solving problems, stopping to think before acting and not getting distracted by what is happening around you. Adults with ASD often have problems with working memory which can have a negative effect on quality of life. The results of this study will help our understanding of the effects of tDCS on working memory. This study will also contribute towards a PhD thesis which will be submitted in fulfilment of the requirements for a PhD in Psychiatry.

Who can take part in this study?

Not everyone can take part in this study. Please check the items listed below. If there is any reason you can not take part please tell us. Remember that you do not have to give us a reason if you do not want to continue with the study. If you have any doubts about any of these points please contact us.

You can take part in this research if:

- You are male.
- You are at least 18 years of age and no older than 35 years of age.
- You have a clinical diagnosis of ASD.
- You are right handed.
- You speak English fluently.

- You have normal vision or corrected to normal.
- You are able to pass the tDCS safety screening.

You should ***not*** take part in this research if:

- You suffer from epilepsy, or have had seizures in the past or febrile convulsions as a child.
- You have a family history of epilepsy.
- You have *any* history of neuropsychiatric or neurological illness.
- You have a clinical diagnosis of a major mood disorder.
- You have taken recreational drugs in the past week.
- You are taking anti-malarial medications at the moment or within the last 3 days.
- You have any metal in your body, including your eyes
- You have a pacemaker or other implantable device
- You are an HGV driver.
- You have ever suffered from migraines.

If you are on prescription medications please tell us about these. Depending on the medication you are on you may not be able to take part.

If you have any metal in your body, including your eyes, or have a pacemaker or other implantable device you will not be able to participate in the study. Teeth fillings are safe but you should discuss other metal dental work (e.g. a brace) with the researcher beforehand. If you feel you do not speak fluent English, please discuss this with us, as you may not be able to take part. We have enclosed a copy of the safety screening forms with this letter so that you can see what questions we will ask you.

Do I have to take part?

No. Your participation in this research project is voluntary. You may withdraw from the research at any time and for any reason, without explaining why, and this will not affect your medical care or legal rights. You will receive your financial compensation, prorata of the time you have spent. If you do decide to continue with the study you will be given this information sheet to keep and you will be asked to fill out a safety questionnaire and will be asked to sign a form agreeing to take part in the study.

Can the investigator interrupt the study?

At any time during the testing, the investigators have the right to terminate the study for any reasons. You will receive your financial compensation, prorata of the time you have spent.

What is tDCS?

tDCS stands for transcranial direct current stimulation. This is a technique which uses 2 large electrodes placed on to the subjects scalp with some conducting solution. The electrodes are held in place with two elastic bands. A very low current is passed through these electrodes, which is up to a maximum of 1.5 milliamp (which is about 1.5/10 000th or 0.015% of that which you use at home). The stimulation lasts for a maximum of 15 minutes. There is a picture of the tDCS machine and electrodes below.

For most people tDCS is a completely painless procedure. Some people do feel a slight tingling sensation under the electrodes, especially when the current is switched on. Participants usually describe this as being similar to an itching sensation. In our experience participants do not have any other sensations. The effects will be minimised by increasing the current very slowly initially, which usually stops this tingling. Remember you can always ask the researcher to stop the stimulation at any point if you become uncomfortable.

What will happen to me if I do take part?

If you do agree to take part you will be given safety questionnaires to complete. These questionnaires ask you about your medical history, any medications you are currently taking and about recent recreational drug use, caffeine and alcohol consumption. This information is only necessary for exclusion from the study for the safety of the volunteers. You will be required to fill out these forms and to sign a consent form before any testing takes place. All information given during the screening process will be kept confidential.

The testing will take place at the School of Psychology, University of Glasgow (contact details are at the end). A friend or relative may accompany you to the facility if you would like. When you arrive a researcher will meet you and take you to the room where the study will take place. They will explain exactly what will happen during the stimulation and will go through the safety questionnaire with you. If you are happy to continue they will then ask you to sign a consent form.

At this point, tDCS will be introduced and you will have the opportunity to become familiar with it. You will be asked to perform some simple tests, a total of nine times every visit, which involve being presented with images on a computer and buzzing sensations on your skin. None of these should be distressing or painful. You will have the opportunity to familiarise yourself with the experimental task until you are comfortable with it. The researchers will be present to answer any questions you may have. Although there is no evidence that tDCS is dangerous, we will still do everything we can to make sure that the procedure does not cause you any difficulties or discomfort.

You are welcome to stop participating at any time without providing any advanced notice nor an explanation. We would not expect you to have any problems as a result of the study. However, if you feel at all unwell at any point, have any strange sensations or any concerns; we encourage you to let us know immediately.

Once the study has finished, you will be asked if they would like to be contacted again for future studies. If you agree the researcher will collect your personal contact details. These details they will be kept by the research team and stored on a database that can only be accessed by a username and password. This is entirely voluntary. If you do not want to be contacted about future studies this will not affect this study.

Will my General Practitioner (GP) be informed?

Your GP will be informed if you provide consent to take part in this study.

How long does the study take?

If you agree to take part in the study you will be invited to attend three times. The first session will last 1 hour followed by two 30 minutes sessions. The timing of these is not crucial, and we are able to arrange times that are mutually convenient. However, the sessions will be at least 48 hours apart, to conform to current safety guidelines.

Will I receive financial compensation?

You will receive a £25 Amazon voucher for your participation in this study as compensation for your time. If you travel in order to meet with the researcher, travel expenses will also be provided

What are the potential side effects?

tDCS uses a very low current and is not known to be harmful. There have been many studies throughout the world using this technique and no side effects have been reported, apart from the slight tingling feeling mentioned above, and occasional headaches. However, as with all techniques that directly stimulate the brain, tDCS has the possibility to induce seizures in people who are more sensitive to them. In order to find out whether you are likely to be more sensitive to seizures we ask you to fill in a safety questionnaire. Although no-one has had a seizure with the technique, it is very important you fill in this questionnaire accurately and if you are at an increased risk of seizures you will not be able to continue with the study. If you wish to read any literature on this, we would be happy to provide it for you.

Are the procedure and results confidential?

All information which is collected about you during the course of this research (including that sourced from NHS Greater Glasgow & Clyde) will be kept anonymous, strictly confidential and stored on a secure network at the University of Glasgow. No one outside of the research team will have access to the information you provide. The representatives of the study sponsor, NHS GG&C, may also need to look at your information to make sure that the study is being conducted correctly. Any information about your identity obtained from this research will be kept private. The study researchers have a duty of care to take appropriate action if they are concerned about you. They will discuss this with you before doing anything. In any sort of report we might publish we will not include information that will make it possible for other people to know your name or identify you in any way. You will be simply referred to by your gender, age and possibly some characteristic such as left or right handedness.

What are the possible benefits?

tDCS studies carried out at the School of Psychology, University of Glasgow are tests, not treatments. We hope that the information we get from this study may help us to better understand how the brain works and help our understanding of the functions of the human brain, as well as help investigate the future potential of using this technique as a therapeutic intervention.

What will happen to the results of the research study?

Where appropriate, the results of this study will be presented at medical and scientific conferences and published in journals. You will not be identified in any report or publication. The results of this study will also help to design future research projects which possibly may lead to new treatment methods.

Can I ask questions about the research project?

You may ask more questions about the study at any time, before, during and after the study. The investigator(s) will provide their telephone number so that they are available to answer your questions or concerns about the study. In addition, Professor Andrew Jahoda who is independent from this research project will be available to answer any questions you may have and offer any required advice.

Phone: 0141 211 0282

Email: Andrew.Jahoda@glasgow.ac.uk

What if something goes wrong and I want to complain?

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against NHS Greater Glasgow and Clyde but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). There are no special compensation arrangements for non-negligent harm.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (using the numbers below). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure.

Phone: 0141 201 4500

Email: complaints@ggc.scot.nhs.uk

Who has reviewed the study?

This research study has been approved by West of Scotland NHS Research Ethics Committee 3.

If you have any questions or concerns about this research then please ask the researcher or any member of the research team (The names and telephone numbers are shown below). You will be given a copy of the information sheet to keep.

Are the procedure and results confidential?

NHS Greater Glasgow and Clyde is the sponsor for this study based in the United Kingdom/Scotland. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly.
NHS Greater Glasgow and Clyde/University of Glasgow will keep identifiable information about you for 12 months after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting the Chief Investigator Abdullah Habib at 07454877103**.**

Site contact details:

University of Glasgow School of Psychology

58 Hillhead Street, Glasgow G12 8QB, Scotland tel: +44 (0) 141 330 5089

If you would like to take part please complete the reply slip below and return the slip only in the FREEPOST envelope. If you return the slip saying you want to take part the researcher will contact you to arrange to meet to discuss the study. Even If you are not interested in taking part in the full study, we would be very grateful if you would consider completing the Working Memory Questionnaire enclosed in the

information package and return it in the FREEPOST envelope- but you do not have to.

Please note that by mailing back the WMQ, you are consenting to us having that information and aware that the research team will use the data and write about the result. It is also important to note that if you only complete the WMQ and not take part in the full study, you will not be able to withdraw as the questionnaires are anonymised and it would be impossible to locate your data.

Once you have completed the questionnaire, if you have any concerns or feel that you would like to discuss any questions that came up during the questionnaire, or you want to ask any questions regarding the questionnaire itself or the significance of the questionnaire, please contact us.

Thank you for taking the time to read this information sheet.

Researcher

Abdullah Habib

Research Institute of Mental Health & Wellbeing

University of Glasgow

Admin Building, Gartnavel Royal Hospital, 1055

Great Western Road,

Glasgow, G12 0XH. Telephone:

07454877103

Email: A.Habib.1@research.gla.ac.uk

Research Team

Professor Craig Melville, Professor of Intellectual Disabilities Psychiatry, University of Glasgow.

