

Enhanced orientation discrimination and higher peak gamma frequency in autism spectrum conditions.

Abigail Dickinson

A thesis submitted for the degree of

Doctor of Philosophy (Ph.D)

The University of Sheffield

September 2015

Publications arising from this thesis

Dickinson, A., Jones, M., & Milne, E. (2014). Oblique orientation discrimination thresholds are superior in those with a high level of autistic traits. *Journal of autism and developmental disorders*, *44*(11), 2844-2850.

Dickinson, A., & Milne, E. (2014). Enhanced and impaired sensory discrimination in autism. *Journal of neurophysiology*, *112*(6), 1599-1599.

Dickinson, A., Bruyns‐Haylett, M., Jones, M., & Milne, E. (2015). Increased peak gamma frequency in individuals with higher levels of autistic traits. *European Journal of Neuroscience*, *41*(8), 1095-1101.

Dickinson, A., Bruyns‐Haylett, M., Smith, R., Jones, M., & Milne, E. (under review). Superior orientation discrimination and increased peak gamma frequency in autism spectrum conditions.

My contribution to this thesis included programming all tasks used, all data collection and analysis and interpretation of the data. Data analysis techniques were developed in collaboration with Dr. Myles Jones.

Abstract

This thesis investigates sensory processing in autism spectrum conditions (ASC), specifically focusing on low-level visual perception. Previous literature indicates that sensory problems are prevalent in ASC, and affect individuals across a range of modalities and in a variety of ways.

Study one of this thesis examines a low-level visual process, orientation discrimination, in neurotypical individuals (n=94) and demonstrates that orientation discrimination thresholds are lower (enhanced) in those with higher levels of autistic traits compared to those with lower levels of autistic traits. Study two (n=96) confirms that enhanced orientation discrimination is also present in individuals with an autism spectrum diagnosis, as individuals with an ASC show significantly lower orientation discrimination thresholds than matched control participants.

As orientation discrimination is closely linked to neural inhibition, the possibility that disruption in the balance of neural excitation and inhibition (E/I) may be present in those with enhanced orientation discrimination was investigated in studies three and four. Peak gamma frequency, a metric said to capture the balance of neural E/I, was measured in both individuals with higher levels of autistic traits and those with a clinical ASC diagnosis. The results of study three (n=33) and study four (n=80) show that visually-induced peak gamma frequency is higher in individuals with higher levels of autistic traits, and those with an ASC diagnosis.

This thesis employs both a psychophysical measure and a neural measure which tap into neural inhibition. In the context of previous literature (e.g. Muthukumaswaramy et al., 2009) the results of the research presented in this thesis suggests, in direct contrast to the increased excitation model of ASC (Rubenstein & Merzenich, 2003), that neural inhibition levels may actually be increased in at least some individuals with ASC.

# Acknowledgements

First and foremost I would like to thank my supervisor, Dr Elizabeth Milne. An acknowledgement section is not long enough to describe how much I have loved working with Liz, or to show how grateful I am for the knowledge and experience she has imparted on me over the last three years.  Her passion for research is contagious and will continue to inspire me long after my PhD is complete.

I would also like to say a huge thank you to the many participants who have kindly donated their time to taking part in my studies and who have been a delight to work with. Without them, this thesis would not have been possible.

I am also extremely grateful to Dr Megan Freeth and Dr Myles Jones who have both provided their own unique support and guidance during my PhD, which has been invaluable.

Working within the Sheffield Autism Research Lab has contributed to the enjoyment of my PhD experience massively, not least because of the other members, both past and present, who I have had the pleasure to work alongside. I would also like to acknowledge Dr Richard Smith who was instrumental in helping to recruit a large number of my participants.

My friends and family have always provided unwavering encouragement in everything, including this PhD. Thank you.

This thesis is for Josh, who sat beside me.

Table of contents

[Publications arising from this thesis 2](#_Toc433107666)

[Abstract 3](#_Toc433107668)

[Acknowledgements 4](#_Toc433107669)

[Table of contents 5](#_Toc433107670)

[List of tables 7](#_Toc433107671)

[List of figures 8](#_Toc433107681)

[List of abbreviations 9](#_Toc433107699)

[1. Chapter one: Perception in autism spectrum conditions. 10](#_Toc433107700)

[1.1. Autism spectrum conditions. 10](#_Toc433107701)

[1.2 Perception in ASC 15](#_Toc433107702)

[1.2.1 Embedded Figures Task 16](#_Toc433107703)

[1.2.2 Block Design Task 17](#_Toc433107704)

[1.2.3 Susceptibility to visual illusions 18](#_Toc433107705)

[1.2.4 Visual search 19](#_Toc433107706)

[1.2.5 Neuroimaging evidence 20](#_Toc433107707)

[1.2.6 Summary 21](#_Toc433107708)

[1.3 Theories of atypical perceptual abilities 22](#_Toc433107709)

[1.3.1 Weak central coherence 22](#_Toc433107710)

[1.3.2 Enhanced perceptual functioning 23](#_Toc433107711)

[1.3.3 Reduced generalisation 24](#_Toc433107712)

[1.3.4 Hypo-Priors 25](#_Toc433107713)

[1.4 Low level perception 25](#_Toc433107714)

[1.4.1 Visual perception 26](#_Toc433107715)

[1.4.2 Auditory perception 28](#_Toc433107716)

[1.4.3 Somatosensory discrimination 29](#_Toc433107717)

[1.5 Summary 29](#_Toc433107718)

[2. Chapter two: Orientation discrimination in relation to autistic traits and in ASC 31](#_Toc433107719)

[2.1 Study one: Orientation discrimination in relation to autistic traits 31](#_Toc433107720)

[2.1.1. Methods 34](#_Toc433107721)

[2.1.2 Results 38](#_Toc433107722)

[2.1.3 Discussion 42](#_Toc433107723)

[2.2. Study Two: Orientation discrimination in ASC 44](#_Toc433107724)

[2.2.1 Method 46](#_Toc433107725)

[2.2.2 Results 52](#_Toc433107726)

[2.2.3 Discussion 56](#_Toc433107727)

[2.3 Chapter Discussion 58](#_Toc433107728)

[3. Chapter Three: Neural excitation and inhibition in ASC 61](#_Toc433107729)

[3.1. Increased excitation in ASC 63](#_Toc433107730)

[3.2. Increased Inhibition in ASC 64](#_Toc433107731)

[3.3. Evidence 65](#_Toc433107732)

[3.4. Conclusion 75](#_Toc433107733)

[4. Chapter Four: Gamma band activity 77](#_Toc433107734)

[4.1 Gamma Abnormalities in ASC 82](#_Toc433107735)

[4.2 Spontaneous gamma band activity in ASC 83](#_Toc433107736)

[4.3 Evoked gamma band activity in ASC 87](#_Toc433107737)

[4.4 Induced gamma band activity in ASC 92](#_Toc433107738)

[4.5 Peak gamma band frequency 95](#_Toc433107739)

[4.6 Conclusion 96](#_Toc433107740)

[5. Chapter five: peak gamma frequency in relation to autistic traits and in ASC 98](#_Toc433107741)

[5.1 Study three: the relationship between peak gamma frequency and autistic traits 99](#_Toc433107742)

[5.1.2 Method 99](#_Toc433107743)

[5.1.3. Results 111](#_Toc433107744)

[5.1.4. Discussion 114](#_Toc433107745)

[5.2. Study four: peak gamma frequency in ASC 117](#_Toc433107746)

[5.2.1. Method 117](#_Toc433107747)

[5.2.2. Results 124](#_Toc433107748)

[5.2.3 Discussion 129](#_Toc433107749)

[5.3 Chapter Discussion 131](#_Toc433107750)

[Chapter 6: Discussion 134](#_Toc433107751)

[6.1 Summary of findings 134](#_Toc433107752)

[6.2 Increased inhibition in ASC 136](#_Toc433107753)

[6.3 Heterogeneity in ASC 138](#_Toc433107754)

[6.4 Alternate explanations 142](#_Toc433107755)

[6.4.1 Attenuated priors 142](#_Toc433107756)

[6.4.2 Attention 143](#_Toc433107757)

[6.4.3 Decision making 145](#_Toc433107758)

[6.4.4 Neuroarchitecture 146](#_Toc433107759)

[6.4.5 The effect of stimulus properties on peak gamma frequency 147](#_Toc433107760)

[6.5 Future Directions 149](#_Toc433107761)

[6.6 Conclusion 150](#_Toc433107762)

[References 151](#_Toc433107763)

List of tables

[Table 2.1 35](#_Toc429476722)

[Table 2.2 48](#_Toc429476722)

[Table 2.3 55](#_Toc429476722)

[Table 3.1 73](#_Toc429476722)

[Table 4.1 85](#_Toc429476722)

[Table 4.2 89](#_Toc429476722)

[Table 4.3 93](#_Toc429476722)

[Table 5.1 118](#_Toc429476722)

[Table 5.2 127](#_Toc429476722)

# List of figures

[Figure 2.1 37](#_Toc429476722)

[Figure 2.2 38](#_Toc429476722)

[Figure 2.3 40](#_Toc429476722)

[Figure 2.4 52](#_Toc429476722)

[Figure 2.5 53](#_Toc429476722)

[Figure 2.6 54](#_Toc429476722)

[Figure 4.1 78](#_Toc429476722)

[Figure 5.1 102](#_Toc429476722)

[Figure 5.2 104](#_Toc429476722)

[Figure 5.3 105](#_Toc429476722)

[Figure 5.4 109](#_Toc429476722)

[Figure 5.5 111](#_Toc429476722)

[Figure 5.6 119](#_Toc429476722)

[Figure 5.7 122](#_Toc429476722)

[Figure 5.8 123](#_Toc429476722)

[Figure 5.9 124](#_Toc429476722)

[Figure 5.10 125](#_Toc429476722)

# List of abbreviations

ASC = Autism spectrum conditions

PDD-NOS = Pervasive developmental disorder not otherwise specified

DSM = Diagnostic and statistical manual

ADOS = Autism diagnostic observation schedule

ADI = Autism diagnostic interview

DISCO = Diagnostic Interview for Social and Communication Disorders

EFT = Embedded figures task

BDT = Block design task

fMRI = Functional magnetic resonance imaging

WCC = Weak central coherence

EPF = Enhanced perceptual functioning

AQ = Autism quotient

ADHD = Attention deficit hyperactivity disorder

OCD = Obsessive compulsive disorder

SRS = Social responsiveness scale

GABA = Gamma-aminobutyric acid

MRS = Magnetic resonance spectroscopy

EEG = Electroencephalography

MEG = Magnetoencephalography

ITPC = Inter trial phase coherence

ICA = Independent component analysis

# 1. Chapter one: Perception in autism spectrum conditions.

* 1. **Autism spectrum conditions.**

Autism spectrum conditions (ASC) are characterised by impairments in social interaction and communication, along with the presence of restricted and repetitive behaviours (American Psychiatric Association, 2013). Common difficulties include maintaining and understanding relationships, and communicating both verbally and non-verbally with others (American Psychiatric Association, 2013). Restricted and repetitive behaviours often manifest as an intense interest, such as a preoccupation with a certain class of items, or as repetitive mannerisms, such as rocking or arm-flapping. The prevalence of sensory problems in ASC has recently been formally recognised, with hyper- or hypo-reactivity to sensory stimuli now included in the diagnostic criteria for the condition under the category of restricted and repetitive behaviours (American Psychiatric Association, 2013). Sensory issues in ASC attract a great deal of research attention, as our understanding of sensory systems provides a means to investigate the underlying neural differences in ASC. This is the approach taken in this thesis, which will focus on sensory perception in ASC, studying vision in particular.

Several conditions which have the same core impairments are typically described as ASC. For instance, Asperger’s syndrome traditionally refers to individuals who show the same ‘triad of impairments’ common to all individuals with an ASC, but have no delays in language development. In addition, pervasive developmental disorder not otherwise specified (PDD-NOS) was used to describe individuals who may not meet all of the criteria for autism, or show atypical autistic symptomology. Until 2013, autism, Asperger’s syndrome and PDD-NOS were all included under the umbrella term of autism spectrum disorder in the DSM. However, the DSM-5 unified these diagnoses into ‘autism spectrum disorder’, which now encompasses all autistic conditions (American Psychiatric Association, 2013).

The precise etiology of ASC is as of yet unknown, and is thought to be a heterogeneous combination of multiple environmental and genetic factors (Landrigan, 2010). However, it is known that genetic factors are likely to play a role, which is supported by the fact that ASC are highly heritable, with siblings of individuals with ASC having an 18% recurrence risk of developing the condition (Ozonoff et al., 2011; see Freitag, 2007, for a review). The prevalence rate of ASC in both children and adults is around 1% (Baird et al., 2006; Brugha et al., 2009). Many epidemiological studies have reported that there are a greater proportion of males as opposed to females diagnosed with ASC. These estimates vary between studies, with estimates ranging from a male: female ratio of 1.33:1 to 15.7:1, with a mean estimate of 5.5:1 (Fombonne, 2009). However, the reasons for this remain unclear. It is likely that there is under recognition of ASC in females (Gould & Ashton-Smith, 2011). Another suggestion put forward is that the genes related to ASC are located on the X chromosome that children inherit from their mothers (Skuse, 2000). Skuse (2000) puts forward the suggestion that whilst girls inherit an additional X chromosome from their fathers which may provide protective factors; boys do not, and are therefore more likely to develop ASC.

As there is currently no biomarker for the condition, diagnosis of ASC centres on behavioural assessment. Depending on the age and language ability of the individual, one of several diagnostic instruments is used to assess behaviour. These include the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), the Autism Diagnostic Interview (ADI-R; Lord, Rutter & Le Couteur, 1994) and the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekam, Libby, Gould & Larcombe, 2002). The ADOS is a standardised, semi-structured assessment used by both clinicians and researchers to assess communication and social interaction in those suspected of having an ASC. Participants take part in different social-communicative sequences with an examiner, each of which are designed to elicit a different combination of particular social behaviours. Participants are scored based on the presence of these behaviours. The ADI-R is a structured interview which is conducted with the parents of individuals aged 18 months and above, who are suspected of having an ASC. The interview involves 93 open-ended questions which cover three main areas: quality of reciprocal communication; communication and language; and restricted and repetitive behaviours. The DISCO is semi structured developmental history interview which is also carried out with parents, or the individual themselves in the case of adults. The interviewer uses different questions to assess strengths and difficulties in several different domains. The ADOS, ADI-R, and DISCO are all considered ‘gold-standard’ diagnostic tools, and are therefore commonly used by trained researchers to validate diagnoses, and gain more information regarding the symptom profiles of participants.

Learning disabilities (IQ<70) are estimated to occur in around 25-40% of individuals with ASC (Baird et al., 2000; Chakrabarti & Fombonne, 2001). Studying ASC without distinguishing between individuals who also have a co-morbid learning disability, and those who have average, or above average intelligence levels, introduces additional heterogeneity into research samples, which can impact on the clarity of the findings (van Elst, Pick, Biscaldi, Fangmeier & Riedel, 2013). It should be noted that most research in ASC is carried out with participants who have either average, or above-average intelligence, including the participants studied in this thesis. Therefore, results from these studies cannot necessarily be generalised across the condition to those with lower intelligence quotient scores.

Evidence suggests that in addition to being present in a clinical population; autistic traits are continuously distributed across the general population (Constantino & Todd, 2003; Wing, 1988). It is suggested that an ASC diagnosis represents the extreme end of certain symptoms which may be present to a lesser degree in other individuals (Constantino, Przybeck, Friesen & Todd, 2000; Piven, Palmer, Jacobi, Childress & Arndt, 1997). As a result, many individuals can be considered to exhibit a high level of autistic traits, but at a subclinical level. To measure such autistic traits the autism quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin & Clubley, 2001; described in chapter two) is a self-report questionnaire commonly used to measure autistic traits in those who do not have a clinical ASC diagnosis.

Several theories attempt to account for the range of symptoms observed in ASC through alterations in a single underlying factor. These include theories which state that differences in information processing, including a particular cognitive style such as weak central coherence (Frith, 1989), deficits in theory of mind (Baron-Cohen, Leslie & Frith, 1985), or executive functioning (Pennington & Ozonoff 1996; Russell, 1997) are present in ASC. Other theories provide low level descriptions of ASC, stating that there may be neural alterations in ASC which have cascading effects and lead to the variety of symptoms reported in the condition. These include the extreme male brain hypothesis (Baron-Cohen, 2002), the mirror neuron dysfunction theory (Williams, Whiten, Suddendorf & Perrett, 2001), and abnormal development of the magnocellular pathway (Milne et al., 2002; Spencer et al, 2000).