Telephone: 0141 211 3878

Email: Craig.Melville@glasgow.ac.uk

Professor Frank Pollick, Professor of Psychology and Associate Academic in the Institute of Health & Wellbeing, University of Glasgow.

Telephone: 0141 330 3945

Email: Frank.Pollick@glasgow.ac.uk

A single blind, randomized controlled trial of anodal transcranial direct- current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism

Name ……

Address …….

……..

…….. Telephone Number ……..

I would like to find out more about the study .

Please return this form in the FREEPOST envelope to:

Professor Craig Melville Mental Health and Wellbeing University of Glasgow Academic Centre

Gartnavel Royal Hospital

1055 Great Western Road

GLASGOW

G12 0XH

NHS Greater Glasgow and Clyde

University of Glasgow

tDCS safety screening questionnaire

Please read the following questions carefully and provide answers. You have the right to withdraw from the screening and subsequent testing if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will be held in secure conditions. If you are unsure of the answer to any of the questions, please ask the person who gave you this form or the person who will be performing the study.

Participants ID:_____ Date of birth: _____

Sex: M / F

Have you ever suffered from any neurological or psychiatric conditions? ***(e.g. stroke, depression, etc)***	***YES***	***NO***
Have you ever suffered from epilepsy, febrile convulsions in infancy or had recurrent fainting spells?	***YES***	***NO***
Does anyone in your immediate or distant family suffer from epilepsy? ***If YES please state your relationship to the affected family member.***	***YES***	***NO***
Have you ever undergone a neurosurgical procedure (including eye surgery)? ***If YES please give details***	***YES***	***NO***
Do you currently have any of the following fitted to your body? (please circle) ***Heart pacemaker Cochlear implant Medication pump Surgical clips***	***YES***	***NO***
Are you currently taking any unprescribed or prescribed medication? ***If YES please give details.***	***YES***	***NO***

Are you currently undergoing anti - malarial treatment, or have been in the last 3 days?	***YES***	***NO***
Or drunk more than 3 units of alcohol in the last 24 hours?	***YES***	***NO***
Have you drunk alcohol already today?	***YES***	***NO***
Have you had more than one cup of coffee, or other sources of caffeine in the last hour?	***YES***	***NO***
Have you used recreational drugs in the last 24 hours?	***YES***	***NO***
Did you have very little sleep last night?	***YES***	***NO***
Have you already participated in a tDCS/ TMS experiment in the last week?	***YES***	***NO***
Do you hold a heavy goods vehicle (HGV) driving license or bus license?	***YES***	***NO***
Have you ever suffered from migraines?	***YES***	***NO***

I have read and understood the questions above and have answered them correctly.

SIGNED…… DATE……

In the presence of …….. (Name) ……..

The Working Memory Questionnaire

Participant ID number:..... Sex:.....

Today's Date.....

How to fill out the questionnaire

Below is a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer.

1. Do you feel that you tire quickly during the day?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
2. Do you find it difficult to carry out a project such as choosing and organising your holidays?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
3. Do you have problems with remembering sequences of numbers, for example, when you have to note down a telephone number?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
4. Do you need to make an effort to concentrate in order to follow a conversation in which you are participating with many other people?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
5. Do you find it difficult to remember the name of a person who has just been introduced to you?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
6. When you shop, do you often spend more than the budget you set for yourself?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
7. Do you have difficulty remembering what you have read?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
8. When you are interrupted during an activity by a loud noise (door slam, car horn) do you have difficulty in getting back to the activity?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
9. Do you find it difficult to carry out an activity with chronological steps (cooking, sewing, DIY)?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
10. Do nearby conversations disturb you during a conversation with another person?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
11. Do you need to re-read a sentence several times to understand a simple text?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
12. Do you have difficulty in organising your time with regard to appointments and your daily activities?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**

13. Do you find it difficult to do two (or several) things at the same time such as: - DIY and listening to the radio at the same time? - Cooking and listening to the radio at the same time?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
14. When you are carrying out an activity, if you realise that you are making a mistake, do you find it difficult to change strategy?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
15. Do you have difficulty understanding what you read?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
16. Do you feel that fatigue excessively reduces your concentration?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
17. When you pay cash for an item, do you have difficulty in realising if you have been given the correct change?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
18. Do you find it difficult to follow the different steps of a user's guide (putting kit furniture together, installing a new electrical device)?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
19. Do you find it difficult to carry out an activity in the presence of background noise (traffic, radio or television)?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
20. Are you particularly disturbed if an unexpected event interrupts your day or what you are in the process of doing?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
21. If a character in a text is designated in different ways (he, him), do you have difficulty in understanding the story?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
22. Do you feel embarrassed when you have a conversation with an unfamiliar person?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
23. Do you find that you hesitate for a long time before buying even a common item? (Aside from the change of currency to the euro!)	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
24. Do you feel that you are very slow to carry out your usual activities?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
25. Do you have to look at a written phone number many times before dialing a number that you don't know off by heart?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
26. Do you have difficulty in managing your paper work, sending social security papers, paying bills, etc.?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
27. If somebody speaks quickly to you, do you find it difficult to remember what you were told or asked?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**

28. Do you find that you tire quickly during an activity which demands a lot of attention (for example, reading)?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
29. After doing your shopping, are you surprised to find that you have bought many useless items?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**
30. Do you find it difficult to participate in a conversation with several people at once?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**

Research Institute of Health and Wellbeing 1st Floor, Admin Building Gartnavel Royal Hospital University of Glasgow 1055 Great Western Rd, Glasgow, G12 0XH

Subject ID:

Working Memory Questionnaire Consent Form

I understand that the researchers will keep my information confidential and safe at the University of Glasgow and that representatives of the study Sponsor, NHS Greater Glasgow and Clyde, may look at it for audit purposes.

Please initial the BOX if you agree with what it says

I confirm that I have read and understand the Participant Information Sheet (Version 1.4 09/04/2018) for the above study. I understand what my role will be in this research, and all my questions have been answered to my satisfaction ☐

I agree to completing the Working Memory Questionnaire (WMQ). ☐

I know that the research team will use the data and write about the result. However, the results will not include my name. No one will be able to identify me from the results. ☐

If I decide to complete the WMQ, I know due to the questionnaire being anonymised that I will not be able to withdraw from the study as it would be impossible to locate my data. ☐

| --- | --- | --- |
| Name of Participant | Date | Signature |

| --- | --- | --- |
| Name of Researcher | Date | Signature |

University of Glasgow

NHS Greater Glasgow and Clyde

A single blind, randomized controlled trial of anodal transcranial direct- current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism

Participant ID _____

Session Number _____

Date _____

Q1. DID YOU EXPERIENCE ANY OF THESE SIDE-EFFECTS DURING THE SESSION?

	Not at all 1	**2**	**3**	**4**	**Very strongly 5**
Headache					
Tingling					
Itching					
Burning					
Pain					

Q2. IF YES, HOW LONG DID THESE SIDE EFFECTS LAST?:

_____

_____

_____

Q3. DID YOU FEEL THESE SIDE EFFECTS AT:

	Yes/ No	**Which side effects in particular?**
The LEFT side		
The RIGHT side		

Q4. CAN YOU GUESS WHICH SESSION INVOLVED SHAM (INACTIVE) tDCS?
(To be completed after session 3).

Please circle

SESSION 1 **SESSION 2** **SESSION 3**

Study Debriefing

A single blind, randomized controlled trial of anodal transcranial direct- current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism.

This aim of this study was to investigate if Transcranial Direct Current Stimulation (tDCS) on the left dorsolateral prefrontal cortex demonstrates (DLPFC) an increase in working memory (WM) performance in Autism Spectrum Disorder (ASD). Previous studies have found that tDCS on the DLPFC demonstrates an increase in WM performance in typically developed individuals (Boggio et al., 2005). Although tDCS has been found to improve cognitive abilities in ASD participants (e.g., D'Urso et al., 2014). tDCS has not been looked at from the aspect of increasing WM in ASD.

How was this tested?

In this study, you were asked to perform two tasks—a three-back WM task, and an IQ test. All participants performed these same tasks at the start of the experiment. tDCS stimulation was applied at a current of 1.5 milliamps. You were asked to perform a three-back WM task pre, during and post stimulation. After a minimum of 2 days you were asked to come back to repeat the whole study but this time you received a sham, anodal or cathodal stimulation. Sham stimulation is a generic term to indicate an inactive form of stimulation (e.g., a very brief or weak one, in your case no stimulation at all) that is used in research to control for the placebo effect. The subject believes he/she is being stimulated normally, but there should not be any real effects. Two days after you were asked to come back a final time and this time you received the final stimulation type.

Hypotheses and main questions:

Our aim is to determine whether anodal tDCS, would modify performance in a three-back working memory task when administered over the DLPFC in adults with high functioning Autism and whether the effects of tDCS on DLPFC is dependent on polarity (anodal versus cathodal stimulation).

We hypothesised that there will be an improvement in working memory scores post active and during tDCS when compared to pre-stimulation and sham stimulation. We also hypothesised that the improvement in working memory scores due to tDCS is dependent on polarity (anodal stimulation only).

Why is this important to study?

This may have important benefits for people with ASD since ASD has been associated with WM deficiencies. In severe cases with memory and attention deficit, pharmacologic therapies such as antidepressants and antipsychotics are recommended (Oswald et al., 2007) but they may cause adverse effects such as nausea, drowsiness, dry mouth, agitation, behavioral activation, and sleep problem (Oswald et al., 2007).Therefore, there is an urgent need for more effective treatment options.

What if I want to know more?

If you are interested in learning more about the study, you may want to consult: Abdullah Habib.

If you would like to receive a report of this research when it is completed (or a summary of the findings), please contact Abdullah Habib at A.Habib.1@research.gla.ac.uk or Dr. Craig Melville at Craig.Melville@glasgow.ac.uk, Professor Frank Pollick at Frank.Pollick@glasgow.ac.uk

If you have any questions or concerns about your rights as a participant in this experiment, please contact Abdullah Habib, Professor Craig Melville, Professor Frank Pollick, of University of Glasgow.

Thank you again for your participation.

Version 1.0 10/07/2017

*Direct Line:*07454877103

E-mail: A.Habib.1@research.gla.ac.uk

11 April 2019

Dear

You are being contacted n regards to the research study you took part in entitled,

A single blind, randomized controlled trial of anodal transcranial direct-current stimulation against cathodal and sham stimulation in Adults with High-Functioning Autism

There has been mandatory updates to the participant information sheet that was given to you when you took part in this study. These updates are regarding data transparency which is UK-wide and in order to comply with General Data Protection Regulation.

The following is the included wording in the current participant information sheet (Version 1.5 05/09/2018)

NHS Greater Glasgow and Clyde is the sponsor for this study based in the United Kingdom/Scotland. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NHS Greater Glasgow and Clyde/University of Glasgow will keep identifiable information about you for 12 months after the study has finished.
Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and

accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information by contacting the Chief Investigator Abdullah Habib at 07454877103.

Thank you for taking the time to

read this letter. Yours sincerely

Abdullah Habib
Chief investigator
Mental Health and Wellbeing, University of Glasgow

Appendix v: Publication arising from this thesis

PLOS ONE

RESEARCH ARTICLE

A meta-analysis of working memory in individuals with autism spectrum disorders

Abdullah Habib[1], Leanne Harris[1], Frank Pollick[2], Craig Melville[1]*

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Abstract

Background

Autism spectrum disorders (ASD) are lifelong neurodevelopmental disorders. It is not clear whether working memory (WM) deficits are commonly experienced by individuals with ASD.

Aim

To determine whether individuals with ASD experience significant impairments in WM and whether there are specific domains of working memory that are impaired.

Methods

We conducted a meta-analysis using four electronic databases EMBASE (OVID), MEDLINE (OVID), PsychINFO (EBSCOHOST), and Web of Science, to examine the literature to investigate whether people with ASD experience impairments related to WM. Meta-analyses were conducted separately for phonological and visuospatial domains of WM. Subgroup analyses investigated age and intelligence quotient as potential moderators.

Results

A total of 29 papers containing 34 studies measuring phonological and visuospatial domains of WM met the inclusion criteria. WM scores were significantly lower for individuals with ASD compared to typically developed (TD) controls, in both the visuospatial domain when investigating accuracy (*d*: -0.73, 95% CI -1.04 to -0.42, $p < 0.05$) and error rates (*d*: 0.56, 95% CI 0.25 to 0.88, $p<0.05$), and the phonological domain when investigating accuracy (*d*:-0.67, 95% CI -1.10 to -0.24, $p>0.05$) and error rate (*d*: 1.45, 95% CI -0.07 to 2.96, $p = 0.06$). Age and IQ did not explain the differences in WM in ASD.

Conclusions

The findings of this meta-analysis indicate that across the lifespan, individuals with ASD demonstrate large impairments in WM across both phonological and visuospatial WM domains when compared to healthy individuals.

Check for updates

OPEN ACCESS

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Competing interests: The authors have declared that no competing interests exist.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by communication difficulties, social impairment and fixated interests along with repetitive behaviours [1]. The symptoms of ASD are evident from young age; usually in children aged two or three, with a higher prevalence in boys than in girls [2]. Autism has become one of the most prevalent and common developmental disability, the Centers for Disease Control and Prevention [3] notes that the incidence of ASD has been increasing in the general population in recent years in the United States of America (USA), with the new estimate of 1 in 68 children having an ASD being roughly 30 percent higher than previous estimates reported in 2012, 1 in 88 children. In the United Kingdom (UK), according to Brugha et al. [4], 1.1% of the population in the UK had an ASD compared to 2009 when it was found 1% of the population studied had an ASD [5]. ASD has significant negative impact on the quality of life of the individual [6]. A meta-analysis [7] concluded that across the lifespan, quality of life is lower for people with ASD when compared to people without ASD. The impairments associated with ASD mean that many people with ASD remain dependent on others for support, such as parents, siblings, and other carers [8]. Thus, many parents of people with ASD are concerned about what to expect from the future and what will happen to their family members when they will not be able to take care of them anymore [9].

Impairments in cognitive abilities are not part of the classification of ASD. However, clinicians and researchers often make a distinction between low-functioning autism (LFA) with an intelligence quotient (IQ) below 65 or 70, and high-functioning autism (HFA) with an IQ above 65 or 70. Although neuropsychological impairments are not part of diagnostic criteria, many people with ASD experience significant cognitive impairments [10, 11, 12]. Executive function deficits are commonly experienced by individuals with ASD [11, 13, 14]. Executive function is an umbrella term for a set of cognitive processes that includes working memory (WM), inhibition, planning, impulse control, and shifting set as well as the initiation and monitoring of action [11].

WM plays an important role in human cognition and a central role in executive function [15]. The most commonly used cognitive model of WM is the revised WM model [16], which is based on the model developed by Baddeley and Hitch in 1974 [17]. The core of the model involves the central executive, concerned with information control and monitoring information processing (attention control center), an episodic buffer enables information integration from the sub-components of WM and long-term memory. Executive functions allow one to engage in purposeful and independent behaviours such as suppressing irrelevant information, shifting among multiple tasks, and revising and monitoring information held in long-term memory. The model also involves two storage systems- the phonological loop and the visuospatial sketchpad- supporting the central executive. The phonological loop provides temporary storage for phonological information while the visuospatial sketchpad allows temporary storage and manipulation of visual and spatial information. Other aspects of the model include the role of attention in WM and the concept of temporal duration when performing memory tasks. However, based on this revised WM model of Baddeley, WM is not only important but also essential for successfully navigating in the social world [18].

Gathercole and Baddeley describe WM as a short-term memory system that controls temporary processing and storage of information [19]. The importance and role of WM in everyday tasks is well established. WM plays a crucial role in supporting various complex high-level cognition activities such as language comprehension and long-term learning [19], reasoning [20], reading comprehension [21, 22], mental arithmetic [23], and problem solving [24]. As a temporary storage system under an individual's attentional control, WM allows processing of

the methods used for the meta-analysis. A systematic literature search was not used to identify potential studies; only two search terms were used "Asperger+ working memory" and "autism + working memory". A literature search that is not comprehensive can lead to relevant studies being missed and biased results from meta-analyses. In order to include studies that used error rate as the measure of WM, Wang et al [41] converted error rate into accuracy by assuming that error rate and accuracy have an opposite direction relationship. For example, if the error rate was 0.8 they converted it to an accuracy score of -0.8 (personal communication). This method is problematic as studies that have measured error rate and accuracy found that ASD participants' accuracy scores did not differ from the control group however the ASD participants made more errors [33, 42]. For studies that had used more than one than one WM task, Wang et al [41] state that they calculated effect sizes for each WM task and then combined these into an unweighted average effect size. However, they excluded WM tasks from the average effect size calculation if participants with ASD did not demonstrate impairments on these tasks. For example, two studies measured reaction time and accuracy [43, 44] but the participants with ASD only had impairments on reaction time so the accuracy scores were excluded. Selection of studies based on the direction of the results creates bias and in this case will have inflated the overall effect size of the meta-analysis. These methodological weaknesses fall well short of guidance on the methods and reporting of systematic reviews and meta-analyses [45], and threaten the validity of the findings in the previous meta-analysis by Wang and colleges.

We previously explained the potential importance of WM in the daily functioning and quality of life of individuals with ASD. Our aim in this study is to determine whether individuals with ASD experience significant impairments in WM and whether there are specific domains of working memory that are impaired. We will also evaluate age and IQ as potential moderators of WM impairments in individuals with ASD.

To achieve these aims, in this systematic review and meta-analysis, we will address the limitations in the previous study [41] by adopting a more systematic and comprehensive search of the available literature, including more rigorous inclusion criteria that controls for matching participants on IQ and age (i.e., no significant difference between the groups) a more stringent selection process to identify relevant studies, avoiding bias by not using study results as the basis for inclusion, and analysing WM accuracy and error rates scores separately, as accuracy and error rate do not necessarily have an opposite relationship (i.e. if accuracy is high, error rate is low). Additionally, looking into only one of the outcomes would reduce the amount of studies included significantly as studies sometimes only report 1 of the outcomes. This was done in order to achieve a more accurate examination of the topic of WM impairments in individuals with ASD.

Method

This study was conducted in adherence with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [45].

Literature search

We conducted a literature based search and manual cross referencing of English language empirical studies relating to both ASD and WM using four electronic databases EMBASE (OVID), MEDLINE (OVID), PsychINFO (EBSCOHOST), and Web of Science from 1986 to May 2017 (subsequent to a previous review by Wang et al. [41]). Search terms were combinations of the following 'autis', 'asperg', 'pervasive development disorder', 'kanner', 'childhood schizophrenia', 'child development disorders', 'Rett', 'working memory', 'memory capacity', 'memory span', 'short-term memory', 'N-back', 'memory', and 'digit span'. The full search

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Medline search strategy is illustrated in the supporting information (S1 Appendix). The reference lists of retrieved studies were also examined to identify relevant papers.

Inclusion criteria

Studies were eligible for this review if they met the following inclusion criteria:

- Published in peer-reviewed journals in English
- Included people with ASD
- Used ADOS [46], ADI- Revised [47], 3Di [48] or a clinician as a method to diagnosis ASD
- Matched the groups on age, gender and IQ or where there was no statistically significant difference between the groups
- Data reported clearly and sufficiently such as mean scores and standard deviation
- Compared ASD groups to TD groups
- Included a valid test of WM, the appropriateness of including tests as measures of WM was determined by referring to Lezak [49] or Baddeley, Wilson and Watts [50]

Research studies were not eligible for this review if they met the following exclusion criteria:

- Conference papers/abstracts
- Review papers
- Unpublished data, grey literature
- Non-English language papers.