However, no one theory is widely accepted to explain the range of symptoms seen in ASC. All of the theories described here account for the cause of social and non-social symptoms of ASC at differing levels of explanation. Mapping these theories onto specific predictions of how sensory processing will be affected is difficult. However, several other theories directly address the perceptual symptoms of ASC. These theories will be discussed later in this chapter.

Although characteristic social and communication difficulties typically define ASC, atypical sensory processing has also been a long observed feature of the condition, and was present in the original descriptions of both autism and Asperger’s syndrome (Asperger, 1944; Kanner, 1943). Atypical perceptual processing has been described as a positive symptom, as it is not present in the general population (Mottron & Burack, 2001). Differences in sensory processing are frequently reported by individuals with ASC and their caregivers and often manifest as hyper- or hypo-responsiveness to sensory stimuli, or problems modulating sensory input (Baranek, David, Poe, Stone & Watson, 2006; Ben-Sasson et al., 2009; Jones, Quigney & Huws, 2003). Bogdashina (2003) report examples of behaviour that reflect hypersensitivity to sensory stimuli, including focusing on tiny pieces of dust and a dislike of bright lights. Examples of hyposensitive behaviours include being attracted to light and looking intensely at objects.

However, atypical sensory perception affects individuals in very different ways and extends to a variety of modalities including vision (see Simmons et al., 2009, for a review), audition (see Haesen, Boets & Wagemans, 2011, for a review) and touch (Cascio et al., 2008). In some individuals sensory abnormalities can be positive. For example, absolute pitch (which is facilitative for musical ability) is more common in ASC (Heaton, Hermelin & Pring, 1998), and some individuals with ASC give very specific anecdotal accounts of how sensory abnormalities have led to positive outcomes. For instance, Temple Grandin gives an eloquent account of how hypersensitivity to visual stimuli and the ability to notice small details led to her success as a livestock facility designer (Grandin, 2009).

On the other hand, sensory processing abnormalities can also cause great difficulties for some individuals with ASC as seemingly un-offensive sensory stimuli can cause great discomfort and distress (Baranek et al., 2006; Khalifa et al., 2004; Leekam, Nieto, Libby, Wing & Gould, 2007). It has also been suggested that this intolerance of sensory stimuli could be a contributory factor in other features of ASC such as social avoidance (Cosbey, Johnston & Dunn, 2010). Therefore, understanding sensory symptoms in ASC may provide insight into other aspects of the disorder, such as social symptoms.

The aim of this thesis is to further investigate the perceptual abnormalities observed in ASC, specifically focusing on low-level visual perception. One particular aspect of visual perception, orientation discrimination, will be investigated in relation to ASC. The latter half of the thesis will focus on the neural underpinnings of orientation discrimination, and investigate factors that may contribute to altered sensory perception.

## 1.2 Perception in ASC

Individuals with ASC commonly report differences in the processing of sensory information, separate to any peripheral sensory problems, such as vision or hearing loss (Baranek, 2002). The prevalence of sensory symptoms in ASC is clearly demonstrated in the results of studies that assess sensory differences in ASC using standardised questionnaires. A popular questionnaire used to assess sensory symptoms is the short sensory profile (SSP; McIntosh, Miller, Shyu & Dunn, 1999). The SSP is a caregiver questionnaire, which uses 38 items to obtain a comprehensive description of a child’s sensory responses. It has been found that 95% of children with ASC show some degree of sensory dysfunction on the SSP, compared to only 16.8% of control participants (Tomchek & Dunn, 2007). Sensory differences are also present in adults with ASC, with over 90% of children and adults estimated to experience some form of atypical sensory perception (Leekam et al., 2007). Sensory modulation symptoms have also been found to be elevated across the spectrum of severity, as well as age, with the greatest differences seen in under-responsivity, over-responsivity and sensation seeking (Ben-Sasson et al., 2009).

Sensory symptoms are reported to be more pronounced in children with severe cases of ASC. However, in adults the two are not related, suggesting that adults who are both severely affected, or high functioning, may show atypical sensory perception (Kern et al., 2007). Abnormalities are also reported across sensory domains including tactile, vestibular, auditory and visual (Harrison & Hare, 2004; Rogers 1998). Symptoms can involve both hyper- and hyposensitivity to sensory stimuli, and the nature of the sensitivity does not always stay constant within individuals (Jones et al., 2003).

In addition to studying perception in individuals with an ASC diagnosis, research has also focused on the relationship between sensory perception and autistic traits in those who do not have an ASC diagnosis. Atypical sensory experiences are more commonly reported in those with high levels of autistic traits than those with lower levels of autistic traits (Horder, Wilson, Mendez & Murphy, 2014; Robertson & Simmons, 2012). This suggests that atypical sensory experiences vary with the level of autistic traits an individual possesses, and that both the expression of autistic traits, and the occurrence of atypical sensory experience occur on a continuum (c.f. Baron-Cohen et al., 2001; Constantino & Todd, 2003).

As most of the evidence for abnormal sensory perception comes from questionnaires which rely on self-report, alternative methods have been employed to assess perceptual differences in a more precise way. One of the first objective indicators that individuals with ASC show perceptual processing abnormalities came from above average performance on certain visuo-spatial tests used to measure cognitive functioning, and the observation that individuals with ASC may not be as susceptible to visual illusions.

### 1.2.1 Embedded Figures Task

One of the first tasks to reveal an ASC advantage is the embedded figures task (EFT), which is often used to assess cognitive functioning (Witkin, Oltman, Raskin & Karp, 1971). This task requires participants to find a target shape which is hidden within a more complex design. Children with ASC have been found to function at a level above that of their general intelligence on the EFT, showing a greater accuracy than matched controls (Shah & Frith, 1983). The adult version of the EFT has found that although adults with ASC do not show any differences in accuracy, they are significantly faster at finding the target shape than controls (Jolliffe & Baron-Cohen, 1997).

The superior performance of children and adults with ASC on the EFT has been replicated in many studies. Some have found evidence for both higher accuracy and faster reaction times in individuals with ASC (Falter, Plaisted & Davis, 2008; Ropar & Mitchell, 2001), whilst others have just found evidence for higher accuracy (van Lang, Bouma, Sytema, Kraijer & Minderaa, 2006), or faster reaction times (Jarrold, Gilchrist & Bender, 2005; de Jonge, Kemner & van Engeland, 2006; Pellicano, Gibson, Maybery, Durkin & Badcock, 2005).

However, similarly to the superior performance found in visual search and the BDT, this enhanced performance does not appear to be present in all individuals with ASC. Brian and Bryson (1996) found that children with ASC showed no superior performance on the EFT, with no significant differences in either accuracy or reaction times. Other studies have also replicated this result (White & Saldaña, 2011; Schlooz et al., 2006). In addition, several studies have also found no evidence of either faster reaction times (Bölte, Holtmann, Poustka, Scheurich, & Schmidt, 2007; Kaland, Mortensen & Smith, 2007), or higher accuracy (Chen, Lemonnier, Lazartigues, & Planche, 2008; Edgin & Pennington, 2005; Horlin et al., 2014; Keehn et al., 2009; Ozonoff, Pennington & Rogers, 1991). It has also been suggested that the accuracy of individuals with ASC is in fact lower than that of matched controls (Burnette et al., 2005).

In addition to being present in those with an ASC diagnosis, individuals with high levels of autistic traits have been shown to demonstrate enhancements on the EFT (Almeida, Dickinson, Mayberry, Badcock & Badcock, 2010; Almeida, Dickinson, Mayberry, Badcock & Badcock, 2013; Grinter et al., 2009; Grinter, van Beek, Maybery & Badcock, 2009).

### 1.2.2 Block Design Task

The block design task (BDT) is a task used as part of many intelligence tests, including the Weschler intelligence scales (Wechsler, 1974) and the British Ability Scales (Elliot, Murray & Pearson, 1979). In the BDT participants are presented with a two-dimensional red and white pattern and asked to reconstruct the pattern from a number of identical blocks which have a white and red pattern on each face.

Several studies have demonstrated that individuals with ASC show superior performance on the BDT compared to other intelligence subtests (Happe, 1994; Lockyear & Rutter, 1970; Shah & Frith, 1983, 1993), with 47% of an ASC sample showing their peak performance on the BDT, compared to only 2% of a neurotypical sample (Caron, Mottron, Berthiaume & Dawson, 2006). However, whilst Siegel and colleagues (Siegel, Minshew & Goldstein, 1996) estimate that 22-38% of autistic individuals who do not have an intellectual disability show peak performance on the BDT, they point out that individuals with ASC can display a wide range of ability levels and patterns on intelligence scales, and there is no single characteristic pattern of performance.

In line with other tasks found to elicit superior performance, those with high levels of autistic traits have been shown to demonstrate similar enhancements to those with a clinical diagnosis of ASC on the BDT (Grinter et al., 2009; Stewart, Watson, Allcock & Yaqoob, 2009).

### 1.2.3 Susceptibility to visual illusions

Happé (1996) initially found that individuals with ASC are less susceptible to several two dimensional visual illusions, including the Ebbinghaus illusion, the Hering illusion and Kanisza triangle. Less susceptibility was demonstrated through more accurate judgements of the illusory figures. Bölte et al. (2007) also found that adults with ASC showed less susceptibility to gestalt illusions. However, other studies have found that individuals with ASC and matched controls are affected equally by visual illusions (Hoy, Hatton & Hare, 2004; Milne & Scope, 2008; Ropar & Mitchell, 1999, 2001).

However, Walter, Dassonville and Bochsler (2009) found in a sample of 145 neurotypical individuals that susceptibility to visual illusions is related to an individual’s score on the systemizing quotient, a self-report questionnaire which assesses an individual’s drive to explore and understand a system in order to discover how the system works (SQ; Baron-Cohen et al., 2003). Walter and colleagues demonstrate that being less susceptible to illusions, is related to a high SQ score, and suggest that results from previous studies may be affected by this trait. As individuals with ASC tend to score highly on the SQ, Walter suggests that it is this factor, and not having ASC per se, that has led to previous studies finding less susceptibility to visual illusions in ASC.

### 1.2.4 Visual search

Visual search tasks require participants to indicate the presence of a pre-specified target amongst several distracters. Feature search and conjunctive search are the two main types of visual search task. In a feature search task the target shares one dimension (e.g. colour) with one set of distracters but is unique in another dimension (e.g. shape). For instance a feature search task might involve searching for a blue X amongst blue T and red A distracters. In contrast, a conjunctive search task has a target which shares one dimension with one set of distracters and another dimension with another set of distracters. For example, a conjunctive search task might require searching for a blue X among blue T and red X distracters.

Several studies have shown that children with ASC have faster search rates and overall faster reaction times than matched controls on both conjunctive and feature search tasks (O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001; Plaisted, O'Riordan, & Baron‐Cohen, 1998b). This result has also been replicated in adults (Kemner, Van Ewijk, Van Engeland, & Hooge, 2008; O’Riordan, 2004) and in two year olds using a gaze based version of the conjunctive visual search task (Kaldy, Kraper, Carter, & Blaser, 2011).

Researchers have investigated whether a visual search advantage in ASC might be due to more efficient search strategies, or better memory. Kemner et al. (2008) used eye tracking to demonstrate that individuals with ASC showed no evidence of using a different search strategy during visual search tasks. Additionally, Joseph and colleagues (Joseph, Keehn, Connolly, Wolfe & Horowitz, 2009) used a dynamic visual search task, in which targets and distracters randomly changed location every 500ms, to demonstrate that it is not better memory for previously visited targets that underlies the superior visual search performance of children with ASC. Children with ASC were significantly faster than controls on both the standard and dynamic visual search tasks, and did not show any disturbance in performance in the dynamic condition, which would be expected if a greater memory for rejected distracters was enhancing visual search ability.

However, more recent reports do not find superior visual search in children with ASC (Keehn, Shih, Brenner, Townsend, & Müller, 2013; Iarocci and Armstrong, 2014). This suggests that enhanced visual search ability may be present in some individuals with ASC, but does not reflect a universal advantage across all individuals with the condition.

Similarly to the BDT and EFT, individuals with high levels of autistic traits also show enhanced performance on visual search tasks (Almeida et al., 2013; Brock, Xu & Brooks, 2011; Milne, Dunn, Freeth & Rosas-Martinez, 2013, although see Gregory & Plaisted-Grant, 2013, for negative findings).

### 1.2.5 Neuroimaging evidence

Along with behavioural studies suggesting atypical perceptual processing in those with ASC, functional imaging studies have revealed that differences in neural activation accompany the atypical performance observed in these tasks. For instance Jolliffe and Baron-Cohen (1997) followed up their behavioural study with an fMRI study using the same cohort of participants (Ring et al., 1999). It was found that control participants demonstrated more extensive task related activation in general during the EFT and also showed activation in prefrontal areas which were not activated in the ASC group. In contrast, participants with ASC showed greater activation of ventral occipito-temporal regions. Several other fMRI studies have also reported atypical neural activations in ASC participants during the EFT (Damarla et al., 2010; Lee et al., 2007; Manjaly et al., 2007; Spencer et al., 2012) the BDT (Bölte, Hubl, Dierks, Holtmann, & Poustka, 2008) and visual search tasks (Keehn, Brenner, Palmer, Lincoln, & Müller, 2008).

Samson, Mottron, Soulieres and Zeffiro (2012) conducted a meta-analysis of activation likelihood estimation studies using functional imaging to assess whether ASC is associated with atypical activations during visual tasks. Overall it was found that individuals with ASC exhibit more activation in temporal, occipital and parietal regions, and less activity in frontal cortex compared to control participants. This suggests that atypical neural processing may be contributing towards the atypical behavioural performance of individuals with ASC on visual tasks. However, the studies included in this meta-analysis spanned a wide variety of visual tasks including sentence comprehension, imitating emotional faces and the Tower of London task. Therefore, these results reflect aggregate findings across tasks, which involve a variety of different cognitive functions, as well as stimuli, which could limit their specificity and accuracy.

### 1.2.6 Summary

Individuals with ASC show superiority on certain visuo-spatial tasks, an observation which is consistent with the atypical sensory perception commonly described through self-report questionnaires. However, enhanced performance is not seen across all studies which have investigated perception in individuals with ASC. Variability in results could be a result of the heterogeneity within the ASC samples used (White, O’Reilly, & Frith, 2009; White & Saldaña, 2011), and the large amount of heterogeneity seen in ASC more generally, including the wide range of sensory symptoms reported. This could also be impacted by the variation in sample sizes employed, with larger studies having a greater amount of statistical power, and some studies with a smaller sample size not possessing adequate statistical power to reveal the effect that they are investigating. The inconsistency between findings could also be due to the fact that many of the studies are studying the abilites of children. These abilities change rapidly, and it may be the case that the different ages employed in different studies is affecting whether a group difference is seen between children with ASC and controls.

## 

## 1.3 Theories of atypical perceptual abilities

As the focus on perceptual processing has increased in ASC, several theories have attempted to account for sensory symptoms. These can be considered seperately from the theories which have focused on finding a unifying theory for both the social and non-social symptoms, as they specifically address perceptual symptoms predominantly.

### 1.3.1 Weak central coherence

One theory that attempts to account for atypical sensory perception in ASC is the Weak Central Coherence (WCC) hypothesis (Frith, 1989). Although the WCC hypothesis was originally forwarded as the single unifying theory for all impairments in ASC it became apparent that social impairments cannot fully be explained by WCC. The WCC hypothesis was therefore reformulated and no longer cited as the core deficit underlying ASC, but rather as a consequence of a locally oriented perceptual style (Happé & Frith, 2006).

The WCC hypothesis explains the perceptual abnormalities observed in ASC based on the principle that global processing is impaired amongst those with ASC, whilst local processing is intact. This impairment in global processing is said to manifest as an inability to draw together separate pieces of information and combine them into a whole, resulting in a more detail-oriented approach. Therefore when the success of a task relies on focusing on smaller details and ignoring the ‘bigger picture’, weak coherence will give rise to superior performance. This theory also predicts that tasks requiring global processing will be more difficult for those with ASC.

However, the WCC hypothesis can be seen as more of a description of the perceptual style in ASC rather than an explanation of its cause. More recent theories have gone on to describe perceptual abnormalities in more detail.

### 1.3.2 Enhanced perceptual functioning

Like the WCC hypothesis, the enhanced perceptual functioning hypothesis (EPF; Mottron & Burack, 2001) also attempts to address the superior local processing which has become an established perceptual characteristic in ASC. The EPF theory states that an increased response to sensory stimulation due to atypical functioning in brain areas responsible for perceptual processing leads to individuals with ASC focusing on low-level sensory stimuli (Mottron, Dawson, Soulieres, Hubert & Burack, 2006).

However, the EPF account questions the presence of a global processing deficit. It suggests that there is no impairment in global processing, but a bias towards local processing. This is reflected in the observation that tasks that create a conflict between local and global processing are more sensitive at picking up weak central coherence ([Happé & Frith, 2006](#_ENREF_34)). Therefore, it is suggested that those with ASC do not have a mandatory higher order control over perception and have a flexible ability to use either a local or global strategy (Perreault, Gurnsey, Dawson, Mottron, & Bertone, 2011). This leads to superior performance on certain tasks that benefit from a local processing strategy, resulting in superior visual processing (Mottron et al., 2006).

This is supported by several studies which have revealed individuals with ASC show enhanced detection of local targets (Plaisted, O’Riordan &Baron-Cohen, 1998b; Plaisted, Swettenham, & Rees, 1999) but a typical global bias (Mottron, Burack, Stauder, & Robaey, 1999; Ozonoff, Strayer, McMahon, & Filloux, 1994). In addition it has been found in both the auditory and visual domain that individuals with ASC show superior performance on tasks requiring local processing, but show no deficit compared to controls when the task relies on global processing (Mottron, Burack, Iarocci, Belleville, & Enns, 2003; Mottron, Peretz, & Menard, 2000). It is now generally accepted in vision that individuals with ASC show superior local processing but intact global processing (Haesen, Boets, & Wagemans, 2011; Robertson & Simmons, 2012).

### 1.3.3 Reduced generalisation

A complementary theory to the EPF account comes from Plaisted (2001) who puts forward reduced generalisation as an explanation for the perceptual abnormalities in ASC. She argues that individuals with ASC are unable to draw disparate pieces of information together into a whole due to reduced processing of similarities between stimuli and situations. This leads to a heightened awareness of the unique features of stimuli and a less sensitive ability to recognise the similarities between stimuli. Therefore in tasks such as visual search, the target will be easier to detect as it is seen as very dissimilar to the distracters.

Plaisted’s theory was originally based on the observation that both children and adults with ASC are better than matched controls at discriminating between highly similar novel stimuli (Plaisted et al., 1998a). O’Riordan and Plaisted (2001) investigated to what extent an enhanced ability to discriminate between stimuli could explain superior visual search performance. Similarity between target and distracter stimuli was manipulated in a conjunctive search task. It was found that increasing the similarity between target and distracter significantly increased the reaction times of neurotypical children, but did not affect the performance of the ASC participants. This supports Plaisted et al. (1998a) who stated that the superior visual search performance of ASC children was due to an increased ability to discriminate between targets and distracters.

It has been suggested that other areas of unusual visual processing may stem from this enhanced ability to discriminate between stimuli (O’Riordan & Plaisted, 2001, Plaisted et al., 1998a). For instance it has been suggested that superior performance on the EFT may stem from a superior ability to discriminate target from distracter shapes, and the different block faces from one another in the BDT (O’Riordan & Plaisted et al., 2001; O’Riordan et al., 2001).

### 1.3.4 Hypo-Priors

Other theories state that reduced top down influences lead to atypical perception in ASC. Pellicano and Burr (2012) describe the atypical perception seen in ASC as a reduction in priors. Priors is a term used in Bayesian decision theory to describe how we use prior experience of our environment to form models of the world which influence how we perceive information. This theory states that it is not sensory processing itself, but the interpretation of the sensory information which leads to atypical perception in ASC. It is also suggested that this leads to a more accurate view of the world, as hypo-priors lead to less bias when interpreting sensory information.

Friston and colleagues (Friston, Lawson & Frith, 2013; see also van Boxtel & Lu, 2013) state that the hypo-priors account of ASC could be reframed in terms of predictive coding, which offers a more explicit link to the neural mechanisms which may result in perception being altered. They state that the precision of the predictions made in ASC may be lower, so perception is dominated by sensory information, which may result in abnormal sensory perception such as WCC. It is suggested that these differences in prediction can be seen in evidence that individuals with ASC do not habituate as strongly to both numerical (Turi et al., 2015), and face stimuli (Pellicano et al., 2007). However, there have been no direct tests of this theory as of yet. Studying the development of pervasive priors such as the light-from-above prior, would reveal whether there are differences in the strength of perceptual priors in ASC.

## 1.4 Low level perception

The difficulty in finding a unifying theory explaining differences on tasks such as the BDT, the EFT and visual search may stem from that they all involve visual perception, but also require higher level cognitive processes, such as executive function. Therefore, the difference could arise from a great many cognitive or perceptual processes. Investigating low level perception in ASC will provide a more accurate description of how sensory processing is altered , without the confound of higher cognitive processes.

### 1.4.1 Visual perception

Numerous aspects of low level visual processing have been investigated in ASC, with some studies reporting visual processing to differ in individuals with ASC, compared to controls (See Simmons et al. 2009, for a review). For instance a study carried out by Ashwin and colleagues suggested that enhanced perceptual processing in ASC extends to a visual acuity so superior that it rivals that demonstrated by birds of prey (Ashwin, Ashwin, Rhydderch, Howells, & Baron-Cohen, 2009). However, methodological issues with this study were quickly raised, and it was suggested that technical details regarding the acuity testing system had led to overestimations of the visual acuity of the ASC participants (Bach & Dakin, 2009; Crewther & Sutherland, 2009). Subsequent studies using both the same and alternative acuity testing systems have since found that visual acuity is not superior in individuals with ASC (Bölte et al., 2012; Falkmer et al., 2011; Kéïta, Mottron, & Bertone, 2010; Tavassoli, Latham, Bach, Dakin, & Baron-Cohen, 2011; Milne et al., 2009). Therefore, although tests including visual search, the BDT and the EFT in individuals with ASC demonstrate enhanced performance, direct tests of eye-based visual ability reveal no abnormalities. This suggests that the basic visual abilities of individuals with ASC are not contributing to their enhanced performance and it is more likely to be due to abnormal neural processing (Robertson & Simmons, 2012).

To assess this, researchers have studied aspects of visual perception which are known to be processed cortically. For instance, several studies have investigated the static contrast sensitivity of individuals with ASC. Contrast sensitivity tests measure the ability of an individual to discriminate between different levels of luminance in an image. The point at which an individual can no longer detect a different between two levels of luminance is known as their contrast sensitivity threshold. It has been found that there is no significant difference between the contrast sensitivity threshold of individuals with ASC and matched controls (Behrmann, Thomas & Humphreys, 2006; de Jonge et al., 2007; Koh, Milne, & Dobkins, 2010ba). The same has been found for dynamic contrast sensitivity thresholds (Bertone, Mottron, Jelenic & Faubert, 2003; Koh, Milne, & Dobkins, 2010b; Pellicano, Gibson, Maybery, Durkin & Badcock, 2005).

However, Bertone, Mottron, Jelenic and Faubert (2005) studied contrast sensitivity in ASC, asking participants to identify whether first order contrast-modulated gratings and second-order texture defined gratings were oriented vertically or horizontally. The difficulty of these decisions was altered by varying contrast levels. The study reports superior performance in those with ASC for first-order contrast modulated stimuli, but decreased performance for complex texture-defined gratings. This demonstrates that contrast sensitivity is enhanced in ASC for first order stimuli, but is inferior for texture defined stimuli. However, this study does not measure orientation discrimination performance in ASC, as it has been reported to in the literature. To do this a task would need to test the smallest difference in orientation a subject can discriminate between two stimuli. Altering the difficulty of this decision by manipulating the amount of tilt would allow measurement of the just noticeable difference, and provide a threshold of orientation discrimination ability in visual degrees.

To the authors best knowledge, only one study has investigated orientation discrimination in ASC using such a task, and found no differences in orientation discrimination between those with ASC and controls (Schwarzkopf, Anderson, de Haas, White & Rees, 2014). Brock et al. (2011) have studied orientation discrimination threshsolds in relation to autistic traits, and found the two to be unrelated. However, this may be due to the orientation discrimination paradgim used not being adequately sensitive to reveal any differences (discussed in chapter two).

Other studies have reported reduced visual discrimination abilities in ASC. For instance, colour discrimination thresholds are significantly higher in participants with ASC compared to those of a matched control group (Franklin, Sowden, Burley, Notman, & Alder, 2008; Franklin et al., 2010; Heaton, Ludlow, & Roberson, 2008; Hurlbert, Loveridge, Ling, Kourkoulou, & Leekam, 2011). However, all of these studies have been carried out in children.

### 1.4.2 Auditory perception

Superior discrimination has been reported in ASC in the auditory modality (see Haesen, Boets & Wagemans, 2011 for a review). Heaton et al. (1998) demonstrate that children with ASC had a superior ability for identifying isolated notes compared to a control group. O’Riordan and Passetti (2006) also found that children with ASC showed superior auditory discrimination relative to a control group. Children with ASC could tell the difference between two alternately played notes of converging frequency for longer than controls, as indicated by their later response. Adults with ASC have also shown superior performance on pitch discrimination tasks relative to matched controls (Bonnel, Mottron, Peretz, Trudel & Gallun, 2003; Meilleur, Berthiaume, Bertone & Mottron, 2014).

Different types of auditory stimuli have also been shown to elicit enhanced auditory perception in ASC. Stanutz et al. (2014) demonstrated that children with ASC show superior pitch discrimination for both pure tones and tones in a melodic context. Enhanced pitch discrimination has also been found for both speech and non-speech stimuli in ASC (Heaton, Hudry, Ludlow, & Hill, 2008).

However, other studies have suggested that enhanced pitch detection is not present in all individuals with ASC. For instance, Bonnel and colleagues state that this enhanced performance is only seen in those with autism and is not present in participants with Asperger’s syndrome; indicating that it may be related to delayed language (Bonnel et al., 2010). Similarly, Jones et al. (2009) found that whilst auditory discrimination was not found to differ between individuals with ASC and matched controls, there was a subset of 20% of ASC individuals who demonstrated exceptional auditory discrimination skills.

### 1.4.3 Somatosensory discrimination

Blakemore et al (2006), measured tactile thresholds, and suprathreshold tactile sensitivity in adults with Asperger syndrome. Adults with Asperger’s syndrome are significantly more sensitive to vibrotactile stimuli presented at 200Hz, but not at 30Hz. Cascio et al (2008) also found that adults with autism had increased sensitivity to vibrotactile stimulation, but the two groups displayed similar thresholds for light touch. However, these results have not been replicated in children (O’Riordan & Passetti, 2006; Güçlü et al., 2007). In addition, Puts et al. (2014) demonstrated that children with ASC showed impaired amplitude discrimination for vibrotactile stimuli compared to control subjects.

## 1.5 Summary

It is well established that individuals with ASC experience atypical sensory perception across sensory modalities. Objective measures of perceptual ability demonstrate that enhanced perceptual discrimination may exist in some individuals with ASC. However, a lack of consistent replications suggests that this may not be universal across individuals with ASC. This may be due to the heterogeneity of the condition, or it may be due to a lack of consistency across studies. For instance, whilst some studies employ large sample sizes with adequate statistical power to investigate group differences, others have small sample sizes and may not possess the required statistical power. Therefore, it is important to recruit samples sizes large enough to reveal differences of the magnitude excpected. Determining if low level perception is altered in ASC and in those with high levels of autistic traits will allow insight into whether atypical low level visual perception may contribute to sensory symptoms experienced in day to day life.

The most well replicated psychophysical finding in ASC is of enhanced pitch discrimination. It is suggested that a comparable task in the visual domain would be orientation discrimination, as they are similar low level perceptual features which are said to rely on the same neural mechanisms, albeit in different domains (discussed in chapter two). However, orientation discrimination has not been well explored in individuals with ASC, with just one study which found no differences (Schwarzkopf et al., 2014). The first study in this thesis will revisit the hypothesis that orientation discrimination may be altered in those with higher levels of autistic traits, using a more sensitive task to measure orientation discrimination. The second study will investigate orientation discrimination thresholds in ASC in a large sample of individuals with ASC.

# 

# 2. Chapter two: Orientation discrimination in relation to autistic traits and in ASC

As discussed in chapter one, individuals with ASC often report experiencing atypical sensory perception, and demonstrate superior performance on several visuo-spatial tasks (Lockyear & Rutter, 1970; O’ Riordan, Plaisted, Driver & Baron-Cohen, 2001; Plaisted, O’Riordan, & Baron-Cohen, 1998; Shah & Frith, 1983; Shah & Frith, 1993). Therefore, it is possible that the processing of basic visual information is altered in ASC. Whilst low level auditory processing has been shown to be altered in ASC, with several reports of enhanced pitch discrimination (Bonnel et al. 2010; Jones et al. 2009; Stanutz et al. 2014), some examples of low level visual perception, such as contrast discrimination, do not seem to be affected (Behrmann et al. 2006; De Jonge et al. 2007; Franklin et al. 2010; Koh et al. 2010b).

It is suggested here that orientation discrimination may offer a more suitable task in the visual domain to compare low level processing in the visual domain with pitch discrimination in the auditory domain, as the two processes are said to both rely on lateral inhibition (Houtgast, 1972; Hubel & Wiesel, 1968). Orientation discrimination has been studied in relation to autistic traits and found to be unrelated (Brock et al., 2011), and also unaltered in ASC (Schwarzkopf et al., 2014). However, there are methodological limitations to both of these studies (discussed in more detail below). Therefore, re-visiting the possibility that orientation discrimination may be altered in ASC using a more sensitive task will lead to more certainty regarding orientation discrimination performance in ASC. Studies one and two of this thesis (chapter two) will measure orientation discrimination in relation to autistic traits, and in a large sample of individuals with an ASC diagnosis.

## 2.1 Study one: Orientation discrimination in relation to autistic traits

Recently researchers have examined the extent to which atypical sensory perception occurs in members of the neurotypical population who have a high level of autistic traits but do not have a clinical diagnosis of ASC. This approach has indicated that atypical sensory experience is reported more frequently in individuals with higher levels of autistic traits than those with lower levels of autistic traits (Robertson and Simmons, 2013). In the auditory domain it has been found that those with higher levels of autistic traits perform better on a pitch identification task, and are more likely to show absolute pitch (Dohn, Garza-Villarreal, Heaton & Vuust, 2012). This suggests that along with the level of autistic traits an individual possesses (Baron-Cohen et al., 2001), atypical sensory experiences also occur on a continuum in the general population.

Of the sensory modalities, the association between visual function and autistic traits has been studied most extensively. Individuals with a high level of self-reported autistic traits have been shown to exhibit superior performance compared to those with a low level of autistic traits on a variety of tasks including visual search, the EFT and the BDT (Lockyear & Rutter, 1970; O’ Riordan, Plaisted, Driver & Baron-Cohen, 2001; Plaisted, O’Riordan, & Baron-Cohen, 1998; Shah & Frith, 1983; Shah & Frith, 1993; discussed in chapter one). However, one aspect of visual perception which appears to be unrelated to autistic traits, however, is orientation discrimination. Brock et al. (2011) found no significant correlation between autistic traits and orientation discrimination thresholds in neurotypical individuals. Therefore, it may be the case that orientation discrimination is not altered in individuals who have higher levels of ASC traits, but no clinical diagnosis. Alternatively, it could be the case that the task employed by Brock and colleagues did not have adequate sensitivity to reveal individual differences associated varying levels of autistic traits.

Brock and colleagues used horizontally oriented target gratings, which participants had to identify from distracter gratings deviating from horizontal during a visual search task. The use of cardinally oriented gratings in this task is relevant, as numerous studies have demonstrated superior performance on a wide range of perceptual tasks employing stimuli aligned at cardinal rather than oblique angles, a phenomenon known as the oblique effect (Appelle, 1972). The oblique effect is demonstrated in orientation discrimination thresholds, which are higher for stimuli oriented at oblique rather than cardinal angles (e.g. Westheimer and Beard, 1998). Therefore it is possible that the use of a cardinally oriented target grating may give rise to ceiling effects and a reduction of inter-participant variability thus masking any relationship between autistic traits and orientation discrimination thresholds. In support of this position, previous research has shown that migraineurs show reduced orientation discrimination thresholds compared to non-migraineurs, but only for oblique, and not vertical stimuli (Tibber, Guedes & Shepherd, 2006).