Selection of studies

The lead researcher (AH) performed the literature search and removed any duplicate studies. The titles and abstracts were screened independently by two authors (AH and CM) and disagreements about inclusion resolved at a consensus meeting. For records retained after screening, the full text was obtained, read in full and both researchers (AH and CM) independently completed an inclusion checklist. If there was any disagreement between the inclusion checklists for a paper final list decided decision about inclusion was made following a consensus discussion.

Data extraction

The following data were extracted by the lead researcher to assess the methodology quality and data synthesis:

- Authors, year of publication
- Number of subjects
- Full scale IQ
- Age
- Gender
- Instruments used to assess WM

- WM scores (where there was multiple task being used, we chose the more challenging task, for example, they study by Williams et al. where multiple loads of the N-Back WM task were used (1-Back, 2-Back and 3-Back). The 3-back results were chosen as the 3-back is what is commonly used as a load when using N-back WM task which also happens to be the more challenging task.)
- The method of diagnosis was recorded for the ASD groups.

Quality assessment

To check the quality of the studies, we used the Standard Quality Assessment Criteria for Evaluating Primary Research Papers tool for quantitative studies developed by Kmet, Lee, and Cook [51]. Each study was assessed against 14 criteria-oriented items. Criteria 5 (if interventional and random allocation was possible, was it described?), 6 (if interventional and blinding of investigators was possible, was it reported?) and 7 (if interventional and blinding of subjects was possible, was it reported?), were not considered during the quality assessment as they are applicable to studies assessing interventions. If the study met the criteria it was scored as 2; 1 if it partially met the criteria; and 0 if it did not meet the criteria. A total score for each study was calculated by adding the score across the criteria and dividing by the total possible score (22). The assessment was completed by two authors (AH and CM) for each study to improve reliability. There was complete agreement between the two reviewers.

Data analysis

Meta-analyses were performed using Comprehensive Meta-analysis version 3.0 (Biostat, Englewood, NJ, USA). Effect sizes were calculated (using means, standard deviations and sample sizes) based on the pooled standardised mean difference (SMD), expressed as Cohen's d [52] and 95% confidence interval (CI). Although studies measured the same outcome of WM, due to the different methodological tests to assess WM, it was necessary to standardise the results on a uniform scale (in order to combine results in the meta-analysis). The effect size was calculated as the difference in mean change between the ASD group and the TD/comparison group divided by the standard deviation pooled between the two groups. Effect sizes were interpreted as small ($d = 0.20$), moderate ($d = 0.50$) and large ($d = 0.80$).

WM was divided into subgroups via the following WM constructs, phonological and visuospatial, consistent with the gold-standard criterion recommendations [53]. Study results were pooled using an inverse variance weighted method of random effects analysis [54]. The significance and degree of heterogeneity were calculated using Cochrane's Q statistic and I^2. Cochrane's Q statistic provides a measure of the variance between the effect sizes (with $p < 0.05$ illustrating evidence of heterogeneity) while I^2 provides a measure of the amount of variance between the studies in terms of heterogeneity, and is described by Higgins et al. [55]. The degree of heterogeneity was measured by the I^2 statistic, with $I^2 \geq 50\%$ indicating substantial heterogeneity. In accordance with the Cochrane handbook for reviews and to explore possible potential heterogeneity, subgroup analysis (post hoc) was conducted for variation in sample characteristics including moderator variables age and IQ considering all of our meta-analysis had 10 or fewer studies.

Publication bias was investigated using visual inspection of funnel plots of the SMD against the standard error of the SMD of the included studies and using the linear regression approach described by Egger et al. [56]. This method examines the association between effect size and standard error for each study and takes into account the sample size and effect size.

Results

Of a total of 8868 studies, 273 duplicate studies were removed, 7995 articles were excluded on reviewing the title and abstract. For the remaining 600 full text articles, those that were conference papers, review articles or not in English, were excluded. We identified a total of 29 papers that evaluated WM performance for individuals with ASD; 16 investigated accuracy as a measure of participants working memory performance, while 13 investigated participant error rates. Five studies were excluded for not reporting the statistics efficiently, such as the means and standard deviations of each group, eight studies were excluded for not matching participants on IQ or there was a significant difference between the two groups, one study was excluded for not measuring full scale IQ, one study was excluded for not having a matched age and IQ control group, one study was excluded for not having a control group, finally, one study was excluded for not measuring the IQ of the control group. Studies where we were not able to contact the authors and/or access their data were excluded from this review. The articles were obtained from 11 different journals and were published between 2001 and 2015. A total of 29 papers containing 34 studies were retained for inclusion in the review and data synthesis. Based on the WM model by Baddeley [17] results were categorised based on which aspect of WM was tested, phonological or visuospatial. Fig 1 shows the study selection process.

Phonological working memory

Accuracy in phonological working memory. Out of the 34 studies, nine studies were identified testing accuracy in phonological WM. A summary of the study characteristics of the nine studies is presented in Table 1. The studies were published between 2001 and 2013 in nine different journals. A total of 447 participants were recruited (226 ASD, 221 TD) across the nine studies, with a mean total ASD sample size of 25.1 and TD sample size of 24.5. Participants' ages ranged from 11 to 31 years with the mean age of ASD participants of 20.7 years and TD participants ages ranged from 11 to 38 years with the mean age of 21.2 years. All nine studies compared ASD participants with TD participants with all participants' IQ scores being above 70.

The combined WM scores from the nine studies were significantly lower in the ASD group than the typical developed group (*d*:-0.67, 95% CI -1.10 to -0.24, $p<0.05$). There was substantial heterogeneity between studies (Q-statistic = 36.82, df = 8 ($p < 0.05$); $I^2 = 78.27\%$). As only nine studies were identified as testing accuracy in phonological WM, publication bias was not assessed. This was due to the limited number of studies to provide adequate power of reliability of tests to detect for presence of publication bias [57]. Representative forest plots from the phonological WM meta-analyses are shown in Fig 2.

Error in phonological working memory. Out of the 13 studies, two studies were identified testing error in phonological WM. A summary of the study characteristics of the two studies is presented in Table 2. A total of 80 participants were recruited (45 ASD, 35 TD) across the two studies, with a mean total ASD sample size of 22.5 and TD sample size of 17.5. Participants' ages ranged from 10 to 31 years with the mean age of ASD participants of 20.9 years and TD participants ages ranged from 11 to 32 years with the means age of 21.5 years. Both compared ASD participants with TD participants with all participants' IQ scores being above 70.

The WM error rates scores from the two studies were significantly lower in the TD group than the ASD group (d: 1.45, 95% CI -0.07 to 2.96, $p = 0.06$). There was substantial heterogeneity between studies (Q-statistic = 8.84, df = 1, ($p<0.05$); I2 = 88.69%). Publication bias was also not assessed for studies testing error in phonological WM. Representative forest plots from the phonological WM meta-analyses are shown in Fig 3.

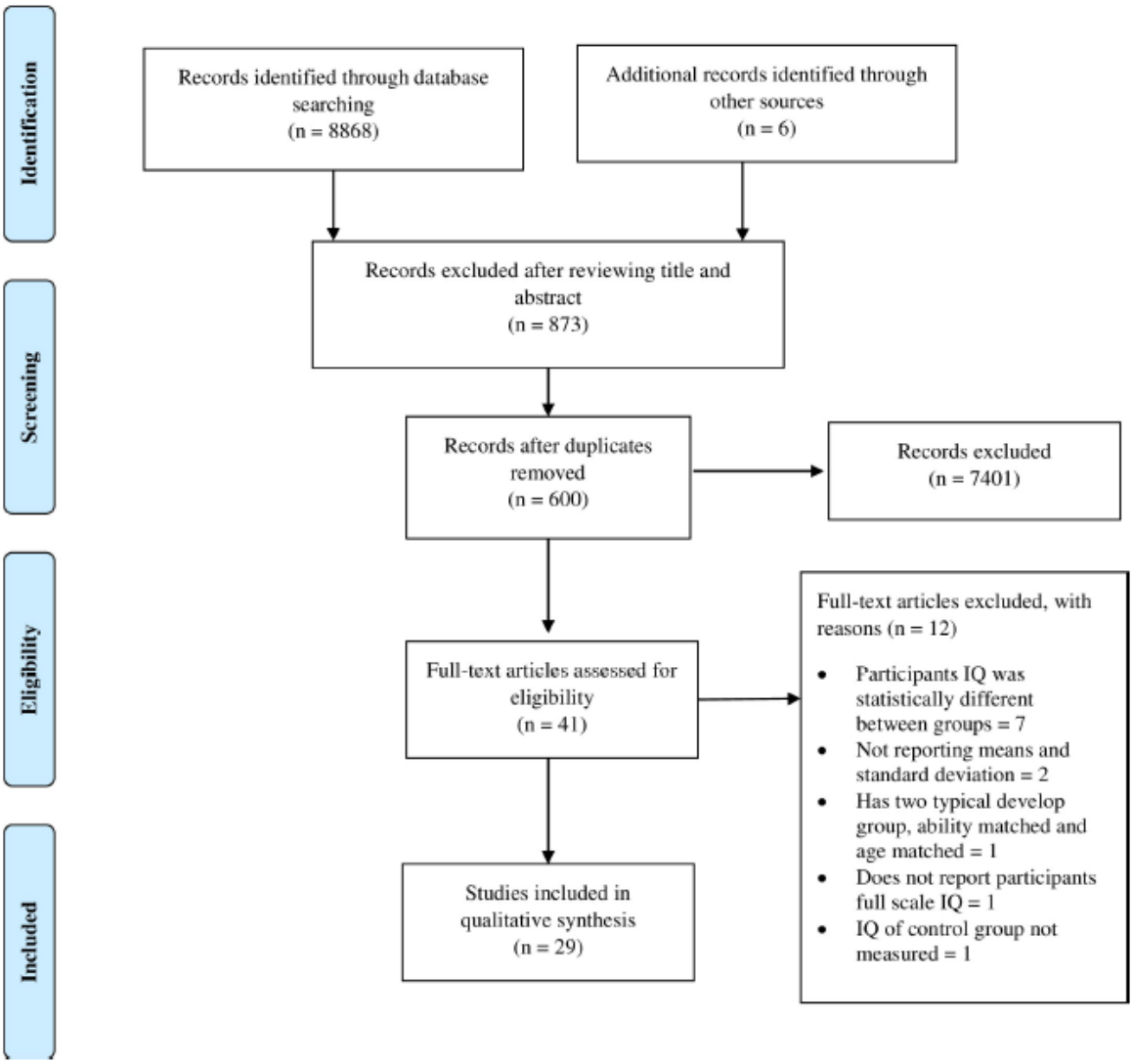

Fig 1. Flow diagram of study selection process in accordance with the PRISMA statement.