The present study aimed to re-visit the hypothesis that orientation discrimination thresholds are correlated with level of self-reported autistic traits. The AQ was used to measure autistic traits (Baron-Cohen et al., 2001) and an orientation discrimination task which measured both vertical and oblique judgements was used to determine orientation discrimination thresholds (Edden et al., 2009). It was reasoned that requiring participants to make oblique-oblique discriminations would introduce enough difficulty into the task in order to increase inter-participant variability, and reveal any atypical orientation discrimination that may exist in those with a high level of autistic traits. If the non-clinical autistic phenotype is associated with increased sensitivity to small differences in orientation, as well as pitch, then those with higher levels of autistic traits may demonstrate lower orientation discrimination thresholds. Vertical orientation discrimination thresholds were also measured, as a non-significant correlation would confirm that there is no relationship between autistic traits and cardinal orientation discrimination thresholds (c.f. Brock et al., 2011).

### 2.1.1. Methods

*Participants*

116 neurotypical volunteers with normal or corrected to normal vision were recruited from the student and local community population. Participants were excluded if they did not complete 1 or more parts of the orientation discrimination task (described below). This led to 14 participants being excluded. A further 8 participants were excluded from the analysis as either their vertical or oblique orientation discrimination threshold was more than 2 standard deviations above the group mean. The final analysis included 94 participants (42 male, 52 female; mean age 24.48; age range = 18 – 61). The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee. Participants provided informed written consent, in accordance with the declaration of Helsinki.

*Autism Spectrum Quotient Questionnaire*

Participants completed paper copies of the AQ, a 50 item self-report questionnaire that measures autistic traits in the general population (Baron-Cohen et al., 2001). Participants are required to state whether they agree or disagree with a series of statements which describe different social and communication centred preferences. Each item is scored as a 0 or a 1, with 1 indicating the presence of an autistic trait. The maximum score on the AQ is 50, and higher scores are indicative of a higher level of autistic traits.

Baron-Cohen et al. (2001) found in a large sample of neurotypical individuals (N=174) that the mean score on the AQ was 16.4 (SD=6.3). It was also reported that in a group of individuals with high functioning ASC (N=58), that the mean score was 35.8 (SD=6.5) and that 80% of these adults had scores over 32, compared to only 2% of individuals without an ASC having a score of over 32. It was also found that men tend to score higher on the AQ.

The AQ has been shown to have high internal reliability (Baron-Cohen et al., 2001; Auyeung et al., 2008; Hoekstra et al., 2008) and can be split into five subscales (each comprised of ten items) which assess different areas: social skill; attention switching; attention to detail; communication and imagination. See table 2.1 for an example item from each of the five subscales. Baron-Cohen et al. (2001) demonstrated that items within these subscales showed moderate to high internal consistency. However, factor analyses studies have since supported that there are not five underlying factors. For instance Hoekstra et al. (2008) suggest that there are just two subscales: social interaction and attention to detail; whilst Austin (2005) suggest that there are three: social skill; details/patterns and communication/mind reading.

**Table 2.1.** Example items from each of the five subscales of the AQ.

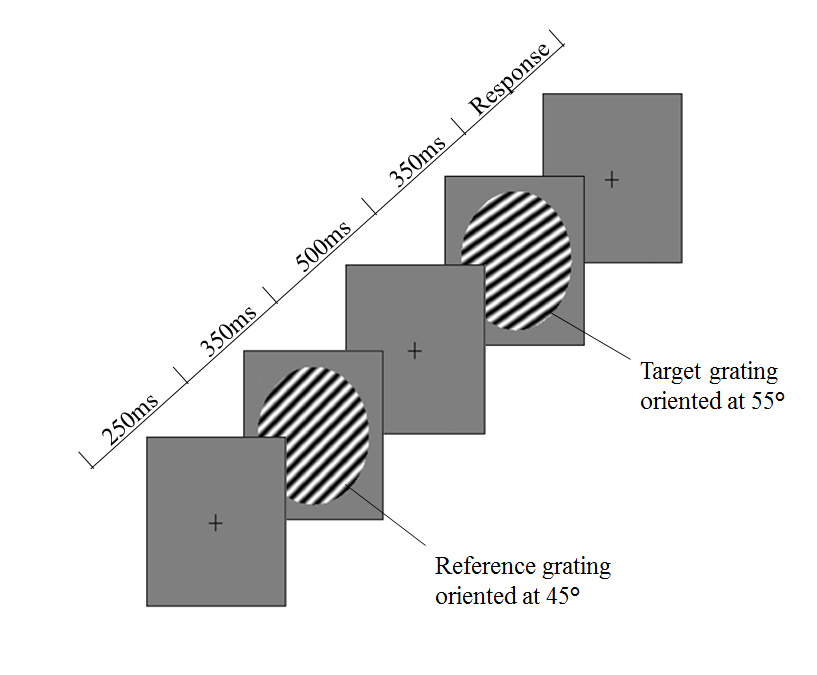
|  |  |
| --- | --- |
| **Subscale** | **Statement** |
| **Social skills** | ‘I prefer to do things with others rather than on my own.’ |
| **Attention switching** | ‘I frequently get so strongly absorbed in one thing that I lose sight of other things.’ |
| **Attention to detail** | ‘I usually notice car number plates or similar  strings of information.’ |
| **Communication** | ‘I enjoy social chit-chat.’ |
| **Imagination** | ‘When I’m reading a story, I can easily  imagine what the characters might look like.’ |

*Orientation discrimination task*

Orientation discrimination thresholds were measured using a two-alternative forced choice adaptive staircase procedure based on that described by Edden et al. (2009). The sequence of events in each trial is illustrated in figure 2.1. On each trial a reference grating and a target grating were presented sequentially, each for 350ms, separated by a 500ms delay. The circular gratings (diameter 4°; spatial frequency 3 cycles/degree; contrast 99%; mean luminance 83 cd/m2) were created and presented in MATLAB (MATLAB, 6.1, The MathWorks Inc., Natick, MA, 2000) using the PsychToolbox set of functions (Brainard, 1997). Participants completed the experiment in a completely dark room. The stimuli were displayed on a linearised AMW MR19C-ABAD LCD monitor with a spatial resolution of 1280 x 1024 pixels and a temporal resolution of 60Hz. Participants were seated 57cm away from the monitor which had a circular aperture placed over it in order to remove any orientation cues provided by the edge of the screen.

Participants were asked to judge whether the target grating had been rotated clockwise or anti-clockwise compared to the reference grating. Each run consisted of four randomly interleaved staircases. There were two conditions, in one condition the reference grating was oriented at 0 degrees (vertical) and in the other it was oriented at 45 degrees. Two staircases were used for each condition. One presented the clockwise transformations of the stimulus and the other presented the anti-clockwise transformations.

Responses were recorded by the participant using the left and right arrow keys on a keyboard. A one-up three-down staircase method was used, which converged on 79% correct performance (Leek, 2001). Therefore, if participants answer correctly three times in a row, the angle of difference between the target and reference grating would decrease. This angle would continue to decrease until participants answered incorrectly. When a participant answered incorrectly, the angle of difference would then increase. This angle would continue to increase until participants answered correctly three times in a row. The point at which the staircase changed the direction of how the angle was changing (i.e. increasing or decreasing) constituted a reversal, and the angle that this occurred at would be a reversal value. The initial target grating was presented at 5 degrees away from the reference grating. The initial step size was 1 degree which decreased by 75% after every reversal.

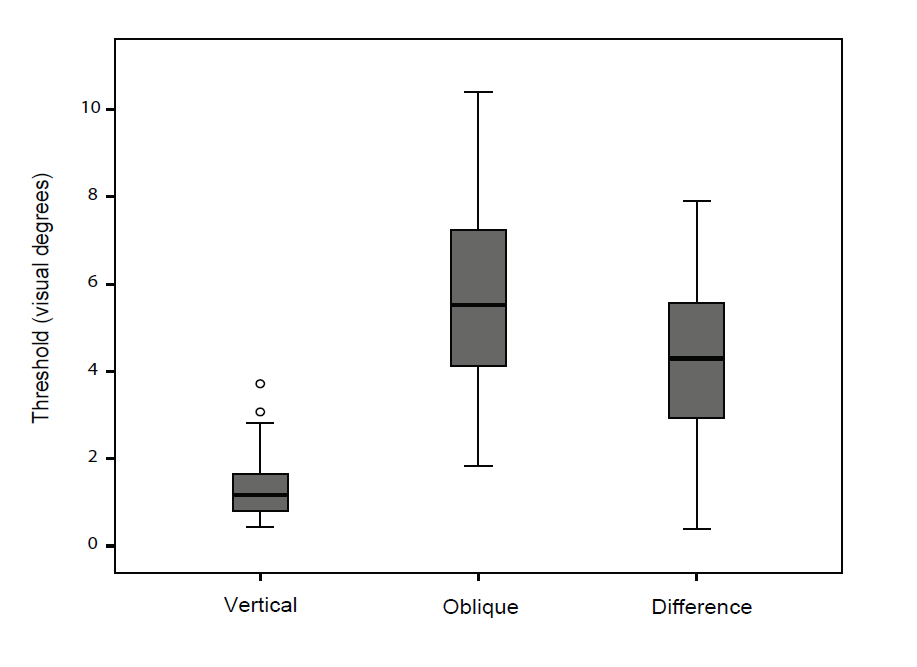
**

**Figure 2.1.** Schematic diagram of the orientation discrimination task.

Participants completed a practice run which continued until each of the four staircases completed 2 reversals. Participants then completed 2 runs which finished when each staircase had reached 10 reversals, with a short self-timed break of around 1 minute between runs. As the design incorporated 4 interleaved staircases, with a one-up three-down design, it was anticipated that the task may become quite long. Therefore if participants hit 120 trials on any one of the staircases, on either of the runs, the task terminated. These participants were categorised as not having completed the task and were excluded from any analysis. As described above, 14 participants were excluded on these grounds. The first 2 reversals for each run were discarded before computing the threshold by averaging over the last 8 reversals. Thresholds were estimated separately for the oblique and vertical conditions by averaging across the thresholds obtained for the clockwise and anticlockwise staircases, over both of the 2 runs.

### 2.1.2 Results

AQ scores ranged from 2 to 42, with a mean score of 16. This is the distribution of AQ scores expected in a neurotypical population based on previous studies (Baron-Cohen et al., 2001; Brock et al., 2011). A classic oblique effect was observed with orientation discrimination thresholds being significantly higher in the oblique than in the vertical condition (*t* (93) = -24.687, *p* = <.0001). The mean orientation discrimination threshold in the vertical condition was 1.3° (*SD*=0.62), whilst in the oblique condition it was 5.7° (*SD*=2.01). The magnitude of the oblique effect was also calculated by subtracting each individual’s vertical threshold from their oblique threshold. The average oblique effect was 4.40° (*SD*=1.73). Thresholds are illustrated in figure 2.2.

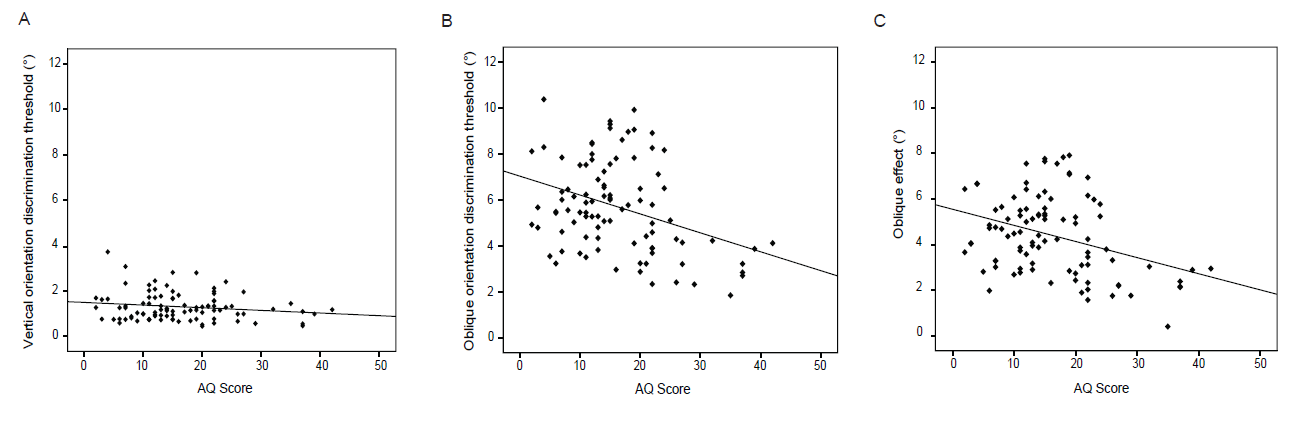


**Figure 2.2.** Box plots demonstrating vertical and oblique orientation discrimination thresholds and the magnitude of the oblique effect.

*Relationship between orientation discrimination threshold and AQ score*

The relationships between AQ score and vertical discrimination threshold, oblique discrimination threshold, and the oblique effect are presented in figure 2.3A, 2.3B and 2.3C respectively. Pearson correlation coefficients indicated that there was a significant negative linear relationship between oblique orientation discrimination thresholds and AQ scores (*r*= -.356, *p* <.0001, *R2* = .127). There was no significant relationship between vertical orientation discrimination thresholds and AQ scores (*r*= -.164, *p* =.114, *R2* = .027). There was also a significant relationship between the magnitude of the oblique effect, and AQ scores (*r*= -.316, *p* <.0001, *R2* = .127). Similar results were obtained using the more robust Spearman’s rho correlation.

Figure 2.3. (A) Correlation between vertical orientation discrimination threshold and AQ score (N=94) (B) Correlation between oblique orientation discrimination threshold and AQ score (N=94) (C) Correlation between magnitude of the oblique effect and AQ score

****

R2 =.127

R2 =.127

R2=.027

**Figure 2.3. (A)** Correlation between vertical orientation discrimination threshold and AQ score (N=94) **(B)** Correlation between oblique orientation discrimination threshold and AQ score (N=94) **(C)** Correlation between magnitude of the oblique effect and AQ score

Significant correlations were also observed between several subscales of the AQ and orientation discrimination thresholds. Oblique thresholds were correlated with the social skills (*r*=-.253, *p*=.014); attention switching (*r*=-.325, *p*=.001); communication (*r*=-.340, *p*=.001) and imagination (*r*=-.240, *p*=.02) sub scales of the AQ. The relation between orientation discrimination and the attention to detail sub scale did not reach significance (*r*=-.199, *p*=.055).

The magnitude of the oblique effect (vertical thresholds subtracted from oblique thresholds) was correlated with all 5 subscales of the AQ. The social skills (*r*=-.249, *p*=.016); attention switching (*r*=-.271, *p*=.008); communication (*r*=-.357, *p*=.000); imagination (*r*=-.250, *p*=.015) and attention to detail (*r*=-.234, *p*=.023) subscales were all negatively correlated with the magnitude of the oblique effect.

The oblique orientation discrimination thresholds obtained by the first (*M*=5.94, *SD*=2.77), and second runs (*M*=5.45, *SD*=2.55) of the orientation discrimination task were not significantly different (*t*(32)=1.66, *p*=.1), thus demonstrating intra subject reliability. AQ score was also not correlated with the difference between the thresholds obtained by the two runs (*r*=.298, *p*=.09), suggesting that differences in performance were not due to differences in engagement in the task over time.

### 2.1.3 Discussion

The aim of the present study was to determine whether orientation discrimination thresholds are associated with the level of autistic traits an individual possesses. Orientation discrimination ability has previously been found to be unrelated to self-reported autistic traits (Brock et al., 2011). It is suggested here that this is not because orientation discrimination superiorities do not exist in individuals with a high level of autistic traits, but rather due to the fact that the task used by Brock and colleagues was not adequately sensitive to reveal any orientation discrimination threshold differences that may be associated with autistic traits. Here a highly sensitive task was used to measure orientation discrimination thresholds, which required participants to make oblique-oblique judgements in addition to vertical-oblique judgements.

As expected, oblique orientation discrimination thresholds were around four times higher than vertical orientation discrimination thresholds, demonstrating a classic oblique effect. In support of predictions it was also demonstrated that oblique orientation discrimination thresholds were significantly correlated with AQ scores. Individuals with a high level of autistic traits showed lower orientation discrimination thresholds, demonstrating superior performance. In addition, it was found that those with higher AQ scores showed a smaller oblique effect, indicating that a higher level of autistic traits is associated with less impairment at difficult oblique judgements. This relationship between orientation discrimination and autistic traits was seen across subscales, and was not just restricted to the attention to detail subscale, as might have been expected.

Vertical orientation discrimination thresholds were not significantly correlated with AQ scores. Therefore whilst these results support those of Brock et al. (2011) who found no correlation between horizontal orientation discrimination thresholds and autistic traits, they extend these findings, demonstrating that when a task is sufficiently difficult to generate substantial inter-participant variability, there is a significant relationship between orientation discrimination ability and autistic traits.

However, the present data relates level of autistic traits with orientation discrimination thresholds through correlation. It is important to bear in mind that this does not imply causality, and it is difficult from these data to interpret how autistic traits and orientation discrimination ability are related. Therefore, it needs to be taken into account that it is possible that another factor drives variability in both of the variables measured here.

In addition, there are limitations to the present study regarding screening participants for other factors which may influence the present results. For instance, as previously stated, migraine can affect orientation discrimination thresholds (Tibber et al., 2006), which participants in the current study were not screened for. Also, the present study employed no measure of intelligence with participants. Therefore, it could be the case that variability in intelligence explained differences in both ASC traits and orientation discrimination. However, as all participants were recruited from a similar population, and were all considered to be high functioning, it is unlikely that there is substantial variability in intelligence levels.

In summary, it is reported here that individual differences in orientation discrimination thresholds are related to individual differences in autistic traits. This relationship is present when orientation discrimination is measured using oblique-oblique discriminations but not when orientation discrimination is measured using vertical-oblique discriminations. It is suggested that this is due to the fact that making vertical-oblique discriminations is easier than making oblique-oblique discriminations, and therefore tasks using these stimuli may not generate sufficient variance to yield significant correlations with other variables (c.f. Brock et al. 2011).

## 2.2. Study Two: Orientation discrimination in ASC

In study one it was reported that individual differences in orientation discrimination thresholds are related to individual differences in autistic traits (Dickinson et al., 2014). Study two of this thesis will investigate whether enhanced orientation discrimination is also present in adults with ASC.

Enhanced performance on several different visuospatial tasks has been reported in ASC (discussed in chapter one). It may therefore be the case that low level visual processing is enhanced in those with ASC, and is driving enhanced performance on higher level visual tasks. However, there is limited evidence to support that low level visual processing is altered in ASC. For instance, visual acuity is not superior in those with ASC (Bölte et al., 2012; Falkmer et al., 2011; Kéïta et al., 2010; Tavassoli et al., 2011).

Others have suggested that it may be an increased ability to discriminate between visual stimuli that leads to an advantage on visuo-spatial tasks. Plaisted’s (2001) reduced generalisation theory predicts enhanced discrimination in ASC, stating that enhanced performance on tasks such as visual search may arise from an enhanced visual ability to discriminate targets from distracters. However, several studies using discrimination paradigms have found no ASC advantage. For instance, colour discrimination is impaired in individuals with ASC compared to a matched control group (Franklin, et al., 2008, Franklin et al., 2010; Heaton et al., 2008; Hurlbert, et al., 2011). In addition, contrast sensitivity has been found to be unaltered in ASC in several studies (Behrmann et al., 2006; MV De Jonge et al., 2007; Milne, Pascalis, Buckley, & Makeig, 2009), yet enhanced in one (Bertone et al., 2005). This is in contrast to the auditory domain, where some individuals with ASC show superior pure-tone pitch discrimination (Jones et al., 2009; Bonnel et al., 2010; Stantutz et al., 2014).

Bertone et al. (2005) studied low-level visual processing in ASC, asking participants to identify whether first order contrast-modulated gratings and second-order texture defined gratings were oriented vertically or horizontally. The difficulty of these decisions was altered by varying contrast levels. The study reports superior performance in those with ASC for first-order contrast modulated stimuli, but decreased performance for complex texture-defined gratings. This demonstrates that low-level visual perception is atypical in ASC, and the nature of this depends on the complexity of the stimuli. However, this study does not measure orientation discrimination performance in ASC. To do this a task would need to test the smallest difference in orientation a subject can discriminate between two stimuli. Altering the difficulty of this decision by manipulating the amount of tilt would allow measurement of the threshold of orientation discrimination ability in visual degrees.

To the authors best knowledge, only one study has measured orientation discrimination thresholds in ASC (Schwarzkopf et al*.* 2014). In this study, the just-noticeable-difference between two obliquely-orientated gratings was measured in a sample of 15 adults with ASC and 12 controls. This study found no significant difference in orientation discrimination thresholds between the two groups. However, the authors reported that participants were not instructed to maintain fixation or keep a constant viewing distance. In addition, given the small sample size and the substantial heterogeneity within ASC (c.f. White & Saldaña, 2011), this study may not have enough power to determine orientation discrimination in ASC. Therefore, the present study will employ a rigorous psychophysical task to measure orientation discrimination thresholds in a large sample of individuals with ASC.

### 2.2.1 Method

*Participants*

Ninety-six volunteers, half of whom had a diagnosis of an autism spectrum condition were enrolled to this study. Participants with ASC were either recruited from an existing participant database, or through a local NHS neurodevelopmental service which provides adult autism spectrum diagnoses. Many of the participants who signed up to the research database were actively seeking out research to be involved in, with many aware of the research due to being involved with the University through studying or employment. Participants recruited from the NHS neurodevelopmental service had all received a diagnosis as an adult. This resulted in the ASC sample for this study being made of high functioning individuals who had a relatively low amount of co-morbid conditions (discussed in more detail below).

Control participants, defined as individuals who did not have a diagnosis of ASC nor a first degree relative with an ASC, were recruited from an existing participant database. There were 24 females in each group. Each participant with ASC was matched to a control participant of the same sex, within +/- 2 years of their age. All participants had normal or corrected to normal vision.

Non-verbal reasoning ability was measured using the matrix reasoning sub-scale of the Weschler Adult Scales of Intelligence. Matrix reasoning data was not available for one neurotypical participant, and one participant with ASC due to familiarity with this measure. The two groups did not differ significantly in non-verbal reasoning ability. Table 2.2 summarises the demographic information for these participants.

Within the ASC sample, 8 individuals were diagnosed with autism and 40 were diagnosed with Asperger syndrome. Six participants with ASC had an additional diagnosis of ADHD, two had an additional diagnosis of OCD, and two had an additional diagnosis of depression. One participant in the control group had been diagnosed with ADHD.

Due to time limitations during testing, or participants being unable to return for a second testing session, nine participants did not complete the autism diagnostic observation schedule (ADOS; described below). Seven of these participants did however score above the clinical cut-off for ASC on the social responsiveness scale (SRS; described below). One of these participants did not complete the SRS and the other completed but obtained a below cut-off score of 47.

Of the thirty nine participants with ASC who completed the ADOS, 31 met cut-off for ASC. Four of the participants who did not meet the clinical cut-off score for ASC on the ADOS, did however meet the cut-off on the SRS. One participant did not meet cut-off on the SRS, with a score of 48. The other three participants did not complete the SRS. Thus, six participants with ASC did not meet the criteria on either ADOS or SRS score, either due to scoring below the clinical cut-off or due to missing data. We retained these participants in our analyses given that they all had a clinical diagnosis of ASC (c.f. Schwarzkopf et al. 2014).

One participant with ASC was taking medication for ADHD, eight were taking antidepressants, one anxiety medication, and one antipsychotic medication. Three control participants were taking antidepressants. One participant with ASC, and two control participants had oblique orientation discrimination thresholds which were more than two standard deviations above the group mean. In addition to the full sample (N=96), results are also reported with individuals taking medication removed (N=82), outliers removed (N=93) and individuals taking medication and outliers removed (N=79) Group differences in orientation discrimination remained consistent for all samples. Participant demographics for all these samples are reported in appendix 1.

**Table 2.2.** Demographic variables of participants included in analyses.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Measure** | **Autism Spectrum Condition Group** | **Control Group** | **Group Comparison** | |
| Mean (*SD*),  Range or number (%) | Mean (*SD*),  Range or number (%) | Student’s t (or X2) | P-Value |
| **Age (years)** | 31.04 (12.77), 18-67 | 27.67 (11.66), 18-65 | 1.35 | .18 |
| **Sex (N females)** | 24(50%) | 24 (50%) | .000 | 1.00 |
| **Matrix reasoning raw score** | 30.38 (2.72), 24-35 | 29.38 (3.79), 16-34. | 1.47 | .16 |
| **Matrix reasoning T-score** | 61.51 (5.82), 47-72 | 58.74 (8.35), 29-70 | 1.86 | .07 |
| **ADOS Communication and Social Interaction Total** (N=39) | 9.60 (4.54), 0-18 |  |  |  |
| **SRS T-Score** (N=31) | 105.38 (29.29), 38-159 |  |  |  |

The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee, the NHS research ethics committee, and the R&D office of the NHS service that assisted with the recruitment of individuals with ASC. Participants provided informed written consent, in accordance with the declaration of Helsinki.

*ADOS*

Module 4 of the ADOS (Lord et al., 2000) was used to assess the social and communicative abilities of participants with ASC. The ADOS is a semi-structured assessment carried out to assess communication and interaction in ASC which is standardised amongst clinicians and researchers. The ADOS is often used by clinicians as part of an assessment battery to determine if an individual has an ASC. For research purposes, the ADOS is commonly used to assess severity of symptoms in participants with ASC.

The four different modules of the ADOS are used to assess the severity of different features of ASC in children, adolescents and adults with different language levels. Module 4 is used for adolescents or adults with fluid speech, and was the most appropriate module for the current sample. During module 4 of the ADOS participants take part in a series of different exchanges with an examiner which are designed to elicit particular social-communicative behaviours. Participants are scored based on the presence of these behaviours. There are 15 items which each press for a certain behaviour. Items are scores from 0 (not abnormal) to 2, or 3 (which indicate most abnormal). The scores on different items are combined to different subscales: communication; social interaction; imagination/creativity and stereotyped behaviours and restricted interests. An individual can score above the cut off on the communication subscale, the social interaction subscale, and a combination of the two. There are two separate cut off values, one for autism, and one for autism spectrum.

The psychometric properties of modules 1-3 have been well established, with validity and reliability reported in several studies (de Bildt et al., 2004; Gray et al., 2008; Papanikolaou et al., 2009). Lord et al. (2000) showed that module 4 can successfully distinguish between ASC and non-spectrum individuals. Bastiaansen et al. (2011) also confirmed that module 4 is a reliable instrument witch good predictive validity, demonstrating that it could discriminate ASC from psychopathy and typical development.

*Social Responsiveness Scale Questionnaire*

The social responsiveness scale (SRS; Constantino & Gruber, 2012) is a questionnaire which is used to measure the social aspects of ASC, with both parent report versions for children and self-report versions for adults. The adult self-report version or the SRS-2 was used in the current study.

The SRS consists of 65 items which assess the severity of social deficits in ASC. Participants answer on a Likert scale (0-3; Not true; sometimes true; often true; almost always true) – with a maximum score of 195, and higher scores indicating greater severity of social deficits. Raw scores are converted to T-score. A T-score of over 60 indicates clinical significance of social deficits. A score of over 60 is indicative of mild deficiencies, over 66 indicating moderate difficulties which would interfere with everyday life, and over 76 indicating severe deficiencies that would have a severe impact on everyday life. Whilst the total score is used to assess the severity of social deficits and indicate whether there is clinical concern, scores can also be split into five treatment subscales based on different items: social awareness; social cognition; social communication; social motivation and restricted interests and repetitive behaviour.

Bölte (2012) assessed the adult version of SRS in high functioning adults with ASC and found scores were higher in those with ASC (M=78.5, SD=37) than in typically developing controls (M=55.5; SD=9.9.) Within the adults with ASC it was also found that SRS scores correlated with ADOS module 4 scores, and AQ scores, demonstrating concurrent validity for the SRS.

*Orientation Discrimination Task*

The orientation discrimination task used in this study is the same as that described in study one. However, the number of reversals that participants completed in each run was changed from 10, to 8. The number of reversals was reduced, as in study one it was found that using a one-up three-down staircase method with 10 reversals led to a lengthy task. Because of the length of the task in study one, 14 participants hit 120 trials on one of the runs. Consequently, 14 datasets had to be discarded in the first study due to missing data. It was also reasoned that reducing the length of the task whilst keeping this stringent adaptive procedure would still lead to accurate thresholds, and would be more appropriate for an ASC population. Participants completed 2 runs, as in study one, but each run finished when the staircase had reached 8 reversals. Again, if participants hit 120 trials on either of the staircases, on either of the runs, the task terminated. Using 8 reversals instead of 10 resulted in no participants hitting 120 trials on either of the runs, and therefore no participants had to be excluded on the basis of not completing the task.

Also, instead of responding with the keyboard, participants were asked to verbally report whether the target grating had been rotated clock-wise, or anti-clockwise, compared to the reference grating and the experimenter recorded each response using the keyboard. This alteration was made as pilot data indicated that this was a more accurate way in which to record responses from individuals with ASC.

### 

### 2.2.2 Results

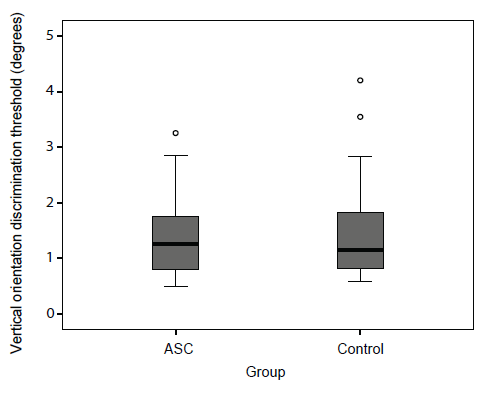
A classic oblique effect was observed, with thresholds significantly higher in the oblique condition (*M*= 6.35, *SD*=2.36) than the vertical condition (*M*=1.40, *SD*=.74; *t*(95) = -24.40, *p*=<.001).

A one-way ANOVA indicated that there was a significant effect of group on discrimination thresholds (*F*(1, 94) =631.92, *p*=<.001) and a significant interaction between group and orientation discrimination condition (*F*(1,94)=6.78, *p*=.01).

Further analyses revealed that individuals with ASC had significantly lower oblique orientation discrimination thresholds (*M*=5.81, *SD*=2.26) than control participants (*M*=6.88, *SD*=2.37; *t*(94)=-2.27, *p*=.026; see figure 2.4). However, there was no significant difference in vertical orientation discrimination thresholds between those with ASC (*M*=1.38, *SD*=.70) and control participants (*M*= 1.42, *SD*=.80; *t*(94)=-.27, *p*=.79; see figure 2.5).

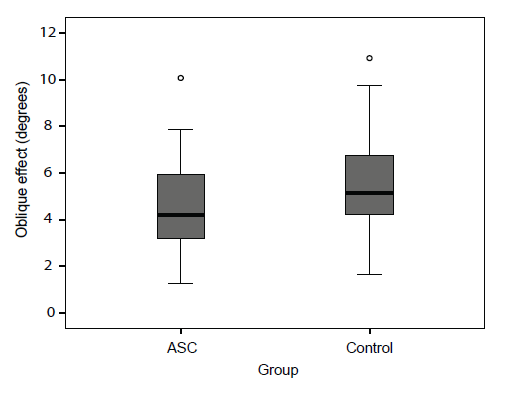


**Figure 2.4.** Box plots demonstrating oblique orientation discrimination thresholds for both ASC and control participants.



**Figure 2.5.** Box plots demonstrating vertical orientation discrimination thresholds for both ASC and control participants.

As there was a significant interaction between group and orientation discrimination threshold, the magnitude of the oblique effect was calculated by subtracting each individual’s vertical orientation discrimination threshold from their oblique orientation discrimination threshold. Participants with ASC had a significantly smaller oblique effect (*M*= 4.43, *SD*=1.85) than control participants (*M*=5.46, *SD*=2.00; *t*(94)=-2.62, *p*=.01; see figure 2.6).