https://doi.org/10.1371/journal.pone.0216198.g001

Subgroup analysis of phonological working memory. The results above show that there was a significant impairment in both accuracy and error rate in phonological WM in people with ASD. However, to examine whether this effect was consistent across lifespan and to explore the variation in effect sizes post-hoc subgroup analysis was performed using age and IQ as moderators (Table 3). Age was dichotomised into children (< 18 years) and adults (≥ 18 years). There were four studies that investigated accuracy in phonological memory in children and five phonological memory in adults. There were no between group differences in age ($Q = 0.25$; $p = 0.62$) for accuracy in phonological WM (adults: d -0.79, 95% CI, -1.53 to -0.04

Table 1. Main characteristics of accuracy in phonological WM studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assessment
Gonzalez-Gadea et al., 2013	0.13	0.09	23	33.00	21	28.29	5.61 (1.31)	5.43 (1.47)	37.43	37.14	DC	BDC
Gracia-Villamisar et al., 2002	-2.98	0.26	16	23.50	16	21.19	48.13 (16.77)	86.88 (7.58)	42.75	43.69	DC	DR
Ham et al., 2011	-0.40	0.10	19	12.10	23	12.00	98.60 (20.20)	107.00 (21.60)	106.00	111.40	ADOS	DR
Maister et al., 2011	-0.61	0.14	15	11.80	15	11.20	30.30 (9.00)	36.10 (10.10)	39.70	40.00	ADI-R	PWS
Minshew and Goldstein, 2001	-0.42	0.05	52	22.33	40	21.55	1.72 (1.44)	2.36(1.62)	92.88	96.53	ADI and ADOS	S-TWM
Poirier et al., 2011	-0.96	0.14	16	31.60	16	34.80	0.64 (0.20)	0.81 (0.15)	100.30	102.40	ADOS	F-BDC
Schuh et al., 2012	-1.27	0.13	18	12.00	18	13.00	16.00 (2.00)	18.00 (1.00)	105.00	104.00	ADI and ADOS	LNS
Williams et al., 2006	-0.22	0.05	38	11.68	38	12.16	8.61 (3.33)	9.26 (2.61)	103.82	107.18	ADI and ADOS	WRAML
Williams et al., 2005 b	-0.20	0.06	29	28.73	34	26.53	10.86 (3.07)	11.38 (2.24)	105.86	109.65	ADI and ADOS	WRAML

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; WM: Working memory;ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; S-TWM: Three-word short-term memory task; WRAML: WMS–III, the Wide Range Assessment of Memory and Learning; DR: Digit recall; BDC: Backward digit recall; F-BDC: forward and backward digit recall; PWS: Phonological word-span task; LNS: Letter-Number Sequencing subtest from the Wechsler Intelligence Scale for Children, 4th Edition.

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vs child: *d* -0.57, 95% CI, -1.01 to -0.13). Mean IQ of study participants was dichotomised (average 90–109; high average 110–119). The accuracy phonological WM scores for all participants was reported as all having a mean average IQ and therefore not divided into subgroups. Moreover, as only two studies measured error in phonological WM, subgroup analysis was not conducted.

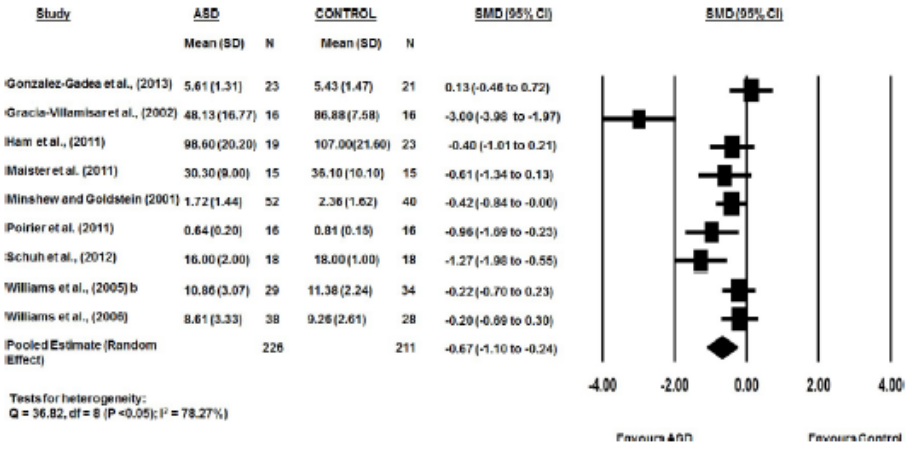

Fig 2. Accuracy in phonological WM between ASD and typically developing controls.

https://doi.org/10.1371/journal.pone.0216198.g002

Table 2. Main characteristics of error rate in phonological working memory studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assessment
Williams et al., 2014	0.68	0.12	17	31.06	17	31.92	0.21 (0.32)	0.05 (0.09)	114.10	117.70	ADOS and DC	PM Task
Yerys et al., 2011	2.22	0.15	28	10.89	18	11.07	65.36 (11.50)	43.11 (7.00)	113.90	118.90	DC, ADI and ADOS	CTT

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; WM: Working memory; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; PM Task: Prospective memory task; CTT: Consonant trigrams test.

https://doi.org/10.1371/journal.pone.0216198.t002

Visuospatial working memory

Accuracy in visuospatial working memory. Twelve studies tested accuracy in visuospatial WM. A summary of the study characteristics of the twelve studies is presented in Table 4. The studies were published between 2005 and 2015 and included 12 different journals. A total of 656 participants were recruited (305 ASD, 351 TD) across the 12 studies, with a mean total ASD sample size of 23.5, and TD sample size of 27. Participants' ages ranged from 11 to 63 years for ASD with a mean of 25.4 years, and TD age ranged from 10 to 63 with a mean age of 25.4 years. All twelve studies compared ASD participants with TD participants with all participants IQ scores being within typical range of 70 or greater.

The combined WM scores from the 12 studies were significantly lower in the ASD group than the TD group (*d*: -0.73, 95% CI -1.04 to -0.42, $p < 0.05$). There was a substantial heterogeneity between studies (Q-statistic = 36.40, df = 11 ($P < 0.05$); $I^2 = 69.75\%$) with a statistically insignificant publication bias (Egger's linear regression P = 0.09; Fig 4). Representative forest plots from the phonological WM meta-analyses are shown in Fig 5. Comparison of Figs 2 and 5 appear to suggest that there is a greater impairment in the visuospatial domain when measuring accuracy.

Error in visuospatial working memory. Eleven studies tested error in visuospatial WM. A summary of the study characteristics of the eleven studies is presented in Table 5. The studies were published between 2005 and 2014 and published between nine different journals. A total of 691 participants were recruited (342 ASD, 349 TD) across the eleven studies, with a mean total ASD sample size of 31.1, and TD sample size of 31.7. Participants' ages ranged from 8 to 28 years, with the ASD mean of 13.8 (range 8–24), and TD mean age of 14.4 (range 8–28). All twelve studies compared ASD participants with TD participants with all participants IQ scores being within typical range of 70 or greater.

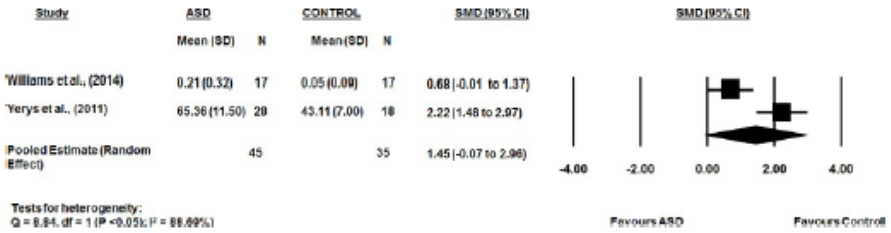

Fig 3. Error rate for ASD and typical developed controls groups in phonological WM.

https://doi.org/10.1371/journal.pone.0216198.g003

Table 3. Subgroup analysis phonological WM.

Study or Subgroup					Heterogeneity			
	K	SMD	95% CI	p-value	Q_{model}	P-value (Q_{model})	I^2	$Q_{between}$ (p-value)
Phonological Accuracy								
Adult	5	-0.79	-1.53 to -0.04	0.038	30.74	<0.001	86.99	0.25 (0.62)
Children	4	-0.57	-1.01 to -013	0.0111	6.08	0.11	50.66	

Note: K = number of studies; WM: Working memory; SMD = standardised mean difference; CI = confidence interval; Q_{model} = heterogeneity statistic for the model; I^2 = index of heterogeneity beyond within-study sampling error; $Q_{between}$ = between-groups heterogeneity statistic

https://doi.org/10.1371/journal.pone.0216198.t003

The combined WM error rate scores from the eleven studies were significant lower in the TD group than the ASD group (*d*: 0.56, 95% CI 0.25 to 0.88, p<0.05). There was a substantial heterogeneity between studies (Q-statistic = 36.01, df = 10 (P < 0.05); I^2 = 72.23%) with statistically insignificant publication bias (Egger's linear regression P = 0.4; Fig 6). Representative forest plots from the visuospatial WM meta-analyses are shown in Fig 7.