****

**Figure 2.6.** Box plots demonstrating the magnitude of the oblique effect for both ASC and control participants.

Any potential attention-related effects were checked by comparing participants’ thresholds on the first and second runs of the orientation discrimination task. A one-way ANOVA revealed orientation discrimination thresholds were significantly higher on the first run (*M*= 7.05, *SD*=2.86) compared to the second run (*M*=5.64, *SD*=2.18; *F*(1,94)=53,28, *p*=<.001), but there was no interaction with group (*F*(1, 94)=.002, *p*=.96), indicating that both groups showed a similar improvement in performance on the second run of the task.

Analyses were repeated after removing any participant who was taking medication, and outliers. The pattern of results stayed the same, see table 2.3.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sample** | **Vertical orientation discrimination threshold** | | | | **Oblique orientation discrimination threshold** | | | | **Oblique effect** | | | |
| **ASC Group** | **Control Group** | **Group difference** | | **ASC Group** | **Control Group** | **Group difference** | | **ASC Group** | **Control Group** | **Group difference** | |
| Mean Threshold (*SD*) | Mean Threshold (*SD*) | Student’s *t* | *P* Value | Mean Threshold (*SD*) | Mean Threshold (*SD*) | Student’s *t* | *P* Value | Mean Threshold (*SD*) | Mean Threshold (*SD*) | Student’s *t* | *P* Value |
| **Full sample**  ASC N=48  Control N=48 | 1.38 (.70) | 1.42 (.80) | -.27 | .792 | 5.81 (2.26) | 6.88 (2.37) | -2.27 | .026 | 4.43 (1.85) | 5.46 (2.00) | -2.62 | .01 |
| **Participants taking medication removed**  ASC N=37  Control N=45 | 1.35 (.71) | 1.42 (.80) | -.38 | .70 | 5.81 (2.39) | 6.93 (2.40) | -2.11 | .038 | 4.45 (1.98) | 5.51 (2.00) | -2.40 | .019 |
| **Outliers removed**  ASC N=47  Control N=46 | 1.34 (.65) | 1.37 (.76) | -.16 | .87 | 5.64 (1.99( | 6.61 (2.01) | -2.32 | .023 | 4.31 (1.67) | 5.24 (1.75) | -2.65 | .01 |
| **Outliers & medication removed**  ASC N=36  Control N=43 | 1.30 (.64) | 1.36 (.77) | -.36 | .72 | 5.60 (2.06) | 6.65 (2.04) | -2.27 | .026 | 4.30 (1.76) | 5.29 (1.74) | -2.51 | .014 |

**Table 2.3.** Group differences for the full sample (N=96), full sample with participants taking medication removed (N=82), sample with outliers removed (N=93), and both outliers and participants taking medication removed (N=79).

### 2.2.3 Discussion

The data reported here demonstrate that individuals with ASC show superior oblique orientation discrimination, compared to matched control subjects. As orientation discrimination thresholds were found to be enhanced in those with higher levels of autistic traits in study one, it was predicted that enhanced orientation discrimination thresholds would also be present in those with a clinical diagnosis of ASC. This hypothesis was supported.

As expected, a strong oblique effect was observed, with oblique orientation discrimination thresholds around 4.5 times higher than vertical orientation discrimination thresholds. The magnitude of the oblique effect was reduced in ASC, in addition to enhanced oblique orientation discrimination thresholds. This finding echoes previous work on mirror symmetry in which individuals with ASC were shown to have a reduced oblique effect (Perreault et al., 2011).

Whilst oblique thresholds and the oblique effect are both reduced in ASC, vertical thresholds are not significantly different. This echoes the results of study one, and it is again suggested that this is due to vertical orientation discrimination thresholds not providing a sensitive enough measure of orientation discrimination ability.

The finding of enhanced orientation discrimination is in line with the auditory literature, in which pitch discrimination is enhanced in ASC. It is suggested that future research should investigate how low level visual and auditory perception are related within the same individuals (Dickinson and Milne, 2014). However, as previously discussed, results from the visual domain do not show the same convincing demonstration that discrimination is superior in ASC. For instance, colour discrimination is impaired in ASC (Frankin et al., 2008; Franklin et al., 2010; Heaton, et al., 2008; Hurlbert et al., 2011) and contrast sensitivity has been found to be unaltered (Behrmann et al., 2006; De Jonge et al., 2007; Milne et al., 2009), with one study finding it to be enhanced (Bertone et al. 2005). Therefore, investigating why orientation discrimination is altered in ASC may help shed light on why superiorities are seen in this aspect of visual perception, but not others. This is discussed in detail in chapter six.

The results of this study stand counter to data from Schwarzkopf et al. (2014) who report that orientation discrimination is unaltered in adults with ASC. One reason for this might be that the paradigm employed by Schwarzkopf and colleagues did not require participants to maintain fixation. Also, the present study employed a larger number of participants with ASC. A larger sample with more statistical power may have been a more efficient way to probe orientation discrimination in ASC, and potentially uncovered an enhanced ability that may not have been revealed in a smaller sample due to the large amount of heterogeneity within the condition (White & Saldaña, 2011).

This also highlights that the present results might be specific to certain individuals with ASC. The sample employed here are relatively homogenous as they represent higher functioning adults with a relatively low incidence of co-morbid conditions. To probe this further, future work should measure orientation discrimination performance in a wider sample of individuals with ASC, including lower functioning adults and children. Data collected during an undergraduate summer project using the same orientation discrimination task employed in studies one and two of this thesis suggests that orientation discrimination thresholds are not enhanced in children with ASC. However, future work should use psychophysical procedures that are appropriately adapted for children, in order to ascertain psychophysical thresholds in a wider sample.

In conclusion, the data reported here indicate that oblique orientation discrimination ability is enhanced in high functioning individuals with ASC compared to control participants. This echoes data from study one which demonstrates enhanced orientation ability in those with high levels of autistic traits.

## 2.3 Chapter Discussion

The first two studies presented in this thesis demonstrate that orientation discrimination is superior in those with high levels of autistic traits, and those with an ASC diagnosis. Both studies support that oblique orientation discrimination thresholds provide an adequately sensitive measure to study inter-individual differences, whereas vertical thresholds do not. It is also demonstrated that the oblique effect is reduced in those with higher levels of autistic traits, and those with ASC.

Similarly, visuospatial task performance is enhanced in ASC and those with high levels of autistic traits (Lockyear & Rutter, 1970; O’ Riordan, Plaisted, Driver & Baron-Cohen, 2001; Plaisted, O’Riordan, & Baron-Cohen, 1998; Shah & Frith, 1983; Shah & Frith, 1993). Plaisted (2000) suggested that this is due to reduced generalisation, and a superior ability to discriminate between visual stimuli, which the data presented here would support. However, it is unclear how performance on tasks such as visual search is related to orientation discrimination ability. For instance, whilst it is plausible that enhanced discrimination of small details in ASC may lead to enhanced performance on tasks such as visual search; data from colour discrimination tasks does not support this position (Frankin et al., 2008; Franklin et al., 2010; Heaton, et al., 2008; Hurlbert et al., 2011). In addition, it needs to be taken into account that tasks such as visual search also involve a variety of higher-level cognitive processes. Therefore, the relationship between low-level visual abilities, such as orientation discrimination, and visual search performance will have to be investigated empirically before any conclusions can be drawn.

Future studies will also investigate how orientation discrimination ability relates to the more general sensory symptoms associated with ASC. As sensory experiences are commonly reported in those with higher levels of autistic traits and those with ASC, differences in low-level visual perception may underlie some of these symptoms. Investigating whether atypical visual experiences are related to orientation discrimination thresholds may help determine whether those with more sensitive visual perception report quantitatively or, or qualitatively different visual symptoms, to those with less sensitive low level perception.

Having established that orientation discrimination thresholds are superior in both individuals with higher levels of autistic traits, and those with an ASC diagnosis, it is important to consider the factors which may mediate this relationship. Although the orientation task used here was chosen in order to measure low level visual perception, it could still be the case that higher order processes are affecting performance on the task. For instance, it could be the case that individuals with better memory could achieve lower orientation discrimination thresholds due to the sequential nature of the stimuli presentation during the task. However, pilot testing revealed that increasing the inter stimulus interval between the reference and target gratings did not affect orientation discrimination thresholds. This suggests that memory processes are having little impact on thresholds. Other cognitive processes which could affect orientation discrimination thresholds include attention and decision making. These are discussed in detail in chapter six.

Other than differences in higher order processes, the present results would suggest that neural processing may be altered in those with high levels of ASC and those with an ASC diagnosis. Inhibitory mechanisms have been highly implicated in the tuning curve of the orientation selectivity of cells, as orientation selective neurons become narrowly tuned to a particular orientation through lateral inhibition (Hubel and Wiesel, 1968). Variability in levels of inhibition would therefore lead to differences in orientation sensitivity, with higher levels of inhibition leading to an enhanced ability to discriminate between orientations. GABAergic inhibition in particular seems to be imperative in determining the orientation profile of neurons in V1. For example, application of the inhibitory neurotransmitter Gamma-Aminobutyric acid (GABA) to neurons in the primary visual cortex has been found to lead to narrower tuning curves and improved orientation selectivity in anaesthetised cats (Li et al., 2008). Conversely, the topical application of GABA antagonists reduces orientation selectivity (Katzner et al. 2011). In addition, resting levels of GABA, measured with magnetic resonance spectroscopy (MRS), have been shown to be related to orientation discrimination thresholds in human volunteers(Edden et al. 2009). This suggests that GABA mediated inhibition plays a major role in establishing the sharp orientation tuning of neurons, leading to enhanced orientation discrimination ability. It is therefore speculated that variation in resting GABA levels may mediate the relationship between orientation discrimination thresholds and autistic traits.

A logical extension to this hypothesis is that individuals with a high-level of autistic traits/ASC have increased resting GABA levels which, in turn, leads to enhanced orientation discrimination. This suggestion is consistent, in part, with the suggestion from Bertone et al (2005) that increased lateral inhibition, which is a corollary of increased GABA, underpins superior discrimination in individuals with ASC. However, this suggestion is at odds with a prominent neural theory of ASC. The next chapter of this thesis will examine neural theories of ASC, and discuss the most appropriate way to investigate whether differences in neural inhibition levels might drive orientation discrimination enhancements in ASC.

# 3. Chapter Three: Neural excitation and inhibition in ASC

Studies one and two of this thesis report that orientation discrimination thresholds are superior in both individuals with a high level of autistic traits, and those with an ASC diagnosis. Having established that individual differences in orientation discrimination thresholds are related to both the presence of ASC and individual differences in autistic traits, it is important to consider why there is enhanced orientation discrimination in both of these populations.

Sensory responses are said to be dominated by neural inhibition, with any disturbance to inhibition resulting in widespread perceptual consequences (Haider, Häusser & Carandini, 2013). The balance of neural excitation and inhibition (E:I balance) depends on both excitatory and inhibitory neurotransmitters which work at the synapses of cortical neurons and together establish the E:I balance (Hensch, 2005). As this balance relies on the relative contributions of both neural excitation and inhibition, an imbalance can be due to increased or decreased excitation, or inhibition. One way that the balance between the two could become distorted is through alterations in excitatory or inhibitory neurotransmitters. The main excitatory neurotransmitter in the mammalian adult brain is glutamate, and the main inhibitory neurotransmitter is GABA. GABA mediated inhibition is especially important for shaping the activity of neurons, and has many important roles, such as determining the critical period in primary visual cortex (Faglioni & Hensch, 2000).

One aspect of perception which has been shown to be mediated by E:I balance is orientation discrimination. As described in chapter two, inhibitory mechanisms have been highly implicated in tuning the orientation selectivity of cells, as orientation selective neurons become narrowly tuned to a particular orientation through lateral inhibition (Hubel and Wiesel, 1968). Modelling studies have shown that narrowing tuning curves through lateral inhibition therefore results in an improved ability to discriminate between different orientations (Gustaffson, 1997a; 1997b). Variability in the strength of neural inhibition would therefore lead to differences in orientation sensitivity, with higher levels of inhibition leading to an enhanced ability to discriminate between orientations.

GABAergic inhibition in particular seems to be imperative in determining the orientation profile of neurons in V1. GABA plays an important role in shaping and regulating neuronal activity, as it exerts its effects by reducing the activity of neurons to which it binds through two main types of GABA receptor, GABAA and GABAB (Bowery, 1983). GABAergic inhibition has been shown to directly influence orientation discrimination ability. For example, application of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) to neurons in the primary visual cortex of anaesthetised cats leads to these cells becoming more narrowly tuned, and increases their orientation selectivity (Li et al., 2008). Conversely, the application of GABA antagonists reduces the orientation selectivity of cells in primary visual cortex (Katzner *et al.* 2011; Sillito, 1975). Most relevant to the current thesis, resting GABA levels are inversely correlated with oblique orientation discrimination thresholds in neurotypical human observers (Edden et al., 2009), suggesting that GABA mediated inhibition plays a major role in establishing the sharp orientation tuning of neurons, and leads to enhanced orientation discrimination.

A logical extension to this hypothesis is that individuals with ASC, and those with a high level of autistic traits, may have increased resting GABA levels, which in turn, enhances orientation discrimination ability. The hypothesis that the E:I balance may be altered in ASC is not a novel suggestion, as both increased inhibition and increased excitation have been used to explain the underlying neural basis of the symptoms of ASC previously (e.g. Bertone et al., 2005; Rubenstein & Merzenich, 2003). Both of these positions will be described in this chapter, including the evidence which has been used to support the existence of an atypical E:I balance in ASC.

## 3.1. Increased excitation in ASC

It has long been proposed that there is an E:I imbalance in the direction of increased excitation in the brains of individuals with ASC (Hussman, 2001; Markram, Rinaldi & Markram, 2007; Rubenstein & Merzenich, 2003). It is suggested that an increase in excitatory processes could be due to an increase in glutamatergic excitatory signalling or a decrease in GABAergic inhibitory signalling, which could be caused by a variety of genetic or environmental factors (Rubenstein and Merzenich, 2003). Others have suggested that it is a reduction in GABAergic signalling in particular which leads to this imbalance (Hussman, 2001; Coghlan et al., 2012).

Increased E:I balance is said to lead to noisy and unstable networks which are prone to increased excitability, which is often referred to as hyperexcitable cortex. Hyperexcitable cortex in several brain areas, including those responsible for perception, language and social interaction (Rubenstein & Merzenich, 2003). As hyperexcitable cortex is less functionally differentiated (Merzenich et al., 1999; Merzenich, 2001), this is said to lead to abnormalities in functions associated with these areas and therefore result in behavioural symptoms such as those observed in ASC.

The most commonly used evidence to support that the idea that neural excitation may be increased in ASC is the observation that seizures disorders, such as epilepsy, are more common in ASC. Many studies have shown that seizures are prevalent in ASC, with estimates ranging from around 5-46% (Bryson, Clark & Smith, 1988; Hughes & Melyn, 2005) with most converging at around 30% (Canitano, 2007). It is also suggested that subclinical epileptiform activity, which may not lead to seizures, is also present in a high proportion of children with ASC (Chez et al., 2006; Hughes & Melyn, 2005; McVicar, Ballaban-Gil, Rapin, Moshe & Shinnar 2005; Rossi, Parmeggiani, Bach, Santucci & Visconti 1995) with one study suggesting that up to 85% of children display such activity (Yasuhara, 2010). Given the role of increased neural excitation in generating seizures (Engel, 1996), this evidence clearly suggests that excitation is increased, or inhibition is decreased in the individuals who have co-occurring seizures and ASC. However, this theory is in direct opposition to one which states that inhibition may be increased in autism.

## 3.2. Increased Inhibition in ASC

An alternative viewpoint states that inhibition is increased rather than decreased in ASC (Bertone et al., 2005; Gustaffson 1997b). Bertone et al. (2005) suggest that there may be altered neural connectivity in ASC which may account for the atypical and enhanced spatial information processing observed. This atypical neural connectivity is said to result in enhanced lateral inhibition which may account for both enhanced and decreased low level information processing in ASC, as the deficits and enhancements seen in autistic visual perception are dependent on the complexity of the neural network required to process a given type of visual stimulus. For instance, Bertone et al. (2003) and Bertone et al (2005) demonstrate that whilst first order movement detection and contrast discrimination are both intact in ASC, second order processes are impaired. It is also suggested that enhanced edge detection caused by increased lateral inhibition might also be the cause of improved autistic performance on other visuo-spatial tasks as they also involve the discrimination of luminance defined stimuli, mediated by low level perceptual processing (Plaisted, 1999; O’Riordan and Plaisted, 2000; Riordan et al, 2001; Caron, Mottron, Rainville & Chouinard, 2004).

The suggestion that there is altered lateral connectivity in ASC is supported by results from a study carried out by Kéïta, Mottron, Dawson and Bertone (2011) who used a lateral masking paradigm to assess lateral neural connectivity within the PVC. Lateral masking paradigms measure how the detection of a stimulus is differentially affected by its context and can be used to assess lateral neural connectivity within the primary visual cortex. Keita and colleagues found that both participants with and without ASC showed increased target sensitivity when the distance between collinear targets and flankers was small but not when the distance was large. However, the effect of small distance facilitation was significantly greater for the participants with ASC. This supports that atypical visual perception in ASC may originate from altered lateral connectivity within primary visual areas.

Rosenberg et al. (2015) state that it is reduced inhibition due to attenuated divisive normalisation which leads to autistic symptomatology. Divisive normalisation is a canonical computation which occurs throughout cortex in which the net excitatory drive to a neuron is divided by the activity of other neurons in the population. Rosenberg and colleagues put forward that there is reduced divisive normalisation in ASC, in that a neuron is less affected by the activity of the neuronal population in which it is embedded, leading to less inhibition. This was modelled in a neural network simulation, with decreased divisive normalisation shown to account for several phenomena reported in ASC, including tunnel vision, reduced oblique effect, and discrepancies between the processing of simple and complex stimuli.

## 3.3. Evidence

The evidence used to examine the E:I balance in ASC is varied, with some studies reporting results which suggest an E:I abnormality, but cannot predict whether this is caused by increased inhibition or excitation. Other results clearly support either atypical excitation or inhibition leading to an E:I balance disruption. However this evidence is inconsistent, as increases in both excitation, and inhibition have been reported.

*Visual Abnormalities*

Evidence to support increased excitation comes from a modelling study of oculomotor control abnormalities which are present in ASC. Hypometria is a saccadic abnormality describing un-coordinated saccadic eye movements which lead to eye movements not reaching their intended position. Hypometria is more common in children and adults with ASC (Rosenhall, Johansson & Gillberg, 1988; Takarae et al., 2004). Vattikuti and Chow (2010) used a computational model to demonstrate that an increase in excitation (achieved through either increasing excitation, or reducing inhibition) can account for increased oculomotor abnormalities of this nature.

Binocular rivalry has also been used to study E:I balance in ASC. Binocular rivalry is a visual phenomenon in which a rivalry between different images presented to each eye results in alterations as to which image an individual consciously perceives (Wheatstone, 1838). This process depends on excitation and inhibition levels, as has been demonstrated through pharmaceutical manipulations of GABA which alter binocular rivalry in humans (van Loon et al., 2013). Therefore, certain alterations in performance on this task reveal alterations in E:I dynamics (Wilson, 2003). Robertson, Kravitz, Freyberg, Baron-Cohen, and Baker (2013) found a slower rate of binocular rivalry in high functioning adults with ASC (N=20) compared to controls (N=19). Whilst they state that this indicates that there is an E:I imbalance in ASC, it does not inform us as to the direction of this imbalance. However, contrary to this finding, Said, Egan, Minshew, Behrmann and Heeger (2012) found no significant differences in binocular rivalry between adults with ASC (N=19) and control participants (N=20). Said and colleagues therefore suggest that if there an E:I imbalance in ASC, it will be small in magnitude, as to not be detected by tests of binocular rivalry.

Vandenbroucke, Scholte, van Engeland, Lamme, and Kemner (2008) also provide support for E:I imbalance in ASC, but suggest that this is due to disruptions in inhibitory lateral connections. Vandenbroucke et al. present evidence that object boundary detection is impaired in adults with ASC. They state that object boundary detection relies on lateral inhibition between orientation selective neurons, and from this conclude that impaired orientation discrimination may lead to the impaired object boundary detection reported in ASC. In contrast to Bertone et al. (2005), they conclude that this impairment is consistent with impaired lateral inhibition in early visual areas. However, whilst they indirectly suggest that orientation discrimination is impaired in ASC, this is in contrast to the orientation discrimination data presented in this thesis, which measures orientation discrimination directly and finds it to be enhanced in ASC.

Foss-Feig et al. (2013) used a motion discrimination paradigm in which participants had to indicate the direction in which drifting gratings that varied in size and contrast were moving. It was hypothesised that if inhibitory mechanisms were altered in ASC this would be demonstrated through atypical spatial suppression. However, spatial suppression was unaltered in ASC – as performance decreases were seen in both groups as the size of stimuli increased. However, whilst participants with ASC were found to have similar performance to controls for low contrast stimuli, they performed systematically better across high contrast stimuli of all sizes. It was suggested that this pattern of performance represents abnormal gain control in ASC. Gain control is an inhibitory mechanism underlying the saturation of neural responses at high contrast (Albrecht & Hamilton, 1982; Katzner et al., 2011). As performance did not fall off as much for individuals with ASC for increases in contrast, this would indicate an increase in response gain and weakening of response gain control, which may therefore indicate a decrease in inhibitory functioning in ASC. Rosenberg et al., (2013) state that decreased inhibition manifested through attenuated divisive normalisation can account for reduced gain control.

*Auditory Perception*

Lateral inhibition has also been shown to play a role in the processing of auditory stimuli (Houtgast, 1972). Akin to the effect on orientation selective neurons, applying a GABA antagonist to neurons in the primary auditory cortex of chinchillas increases the range of frequencies to which the neurons respond (Wang et al. 2000; Wang et al. 2002), indicating that higher levels of GABAergic inhibition lead to superior auditory discrimination. A number of studies have demonstrated that, at least some, individuals with ASC have superior pure-tone pitch discrimination (Bonnel et al. 2010; Jones et al. 2009; Meilleur et al., 2014; Stanutz et al. 2014) which is consistent with higher levels of inhibition.

*Minicolumns*

One aspect of neuro-architecture which has received a great amount of research attention in ASC is mini columns. Mini columns are basic repeating architectonic elements which are found in all regions of cortex and constitute the smallest neocortical module capable of processing information (Mountcastle, 1997). Minicolumns ascend radially through layers VI and II and usually consists of around 80 to 100 pyramidal cells which, along with their projections, constitute the core of the minicolumn. Cells within a minicolumn have the same receptive field locations, sizes and shapes (Favorov, Diamond & Whitsel, 1987). Surrounding this core is peripheral neuropil space which contains GABAergic inhibitory interneurons (Favorov & Kelly, 1994) which insulate the excitatory flow in the core from the activity of surrounding minicolumns (De Felipe, 1999). Less neuropil space would limit the effectiveness of this inhibitory sheath, and thus result in excitatory flows spreading between neighbouring minicoulmns.

Post mortem analysis has revealed that individuals with ASC show minicolumnar abnormalities in the frontal and temporal regions of the brain (Buxhoeveden et al., 2006; Casanova, Buxhoeveden, Switala and Roy, 2002a; 2002b; Casanova et al., 2006). Specifically it was found that minicolumns in these areas have reduced neuropil space (Buxhoeveden et al., 2006; Casanova et al., 2002b; Casanova, Buxhoeveden & Gomez, 2003). It is therefore postulated that the reduced neuropil space would limit the effectiveness of GABAergic interneurons and lead to deficits in inhibitory processes (Casanova et al., 2003). This inhibitory deficit is said to cause a readjustment in the signal to noise bias and lead to abnormal information processing (Buxhoeveden, Switala, Litaker, Roy & Casanova 2001). Additional support is provided by a study in which low frequency repetitive transcranial magnetic stimulation (rTMS) was used to selectively increase the surround inhibition of minicolumns in ASC (Sokhadze et al., 2009). It was found that after using this rTMS procedure twice a week for two weeks, behavioural measures of ASC improved, as participants became less impaired on measures of repetitive behaviour, social awareness, irritability and hyperactivity

In contrast to the suggestions that narrower minicolumns in ASC are associated with lower levels of inhibition, computational modelling work (Gustaffson 1997a) and experimental studies in cats (Hensch and Stryker, 2004), have shown that in fact narrower minicolumns would lead to higher levels of inhibition. This would suggest that the narrower minicolumns reported in ASC are in fact associated with higher, rather than lower levels of GABAergic inhibition. Therefore, it is not entirely clear how the atypical minicolumnar structure observed in ASC relates to the E:I balance.

In addition, in contrast to previous findings, wider minicolumns have recently been found in ASC, in sensory areas of cortex, as well as higher order cognitive areas (McCavanagh, Buckley & Chance, 2015). The authors of this paper point out that computational models predict that less inhibition would lead to wider minicolumns (Gustaffson, 1997a), and therefore conclude that these results provide evidence that excitation is increased in ASC.

Therefore, whilst it has been long supposed that narrower minicolumns are present in ASC, recent evidence suggests that this may not be the case, reporting wider minicolumns in ASC. However, despite reporting disparate differences in neural architecture, both of these findings are said to lead to reductions in neural inhibition, and as a result, increased excitation. Minicolumns are a major aspect of neural architecture, and it is likely that differences in their structure would have widespread consequences. However, the nature of atypical minicolumn structure is not currently clear in the ASC literature, nor is it clear the consequences this would have for E:I balance.

*Cellular Abnormalities*

Evidence from studies which find post-mortem cellular abnormalities in ASC has been used to support the supposition that there is an E:I imbalance in ASC, particularly the increased excitation theory. Whilst many of these studies have been reported, this discussion will only highlight the main cellular abnormalities found in ASC (for a thorough review see Coghlan et al., 2012).

Many histological studies have reported GABA receptor abnormalities in post-mortem brain tissue of ASC subjects. The two types of GABA receptor, GABAA and GABAB, have both been found to be altered in ASC (Blatt et al., 2001; Fatemi et al., 2009a, b; 2014; Oblak, Gibbs & Blatt, 2009; 2010; 2011). Fatemi et al. (2009b) found reductions in GABAA receptors in parietal, cerebellar and superior frontal regions in ASC. Reductions in receptor numbers may suggest a decreased affinity for GABA binding in ASC, and therefore decreased levels of inhibition (Fatemi et al., 2009b).

However, it is hard to predict how a disruption in receptors would affect overall E:I balance. For instance, low levels of GABA receptor expression may be counterbalanced by higher levels of GABA being released from presynaptic terminals (Dhossche et al., 2002; Fatemi et al., 2009b). In addition, whilst reduced GABA receptors have been put forward by some as indicating decreased levels of GABA in ASC, similar abnormalities have also been found in one of the types of glutamate receptor, AMPA receptors. For instance, reduced density of AMPA receptors has been found in the cerebellum of children with ASC (Purcell et al., 2001).

Other studies have reported that the synthesis of GABA and glutamate is altered in ASC. There are two key synthesising enzymes for GABA, glutamic acid decarboxylase type 65 and 67 (GAD65; GAD67). Post mortem studies of adult ASC brains have revealed that both GAD65 and GAD 67 are reduced in the cerebellum and parietal cortex of individuals with ASC (Fatemi et al., 2002; Yip, Soghomonian & Blatt, 2007). However, the synthesis of glutamate is alsoabnormal in ASC. Glutamate is synthesised from glutamine, which is then broken back down into glutamine, and re-used, a process known as the glutamate-glutamine cycle. Shimmura et al. (2013) found that enzymes associated with the glutamate-glutamine cycle are decreased in post mortem brain tissue of individuals with ASC, suggesting a dysfunction in excitatory neurotransmission.

*Animal Models*

Cellular abnormalities are also investigated in mouse models of ASC. Numerous animal models suggest that the E:I balance is altered, with altered GABAergic and glutamatergic transmission observed in several different mouse models of ASC (for a review of animal models of ASC, see Pizarelli & Cherubini, 2011). However, mouse models do not provide a conclusive demonstration regarding the direction of an E:I imbalance. For instance, whilst Makram et al., (2008) find defective inhibitory transmission in one mouse model of ASC, other models reveal increased inhibitory transmission, or decreased glutamatergic transmission (Blundell et al., 2010; Tabuchi et al., 2007).

Other animal studies have shown that an imbalance in the direction of increased excitation leads to behavioural symptoms, which may be associated with ASC. Yizhar et al. (2011) optogenetically altered the E:I balance in freely moving mice, finding that elevating the cellular E:I balance in the prefrontal cortex led to behavioural impairments associated with social function, and compensatory elevation of inhibition reversed these social deficits.

The results of mouse model studies are therefore extremely variable regarding the E:I balance in ASC. It also needs to be taken into account that whilst there are standardised ASC behavioural assays for mice (Crawley et al., 2012), that the mouse model used throughout studies is not consistent, which introduces even more variability into findings (Crabbe, Wahlsten & Dudek, 1999).

*Blood Plasma Measurement*

Several studies have attempted to quantify glutamate and GABA levels through blood plasma measurements in humans. Again, the results are mixed, with both increases (e.g. Hassan et al., 2013) and decreases (Rolf, Haarmann, Grotemeyer & Kehrer, 1993) being reported in glutamate levels. Similarly, whilst Dhossche et al (2002) reported higher GABA levels in blood plasma of children with ASC, decreased platelet levels of GABA have also been reported (Rolf et al., 1993). However, amino acid neurotransmitters do not easily cross the blood-brain barrier. Therefore, it is difficult to interpret the results of studies which measure GABA levels in this way (Rojas, Becker & Wilson, 2015).

*MRS Studies*

There is only one way to directly measure neural glutamate and GABA levels non-invasively in human subjects. This method is proton magnetic resonance spectroscopy (MRS). MRS allows the quantification of different neurochemicals within brain tissue. Many -MRS studies combine the resonances of glutamate and its precursor, glutamine into one single measure: Glx.

Several studies have measured glutamate or Glx levels in ASC, with a roughly equal number of studies reporting increases or decreases in ASC (for a review see Rojas et al., 2015). However, the only study which has measured Glx levels in the occipital cortex of individuals with ASC found reduced levels of Glx in 26 children with autism compared to controls (N=29; DeVito et al., 2007). Therefore there is no evidence that there is increased excitation in visual areas of individuals with ASC, with evidence pointing towards decreased glutamate. However, in auditory areas both glutamate and Glx levels have found to be increased in 13 adults with ASC compared to 15 controls (Brown et al., 2013).

A small number of studies have attempted to measure inhibition in ASC directly by using MRS to measure levels of resting state GABA (Cochran et al. 2015; Gaetz et al., 2014; Harada et al., 2011; Rojas, Singel, Steinmetz, Hepburn & Brown 2014). Results are generally in favour of lower levels of GABA in ASC at least in the motor cortex (Gaetz et al., 2014) and the ACC (Cochran et al. 2015).

Only a limited number of MRS studies have measured GABA or glutamate/Glx levels in sensory areas in ASC, these studies are summarised in table 3.1. In auditory cortex it has been found that GABA levels are decreased (Gaetz et al., 2014: Rojas et al., 2014), and Glx/glutamate levels are increased (Brown et al., 2013).

However, an opposite pattern of results are seen in occipital cortex. Glx levels are decreased in occipital cortex of children with ASC (DeVito et al., 2007). Currently, only one study has measured resting levels of occipital GABA using MRS in ASC. This study found an, albeit non-significant, increase in occipital GABA in individuals with ASC compared to matched controls (Gaetz et al., 2014). This study was small, reporting data only from eight individuals with ASC and 10 controls. Nevertheless, the direction of the finding is in-line with the finding that Glx is decreased. This suggests that while GABA may be decreased, and glutamate increased in several brain areas in ASC, there is no evidence for this in occipital cortex, and the only available evidence actually indicates increased inhibition, and decreased excitation (DeVito et al., 2007; Gaetz et al. 2014).

The available data therefore suggests that whilst excitation is increased in auditory cortex of those with ASC, it is decreased in occipital cortex, and vice versa. This opposite pattern of results suggest that there may not be a consistent alteration in E:I balance across cortex in ASC. This is a possibility, as GABA levels are altered across different cortical regions within individuals (Gao et al., 2013).