Subgroup analysis of visuospatial working memory. Eight studies investigated visuospatial accuracy in children, four in adults and nine studies measured visuospatial error rate in children, two in adults, presented in Table 6. There, were no between group differences in age (Q = 1.67; p = 0.20) for accuracy in visuospatial WM (adults: *d* -0.47, 95% CI, -0.91 to -0.03) vs

Table 4. Main characteristics of accuracy in visuospatial WM studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean Age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assessment
Brenner et al. (2015)	-0.45	0.08	27	12.68	25	13.41	9.54 (2.80)	10.82 (2.91)	101.31	106.96	ADI and ADOS	TRT
Crane et al. (2013)	-.067	0.08	28	41.57	28	40.53	10.16 (3.13)	11.89 (1.92)	117.18	115.11	DC	WMS-III
Cui et al. (2010)	-0.93	0.13	12	7.46	29	7.37	8.00 (1.76)	9.28 (1.19)	100.03	108.31	DC	BR and VPT
Geurts and Vissers (2012)	-0.88	0.10	23	63.60	23	63.70	6.60 (1.70)	8.10 (1.70)	109.50	109.80	DC	WMS-III
Jiang et al. (2014)	-1.96	0.14	21	11.00	21	10.90	1.51 (0.30)	2.01 (0.20)	110.50	111.90	ADI and ADOS	SWMT
Maister et al. (2011)	-0.38	0.14	15	11.80	15	11.20	12.30 (2.50)	13.10 (1.60)	39.70	40.00	ADI and DC	MST
Nakahachi et al., 2006	-0.51	0.10	16	28.00	28	28.30	31.90 (12.30)	37.40 (9.70)	101.00	103.00	DC	ATMT
Schuh et al. (2012)	-1.00	0.13	18	12.00	18	13.00	9.00 (2.00)	11.00 (2.00)	105.00	104.00	ADI and ADOS	FW
Williams et al. (2005) a1	0.13	0.07	31	26.58	25	26.76	570.03 (128.91)	554.08 (121.34)	108.65	109.76		N-Back
Williams et al. (2005) a2	-0.32	0.07	24	11.75	44	12.39	576.79 (127.26)	623.14 (150.98)	109.67	109.95	ADI and ADOS	N-Back
Williams et al. (2005) b	-1.58	0.08	29	28.73	34	26.53	7.28 (3.02)	11.85 (2.79)	105.86	109.65	ADI and ADOS	WMS-III
Williams et al. (2006)	-0.47	0.05	38	11.68	38	12.16	8.63 (2.83)	9.92 (2.66)	103.82	107.18	ADI and ADOS	WMS-III

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; WM: Working memory; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; BR: Block recall; ATMT: Advanced Trail Making test; VVT: variant-visual-pattern test; MTS: A visuo-spatial delayed match-to-sample task; FW: Finger Windows subtest from the Wide Range Assessment of Memory and Learning; WMS-III: Wechsler Memory Scale; SWMT: Spatial working memory task; TRT: The time reproduction task.

https://doi.org/10.1371/journal.pone.0216198.t004

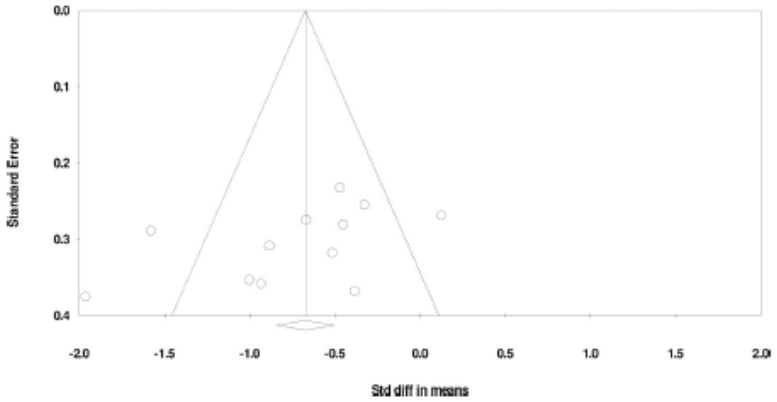

Fig 4. Funnel plot for accuracy in visuospatial working memory, Egger's linear regression P = 0.09. SMD effect size plotted against standard error. The circles represent the studies in the analysis. The vertical line represents the population effect estimate and the diagonal lines represent the 95% confidence intervals.

https://doi.org/10.1371/journal.pone.0216198.g004

child: *d* -0.86, 95% CI, -1.27 to -0.46) or in age (Q = 0.38; p = 0.54) for error in visuospatial WM (adults: *d* 0.02, 95% CI, -0.93 to 1.97 vs child: *d* 0.64, 95% CI, 0.35 to 0.92).

Two studies included participants categorised as having high average IQ (*d*: -1.29; 95% CI -2.56 to -0.02) and ten studies included participants with average IQ (d: -0.62; 95% CI -0.93 to -0.32) in accuracy visuospatial WM. There was no between group difference in accuracy in visuospatial WM (Q = 1.00; p = 0.32). Three studies involved participants categorised as having high average IQ (d: 0.48; 95% CI -0.53 to 1.49) and eight studies with participants with average IQ (d: 0.61; 95% CI 0.30 to 0.92) in error visuospatial WM. There was no significant between group difference for error in visuospatial WM (Q = 0.05.; p = 0.81).

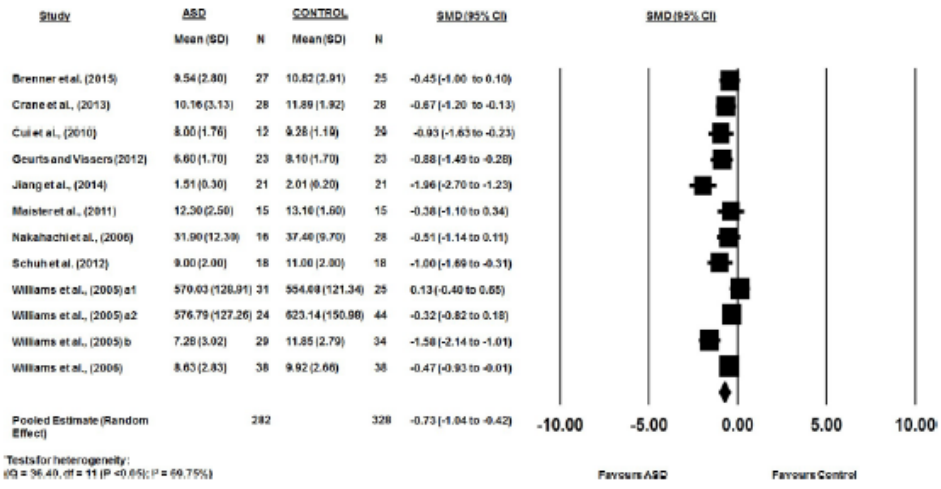

Fig 5. Accuracy in visuospatial WM between ASD and typically developing controls.

https://doi.org/10.1371/journal.pone.0216198.g005

Table 5. Main characteristics of error rate in visuospatial WM studies included in the meta-analysis.

Author	Cohen's *d*	Variance	ASD N	ASD mean age	TD N	TD mean age	ASD WM scores	TD WM scores	ASD FSIQ	TD FSIQ	Diagnosis	WM assessment
de Vries and Geurts 2014	0.44	0.03	79	10.70	71	10.30	9.60 (6.10)	7.30 (3.90)	109.30	107.70	ADI and DC	N-Back
Happe et al., 2006	0.59	0.07	32	10.90	32	11.20	46.90 (8.80)	42.30 (6.60)	99.70	106.80	DC	CANTAB
Jospeh et al., 2005	0.70	0.09	24	8.11	24	8.11	5.60 (2.70)	3.90 (2.10)	96.00	92.00	ADOS, ADI and DC	SOPT
Kaufmann et al., 2013	0.57	0.21	10	14.70	10	13.80	24.60 (19.50)	14.60 (15.60)	102.30	109.50	ADOS and ADI	CANTAB
Koshino et al., 2008	-1.01	0.21	11	24.50	11	28.70	12.50 (2.90)	15.90 (3.80)	104.50	108.60	ADOS and ADI	N-Back Faces
Landa and Goldberg 2005	1.02	0.12	19	11.01	19	11.00	52.70 (17.90)	35.80 (15.30)	109.70	113.40	ADOS and ADI	CANTAB
Sachse et al., 2013	0.99	0.08	30	19.20	28	19.90	33.30 (22.20)	15.60 (11.80)	105.30	109.30	ADOS, ADI and DC	CANTAB
Sinzig et al., 2008	-0.54	0.10	20	14.30	20	13.10	-0.62 (1.31)	0.01 (1.00)	112.00	113.00	DC	CANTAB
Solomon et al., 2009	0.98	0.10	22	182.00	23	191.00	0.26 (0.20)	0.11 (0.09)	107.00	113.00	ADOS and DC	Pop task
Steele et al., 2007	1.02	0.08	29	14.83	29	16.93	0.17 (0.11)	0.08 (0.06)	107.80	110.80	ADOS and ADI	CANTAB
Verte et al., 2006	0.90	0.03	66	8.70	82	9.20	21.1 (7.70)	14.90 (6.20)	101.50	112.20	ADI and DC	SOPT

Note: ASD: Autism spectrum disorder; TD: Typically developing; FSIQ: Full scale intelligence quotient; N: Number; WM: Working memory; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; DC: Diagnosed by a clinician; CANTAB: Cambridge Neuropsychological Test Automated Battery; POP: Preparing to Overcome Prepotency; SOPT: Self-ordered pointing task.

https://doi.org/10.1371/journal.pone.0216198.t005

Quality assessment. Assessment scores were converted to a percentage score, scores ranged from 81 to 100%. Nineteen studies were assessed as very good quality and were scored 22/22 = 100% and 21/22 = 95%. Ten studies were assessed as good quality and were scored 20/22 = 91%, 19/22 = 86%, and 18/22 = 81%. Results are presented in Table 7 along with scores from the quality assessment checklist. All papers were considered of sufficient quality.

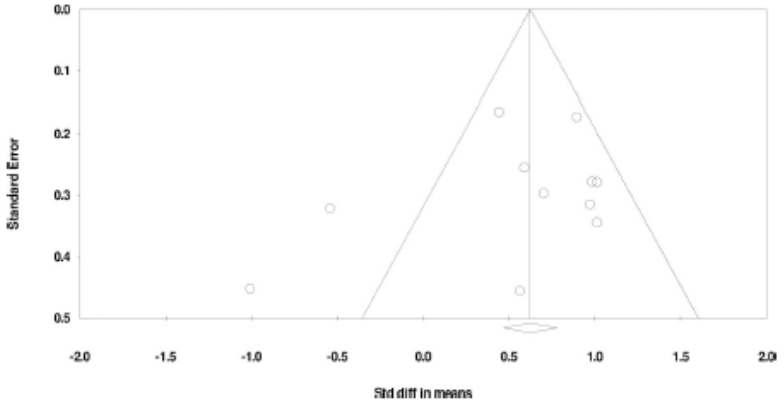

Fig 6. Funnel plot for error rate in visuospatial working memory, Egger's linear regression P = 0.4. SMD effect size plotted against standard error. The circles represent the studies in the analysis. The vertical line represents the population effect estimate and the diagonal lines represent the 95% confidence intervals.

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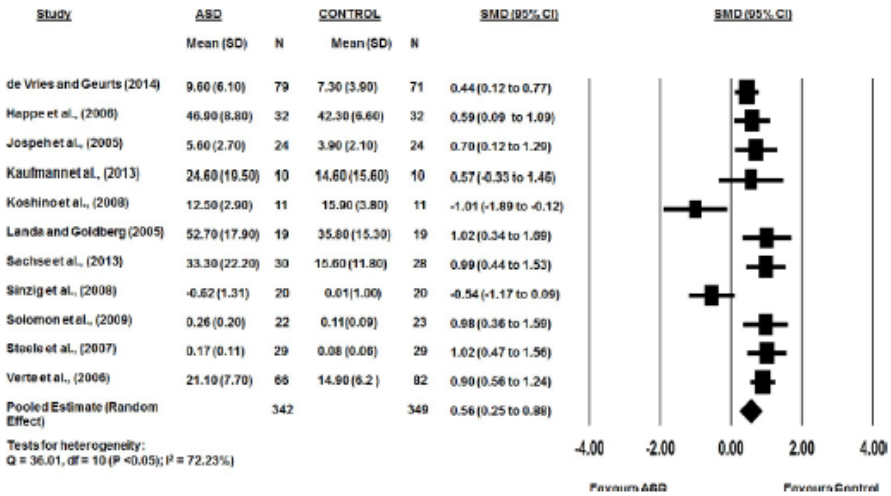

Fig 7. Error rate in visuospatial WM between ASD and typically developing controls.

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Discussion

The analyses demonstrated relatively large and statistically robust overall effect sizes, indicating significantly impaired performance when investigating accuracy and error rate among individuals with ASD across age groups which is consistent with previous research [18, 58, 59].

Working memory deficits in ASD were found across diverse methods to measure WM and different outcomes of working memory. Therefore, the present study indicates that working memory deficits in ASD are independent of the specific modality of the task. The publication bias results suggest that studies of working memory in ASD are equally likely to be published regardless of magnitude or statistical significance. Therefore, the probability that these results

Table 6. Subgroup analysis visuospatial WM.

Study or Subgroup					Heterogeneity			
	K	SMD	95% CI	p-value	Q_{model}	P-value (Q_{model})	I^2	$Q_{between}$ (p-value)
Visuospatial Accuracy								
Adult	4	-0.47	-0.91 to -0.03	0.037	7.22	0.07	58.44	1.63 (0.220)
Children	8	-0.86	-1.27 to -0.46	<0.001	25.58	0.001	72.63	
Average IQ	10	-0.62	-0.93 to -0.32	<0.001	23.88	0.004	62.31	
High Average IQ	2	-1.29	-2.56 to -0.02	0.046	7.75	0.005	87.09	1.00 (0.32)
Visuospatial Error rate								
Adult	2	0.02	-1.93 to 1.97	0.982	14.06	<0.001	92.89	0.38 (0.54)
Children	9	0.64	0.35 to 0.92	<0.001	21.27	0.006	62.40	
Average IQ	8	0.61	0.30 to 0.92	<0.001	20.26	0.005	65.44	
High Average IQ	3	0.48	-0.53 to 1.49	0.351	14.91	0.001	86.59	0.05 (0.81)

Note: K = number of studies; WM: Working memory; SMD = standardised mean difference; CI = confidence interval; Q_{model} = heterogeneity statistic for the model; I^2 = index of heterogeneity beyond within-study sampling error; $Q_{between}$ = between-groups heterogeneity statistic

https://doi.org/10.1371/journal.pone.0216198.t006

Table 7. Quality assessment.

Study	Question / objective sufficiently described?	Study design evident and appropriate?	Method of subject/ comparison group selection or source of information/ input variables described and appropriate?	Subject (and comparison group, if applicable) characteristics sufficiently described?	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	Sample size appropriate?	Analytic methods described/ justified and appropriate?	Some estimate of variance is reported for the main results?	Controlled for confounding?	Results reported in sufficient detail?	Conclusions supported by the results?	Total score	Percentage
Brenner et al. (2015)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Crane et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Cui et al. (2010)	2	2	2	2	2	0	2	2	2	2	2	20	91%
de Vries and Geurts (2014)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Geurts and Vissers (2012)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Gonzalez-Gadea et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Gracia-Villamisar (2002)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Ham et al., (2011)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Happe et al., (2006)	2	2	2	2	2	1	2	2	2	2	2	21	95%
Jiang et al. (2014)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Jospeh et al., (2005)	1	2	2	2	2	2	2	2	2	2	2	21	95%
Kaufmann et al., (2013)	2	2	2	2	2	0	2	2	2	2	1	19	86%
Koshino et al., (2008)	1	2	2	2	2	0	2	2	2	2	2	19	86%
Landa and Goldberg (2005)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Muister et al. (2011)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Minshew and Goldstein (2001)	2	2	2	2	2	2	2	2	2	2	2	22	100%

(*Continued*)

Table 7. (Continued)

Study	Question / objective sufficiently described?	Study design evident and appropriate?	Method of subject/ comparison group selection or source of information/ input variables described and appropriate?	Subject (and comparison group, if applicable) characteristics sufficiently described?	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	Sample size appropriate?	Analytic methods described/ justified and appropriate?	Some estimate of variance is reported for the main results?	Controlled for confounding?	Results reported in sufficient detail?	Conclusions supported by the results?	Total score	Percentage
Nakahachi et al., (2006)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Poirier et al. (2011)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Sachse et al., (2013)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Schuh et al. (2012)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Sinzig et al., (2008)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Solomon et al., (2009)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Steele et al., (2007)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Verte et al., (2006)	1	2	2	2	2	2	2	2	0	2	2	19	86%
Williams et al (2006)	0	2	2	2	2	2	2	2	2	2	2	20	91%
Williams et al. (2005a)	1	2	2	2	2	2	2	2	2	2	2	21	95%
Williams et al. (2005b)	0	2	2	2	2	2	2	2	0	2	2	18	81%
Williams et al., (2014)	2	2	2	2	2	2	2	2	2	2	2	22	100%
Yerys et al., (2011)	2	2	2	2	2	2	2	2	2	2	2	22	100%

Note: 2 = Yes, 1 = Partial, 0 = No, N/A = Not applicable.

https://doi.org/10.1371/journal.pone.0216198.t007

would be altered by including unpublished studies, studies there were not in English; studies that did not consider IQ or compared ASD to another clinical population is low. These findings are consistent with our hypothesis that individuals with ASD experience impairments in WM and support the growing view that cognitive and executive abnormalities may be just as important as the core symptoms in ASD, which demonstrates the significance and the importance of investigating working memory in ASD and the difficulties arising from these deficits. Exploratory post hoc subgroup analyses were conducted to investigate the effects of sample characteristics on the effect sizes for each outcome. Moderator variables (age and IQ) however, did not explain a significant amount of the between study variation.

There are a number of differences between the current meta-analysis and the one conducted by Wang and colleagues. By adopting a more extensive search of the available literature and a more stringent inclusion criteria the results of the literature search of the current meta-analysis found 8868 studies in the initial search compared to the 499 studies found by Wang et al. Moreover, a number of studies considered in the current meta-analysis, which met the inclusion criteria of Wang and colleagues, were not included in their meta-analysis. The studies that are present in their meta-analysis and not in the current one are due to those studies not meeting our inclusion criteria of matching participants on IQ and age. Therefore, the results presented here provide a less biased, and more comprehensive, synthesis of studies examining working memory in ASD.

Wang and colleagues found that there was a significant impairment in WM in individuals with ASD when investigating accuracy. The moderation results showed that visuospatial WM was more impaired than verbal WM and cognitive processing (maintenance vs. maintenance plus manipulation) did not explain the severity of the impairment. While they did conduct a meta-regression on IQ and age and found that they are not predictors of the impairment in WM, it is unreliable to draw such a conclusion while not controlling for IQ and age in the meta-analysis, as some of the studies included in their analysis did not control for IQ and age between their participants (Table 7). Similar to Wang, we found difference in WM accuracy that were not moderated by IQ and age. However, we found a larger effect size in both visuospatial (*d*: -0.73) and phonological (*d*:-0.67) WM showing a medium effect size compared to Wang (visuospatial, *d*: −0.72 and phonological, *d*: −0.44) showing a medium and a low effect size. Since Wang converted error rate scores into accuracy, this is the first study to show differences in WM error rates. This shows that individuals with ASD make more errors on WM task compared to the TD controls. This is an important as a few studies show that while testing WM performances, ASD participants did not differ on their accuracy from the TD controls but when made more errors, demonstrating that accuracy is not the only way to identity WM weaknesses, which could mean that ASD individuals are not only have impairments choosing the correct response by identifying them as well.

While there was an observed effect size difference between visuospatial (*d*: -0.73) and phonological (*d*:-0.67), we could not run a subgroup meta-analysis as the data in the groups was not independent (i.e. the same study participants contribute to more than one of the subgroups in the forest plot; [55]). Wang and colleagues conducted meta-analysis on WM type (spatial vs verbal) although the data was also independent as evident from their forest plots, which is another concern with the validity of their findings. There may be multiple explanations for the suggested larger impairment in visuospatial memory compared to phonological memory impairment. It may be that visuospatial tasks are more challenging simply due to the task being less familiar for automatic response. Letters or numbers are typically used to test phonological memory and that may be one of the reasons that visuospatial memory exhibits more impairments, since phonological tests can be associated to spoken and written material that may be used or observed in everyday life.

Another explanation for the observed larger impairment in the visuospatial domain in ASD individuals is that there may be another underlying cause such as using different brain regions during WM tasks. Functional magnetic resonance imaging (fMRI) studies have demonstrated prefrontal cortex (PFC) activity during WM task performance [60, 61, 62, 63] and the left dorsolateral prefrontal cortex (DLPFC), a specific region of the PFC, is considered to play a crucial role in WM ([64, 65, 66], for meta-analytic reviews, see [67, 68, 69]). fMRI studies have also investigated WM in individuals with ASD, for example, Koshino et al.[70] examined brain activation of a group of adults with high-functioning autism during an n-back working memory task with letter. Their results demonstrated that individuals with ASD exhibited similar activation in the right hemisphere compared with the control group in contrast to substantially less activation in the left hemisphere in the dorsolateral prefrontal cortex and the inferior frontal gyrus. Individuals with autism showed more right lateralized activation in the prefrontal and parietal regions, whereas the control group demonstrated more activation in the left than the right parietal regions. In addition, individuals with ASD had more activation than the control group in the posterior regions including inferior temporal and occipital regions. Luna and college [71] investigated the abnormalities in prefrontal circuitry and their effects on spatial working memory, they found that individuals with ASD demonstrated significantly less task-related activation in dorsolateral prefrontal cortex and posterior cingulate cortex in comparison with healthy subjects during a spatial WM task. This has been supported further by multiple studies such as the studies by Vogan et al.[72] that investigated neural correlates of verbal WM using a one-back letter matching task with four levels of difficulty. They found that neural patterns of activations differed significantly between TD and ASD groups. TD group had activation in the lateral and medial frontal, as well as superior parietal brain regions, while the ASD group showed little recruitment of frontal and parietal regions. In addition, the study by Silk et al.[73] demonstrating that individuals with ASD displayed less activation in lateral and medial premotor cortex, dorsolateral prefrontal cortex, anterior cingulate gyrus, and caudate nucleus during a visuospatial mental rotation task. Future research should consider these observed differences in WM impairments and investigate them fully in order to clarify this issue.

Given that WM allows individuals to maintain information actively in a readily accessible format, various researchers have investigated its relationship with wider intellectual ability measures, such as fluid intelligence and scholastic aptitude [74]. Such research provides various viewpoints explaining the relationship between the two constructs. For instance, Engle et al. [24] and Colom, Flores-Mendoza, and Rebollo [75] investigated the WM- intelligence association and found that WM is strongly related with intelligence. In light of the WM correlation with intelligence, we ensured that our inclusion criteria included only studies that matched groups on IQ or there was no significant difference between the groups, thus, eliminating intellectual weakness as a cause of impaired WM. Therefore, the results of the study suggest that working memory deficit is not simply attributable to IQ deficits. However, Poirier et al., [76] note that when participant groups are matched on verbal IQ as measured by the Wechsler scales, group differences on WM tasks may be underestimated because the test on which participants are matched (i.e., the WAIS), includes a sub-test of short-term/working memory (the digit span). In other words, participants might partly be matched on the domain that is of interest. While Poirier and colleagues took this into consideration and matched their participants on WAIS scores that purposefully excluded the digit span sub-tests while other studies did not, thus, this could be a critical methodological issue that future studies should take into consideration.

Strengths and limitations

Despite that there have been a number of comprehensive reviews of WM and ASD [18, 41, 58, 59], this is the first comprehensive review and meta-analysis of the current literature that investigates WM in ASD, while controlling for confounders such as age and IQ. We also divided WM into constructs, phonological and visuospatial, which consistent with the criterion recommendation [53], which is aimed to minimise heterogeneity and improve reliability in the results found. By conducting separate meta-analysis on the different possible outcomes of WM (accuracy and error rate) it allowed us to have a clear conclusion on the results of whether there are significant impairments in individuals with ASD. As the WM tasks used in experiments are not often identical, the search strategy used was vital. Using a large number of relevant key terms in the literature search allowed us to gain access to a wide range of studies. We ensured that our search strategy was inclusive of any studies that specifically state the testing of working memory despite the terminology used for the task. We also used the most commonly used understanding of working memory [17].

Using stringent criteria for inclusion in the meta-analysis lead the study to have some limitations. Some of the limitations of the study were that only published and English language studies were included in this review excluding studies that can potentially meet the inclusion criteria. Another limitation of the study was that we reviewed studies that tested older ASD individuals even though research has shown that WM is among the cognitive functions that decline with age [77, 78]. However, we felt it was important to investigate if the WM impairment is displayed across the life span of ASD individuals.

Due to the small number of studies included in this review, in particular phonological WM in ASD in comparison to matched TD, results should be interpreted with caution [55]. Furthermore, there are some factors that contributed to the large heterogeneity found in this meta-analysis. A large range of methods used to measure WM, and the outcome measured of each method (apart from accuracy and error rate). For example the study by Williams et al. [79] where they reported the accuracy mean as 570 for the ASD group using an N-back task compared to the study by Cui et al. [38] reporting the ASD group mean as 8 using a Block recall task. Another factor that could have contributed to the large heterogeneity is the is the different age groups used, for example the study by Gonzalez-Gadea et al. [80] looked at adults with a mean age of 33 in the ASD group and a mean of 38 in the control group, compared to the study by Ham et al. [81] where they looked at children with a mean age of 12 for the ASD and control groups. However, variation between studies is expected and was accounted for using the random effects model, which assumes heterogeneity.

It is important to note that the WM tasks across the studies were not matched and this must be considered when making any conclusion drawn from the current review as the results on the task may be influenced by psychometric properties of the test itself. In addition, individuals with ASD often have many comorbidities, such as Attention deficit hyperactivity disorder [82], learning difficulties (e.g. dyslexia) [83], and Obsessive-compulsive disorder [84]. Most of the studies in this review did not control for such confounders (or reported that they did) and thus these concurrent disorders may have contributed to the WM impairment observed.

Theoretical and clinical implications

Nevertheless, despite the study's limitations, as evident by the effect size the findings from this study will have important implications for people with ASD. WM impairments impact upon academic achievement [85, 86, 87] because many academic activities depend on WM such as remembering instructions, solving problems (mental arithmetic), controlling impulses and focusing attention [88, 89]. Therefore, academic progress of children and young people with

ASD may be impaired due to WM impairments described in this study. WM impairments also has an impact on everyday life as it is plays a crucial role for several everyday functions such as the development of theory of mind [90], navigation [91], every day problem solving [92], reading skills [93, 94] and language development [94]. Moreover, it has been demonstrated that WM deficiencies contribute to social problems in people with ASD [29] as it is necessary to keep social information constantly changing in WM for social flexibility [95]. WM also encodes emotions observed on faces [96], regulate emotional responses [97], slow learning [98] and learning disabilities [25], language development [19], and break from restrictive or repetitive behaviours [31]. Thus, clinicians should acknowledge that WM is significantly impaired and possibly a core issue in individuals with ASD. Additionally, clinicians should take into consideration that complains in regards to difficulties in everyday life from ASD patients could be related to the impairment of WM. The treatment of WM deficits could therefore improve some of the core cognitive and behavioural deficits characterising ASD.

Future research

The findings of this study help extend the literature on ASD and can be used to develop future studies centred on the most effective way to improve memory and consequently enhance the quality of life for individuals with ASD. Future research should investigate the nature of severity of WM deficiencies in individuals with ASD while controlling for confounding factors, such as comorbid psychiatric or developmental disorders. In the future, it may be possible to examine the results from studies that include individuals with LFA to investigate whether the deficit is present across the spectrum, studies should also consider using larger sample size as many of the studies have a small sample size that could lead the study to being underpowered. Future studies can also investigate if parents or siblings of individuals with ASD also experience WM impairments.

Conclusion

This review revealed that individuals with ASD display significant impairment in WM in both phonological and visuospatial domains across age groups this is important for the ASD population to help understand the disorder further and inform the development of interventions and intervention studies to improve WM in people with ASD.

Supporting information

S1 Appendix. Full search strategy of Medline database.
(DOCX)

S1 Table. Excluded studies.
(DOCX)

S1 Checklist. Prisma checklist.
(DOC)

S1 References. References of studies included in the meta-analyses.
(DOCX)

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