**Table 3.1.** Studies measuring either GABA or glutamate/Glx in sensory areas in individuals with ASC.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Study** | **N, (mean age in years)** | **Region of Interest** | **Measure** | **Group Difference** |
| **Occipital Cortex** | De Vito et al., 2007 | ASC: N=26 (9.8)  TD: N=29 (11.1) | L/R Occipital cortex | Glx | Decreased in ASC. |
| Gatez et al. 2014 | ASC: N= 8 (13)  TD: N=10 (13.3) | L/R Occipital cortex | GABA | Trend towards an increase of GABA in individuals with ASC, however this was not significant. |
| **Auditory Cortex** | Brown et al. 2013 | ASC: N=14 (36.89)  TD: N=13 (41.08) | L/R Heschl’s gyrus | Glx/Glu | Increased Glx & glutamate in ASC. |
| Rojas et al. 2014 | ASC: N=17 (12.44)  TD: N=17 (14.01) | L auditory cortex | GABA | Decreased in ASC. |
| Gaetz et al. 2014 | ASC: N=17 (11.5)  TD: N=15 (12.7) | L auditory cortex | GABA | Decreased in ASC. |

There are a number of limitations to using MRS to measure E:I balance which need to be taken into account when evaluating evidence for the E:I balance in ASC. GABA measurement in particular is difficult due to overlap between its resonance and those of creatine and macromolecules (Puts & Edden, 2012). Therefore, when measuring GABA, MRS actually measures a mix of macromolecules and homocarnosine, as well as GABA (Gao et al., 2013). As MRS studies are limited to particular regions of interest due to acquisition time, this makes comparison across studies particularly hard due to regional differences (Rojas et al., 2015). Also, MRS measures GABA in a relatively large volume of brain, and it can be hard to localise this voxel to a particular brain structure (Puts & Edden, 2012). Stagg, Bachtiar & Jahansen-Berg (2011) also highlight that MRS is only capable of telling us the total concentration of a GABA within a particular volume, it is still unclear as to how this relates to phasic and tonic GABA activity. Therefore caution needs to be taken when interpreting findings of MRS studies measuring glutamate and GABA, due the presence of other factors in the signal, the large area the measurement is taken from, and lack of knowledge regarding how MRS measures relate to synaptic activity.

## 3.4. Conclusion

Several different measurement techniques have been employed to quantify E:I balance in ASC and produce conflicting results both within, and across techniques. Recent advances allow direct measurement through MRS spectroscopy. However, as has been discussed, this technique has its disadvantages and is often used in small sample sizes. For instance, Rojas et al. (2015) highlight that 11 of the 13 studies included in their study which measure GABA or glutamate/Glx levels have sample sizes of less than 20 individuals with ASC. This is particularly a problem in ASC, when large sample sizes are required due to the heterogeneity of the condition. It is important to note that although there is no unequivocal demonstration that either inhibition, or excitation is increased in ASC, reports discussing the E:I balance in ASC often assume that there is a strong basis for increased excitation. For instance, there are many examples in the literature of authors’ introducing the idea of E:I imbalance in ASC by describing studies which report cellular abnormalities indicating increased excitation, but overlook the cellular abnormalities which indicate increased inhibition, or no difference. This bias results in the impression that excitation is increased in ASC, and could lead to other positions being overlooked.

One way of studying E:I balance is to measure high frequency neural activity in the gamma band. This is not reviewed here, as it is the focus of the next chapter. Gamma activity is said to represent the E:I balance, and has been well explored in ASC. The next chapter will give an overview of gamma activity including examples of how it has been studied in ASC in the past, and how applying a novel metric of gamma activity to ASC may allow us to make more specific inferences regarding E:I balance in ASC.

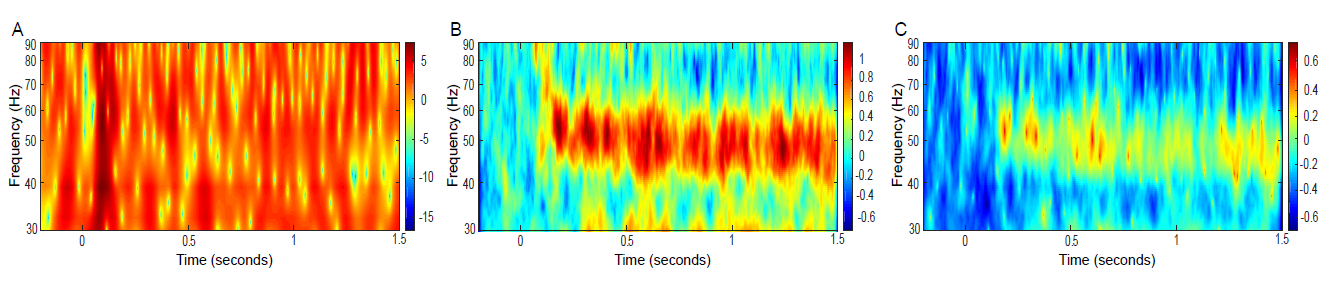
# 4. Chapter Four: Gamma band activity

Brain activity can be studied non-invasively using techniques such as electroencephalography (EEG) or magnetoencephalography (MEG) which measure the electrical and magnetic fields of the brain, respectively. These signals are generated when a population of neurons fire in synchrony, causing a large enough change in voltage to be picked up from the surface of the scalp (Mitzdorf & Singer, 1979). Only synchronised neuronal activity can be measured; as the changes produced by the synaptic events of unsynchronised neurons cancel each other out (Hillyard & Picton, 1987). EEG uses electrodes placed on the scalp to measure the voltage fluctuations caused by changes in the ionic gradient of a firing neuron on a scale of microvolts (µV). MEG measures magnetic fields produced by the same underlying neuronal electrical changes using sensors located within a container surrounding the head. Both EEG and MEG possess sufficient temporal resolution necessary to measure very brief changes in electrophysiological signals (Havenith et al., 2011) and are therefore well suited to study high-frequency gamma band activity, which is the focus of this chapter.

Brain activity measured during EEG or MEG can be split into two main categories: spontaneous brain activity or task/stimulus related activity. Spontaneous activity is normally recorded under task-free conditions, whilst the participant either has their eyes open, or closed. Conversely, task or stimulus related activity measures perturbations in the signal associated with the participant being presented with a stimulus or task.

As well as in the time domain, brain activity can also be studied in the frequency domain. When neurons fire repeatedly this leads to regular and synchronised rhythmic activity. Measurement of these signals allows observation of several patterns of brain activity oscillating at different frequencies. These have been classified into traditional frequency bands: delta (1-4Hz); theta (4-8Hz); alpha (8-12Hz); beta (12-30Hz) and gamma (>30Hz). These bands coexist but each facilitates distinct cognitive functions (Buschman & Miller, 2007; Buzsaki & Draguhn, 2004). This has led to a common analysis strategy in which the signals recorded from neuron populations are quantified by computing the relative power in each of the frequency bands (Uhlhaas & Singer, 2006). Time frequency analysis techniques allow us to extract frequency information from a signal, simultaneously with how this changes over time. Time frequency analysis will be discussed in more detail in chapter five.

The changes in power elicited by stimuli can be further sub divided into two main categories: evoked and induced (Galambos, 1992). Evoked responses are phase locked to the onset of a stimulus and can be detected by averaging single trial responses before time frequency analysis. Induced gamma band activity often occurs later than evoked activity, and whilst it is time-locked, it is not phase locked to the stimulus. Due to this the conventional averaging used to reveal evoked responses cannot be used and time-frequency analysis techniques are required to be performed on each trial before they are averaged (Tallon-Baudry & Bertrand, 1999). However, whilst these two different analysis methods can be used to study the two types of activity, it is difficult to clearly separate evoked and induced activity. For instance, whilst averaging before time frequency analysis will favour evoked responses, there will always be non-phase locked activity. Similarly, whilst carrying out time frequency analyses before averaging will allow induced activity to be detected, the signal will also include evoked activity. Further attempts to isolate induced activity can be made by computing evoked power and subtracting this off the signal gained by averaging after time frequency analysis. This removes the evoked activity from the signal and is the current best method to isolate induced activity. An example of data analysed in this way is provided in figure 4.1.



**Figure 4.1. (A)** Example of a gamma response which has been averaged before undergoing time frequency analyses, and therefore only contains phase locked evoked activity **(B)** Example of a gamma response which has been analysed in the time frequency domain before averaging, in order to preserve induced activity, and will also contain some phase locked evoked activity **(C)** Example of the resulting gamma band response when evoked gamma activity (4.1A) is subtracted off a full signal containing both evoked and induced activity (4.1B), resulting in a gamma response containing just induced activity.

Of particular interest in ASC is gamma band activity, which has been said to be involved in several different cognitive functions (see Kaiser & Lutzenberger, 2005, for a review). This high frequency activity is generated by the activity of inhibitory GABA-ergic interneurons in neuronal networks involving excitatory pyramidal cells and inhibitory interneurons (Bartos, Vida & Jonas, 2007; Cardin et al., 2009; Traub et al., 1998; Whittington & Traub, 2003; Whittington, Traub, Kopell, Ermentrout & Buhl, 2000). The role of inhibitory interneurons in mediating gamma band activity is demonstrated through manipulation of the activity of inhibitory interneurons (Cardin et al., 2009) or GABA itself (Lewis et al., 2008). For instance, Cardin et al. (2009) optogenetically manipulated the activity of fast spiking interneurons in rat barrel cortex and found that it selectively mediated gamma band oscillations. Manipulation of GABAergic inhibition demonstrates that it directly influences gamma rhythms, as pharmaceutical manipulation to enhance GABA transmission in individuals with schizophrenia has been shown to lead to increased frontal gamma band power (Lewis et al., 2008).

The functional role of gamma band activity has been attributed to several different processes. Attention was one of the first cognitive functions found to be reflected by human gamma band responses (Tiitinen et al., 1993). Several lines of evidence have supported the position that gamma band activity plays a role in attention, with studies showing that gamma band activity is specifically elicited by attending to stimuli (Bauer, Oostenveld, Peeters & Fries, 2006; Gruber, Müller, Keil, & Elbert, 1999; Herrmann, Mecklinger & Pfeifer, 1999; Müller, Gruber & Keil, 2000; Tittinen et al., 1993). Sokolov, Pavlova, Lutzenberger & Birbaumer (2004) also demonstrated that when attention was shifted between visual and auditory modalities, there was a corresponding increase in the gamma band specific to the cortical area of the attended modality. This has also been observed in premotor cortex during the shift of attention towards an upcoming target (Brovelli, Lachaux, Kahane & Boussaoud, 2005).

Another postulated role of neural synchrony in the gamma band is that of binding together the activity of different neurons (Tallon-Baudry and Bertrand, 1999). As anatomically distinct brain areas process different features of objects (Courtney & Ungerleider, 1997; Posner & Raichle, 1994), the need for the combination of this information into a coherent whole is known as the binding problem (von der Malsburg, 1994). It was originally suggested that synchronisation of oscillatory activity in the gamma band might be the mechanism by which binding is achieved (Damasio, 1989; von der Malsburg and Schneider, 1986; Milner, 1974; Rodriguez et al., 1999; Singer & Gray, 1995). This proposition was backed up by the fact that stimulus specific gamma band activity was found to be observed more often in response to one coherently moving bar than when presented with two independently moving bars in cats (Brosch, Bauer, Schnaze & Eckhorn, 1997; Eckhorn et al., 1988; Engel, König, Kreiter & Singer, 1991; Freiwald, Kreiter & Singer, 1995; Gray, König, Engel & Singer, 1989), monkeys (Eckhorn, Frien, Bauer, Woelbern & Kehr, 1993; Frien, Eckhorn, Bauer, Woelbern & Kehr, 1994; Gail, Brinksmeyer & Eckhorn, 2000; Kreiter and Singer, 1992; Maldonado, Friedman-Hill & Gray, 2000) and humans (Müller et al. 1996; Müller, Junghöfer, Elbert & Rochstroh, 1997).

As gamma band activity has been related to a range of cognitive functions, Hermann and colleagues (Hermann, Munk & Engel, 2004) put forward the suggestion that gamma activity underlies these disparate cognitive functions as it is involved in the match of sensory information with memory contents. They suggest that early gamma band activity reflects the matching of information with memory contents, and late gamma band activity reflects the use of the signals derived from comparison, such as re-directing attention. Studies which involve comparing a stimulus with memory contents find stimuli that match memory contents lead to significantly more early gamma band activity than novel stimuli, supporting this position (Debener, Hermann, Kranczioch, Gembris & Engel, 2003).

Within the gamma band response both evoked and induced activity are observed, as described above. Evoked gamma band activity has been identified at around 100msec post stimulus onset over somatosensory, visual and auditory regions (Bertrand & Tallon-Baudry, 2000; Hermann and Mecklinger, 2001; Pantev, 1995; Yordanova, Kolev & Demiralp, 1997). These different types of stimulus related gamma activity are thought to reflect differing underlying neural processes (Pulvermüller, Birbaumer, Lutzenburger & Mohr, 1997; Tallon-Baudry & Bertrand, 1999). For instance, evoked gamma band activity is thought to reflect early sensory and attention processes, whilst induced activity is thought to reflect higher order sensory processes, such as perceptual closure and feature binding (Tallon-Baudry, Bertrand, Delpuech & Pernier, 1996). However, others have suggested that these two types of activity are generated by similar mechanisms and are not as separate as previously reported (David, 2006).

Several studies also compute the inter trial phase coherence (ITPC) of a signal, which provides a phase locking factor which represents the degree to which the phase angle remains consistent across trials in respect to the onset of a stimulus. Rojas et al. (2008) suggest that the phase locking factor informs us as to the nature of response, as a signal with high inter trial phase coherence will also have high evoked power, due to the nature of evoked activity. Conversely, low inter trial phase coherence may reflect higher induced activity. This is supported by data presented which shows low inter-trial phase coherence, accompanied by reduced evoked power, and increased induced power in ASC (Rojas, Maharajh, Teale & Rogers, 2008). However, the relationship between phase coherence and evoked power may not be as straightforward as suggested, as another study finds no group differences in either evoked or induced power, but reduced ITPC (Gandal et al., 2010).

## 4.1 Gamma Abnormalities in ASC

There has been increasing evidence which suggests that abnormal neural synchrony may be an important pathophysiological mechanism in several neuropsychiatric disorders (Uhlhaas et al., 2009). Abnormal gamma band activity has been implicated in schizophrenia, epilepsy, and Alzheimer’s disease (Light et al., 2006; Uhlhaas and Singer, 2006).

For instance, there is reduced synchronisation of spontaneous gamma band activity in individuals with Alzheimer’s disease (Ribary et al., 1991; Stam et al, 2002). Reduced evoked gamma power has also been found in individuals with schizophrenia (Haig et al., 2000; Spencer et al., 2003). However, Lee, Williams, Haig & Gordon (2003) demonstrated that positive and negative symptoms of schizophrenia are associated with differences in gamma band activity. They found that participants who mainly experienced negative symptoms had reductions in gamma band power, whereas participants with mainly positive symptoms had increased gamma power, compared to controls. Epilepsy is also associated with increases in gamma band power, as the amplitude of spontaneous gamma activity is several times higher in those with epilepsy (Willoughby et al., 2003).

As temporal binding has been put forward as a deficit in ASC (Brock, Brown, Boucher & Rippon, 2002), gamma band activity in individuals with ASC has received considerable attention. It is suggested that a deficit in the temporal co-ordination of neural synchrony may contribute to the symptoms observed in the condition (Uhlhaas and Singer, 2007), which several studies have investigated by examining gamma band activity in individuals with ASC. As this thesis is focusing on perception in ASC, the studies discussed here will be limited to those that have investigated gamma activity in ASC using low level sensory stimuli (see tables 4.1 to 4.3). Studies which have used higher-order cognitive stimuli such as language stimuli will not be reviewed here, but are included in a recent review (Rojas and Wilson, 2014).

## 4.2 Spontaneous gamma band activity in ASC

Spontaneous EEG has been studied extensively in the different power bands in ASC. This chapter will be restricted to describing studies which report activity in the gamma band, however Wang et al. (2013) provide a recent review of resting EEG across the frequency bands. They describe that power is increased in high (gamma and beta) and low (theta and delta) frequencies in ASC, but is decreased in mid frequencies (alpha; Wang et al., 2013).

Most studies of spontaneous gamma power in ASC have found power to be increased, as described in table 4.1. Studies which assess spontaneous activity report either absolute power or relative power. Whilst most studies report the absolute power in the gamma band, the relative power constitutes the absolute power within the gamma band, divided by the total power. Whilst differences in absolute power inform us about the raw power spectra, relative gamma power tells us about the distribution of power across frequency bands (Cornew et al., 2012).

Studies which have examined spontaneous gamma band power under eyes open conditions have also found increased gamma power in ASC (Machado et al., 2013), including Edgar et al. (2015) who examined pre stimulus baseline power in ASC, reporting increases in theta, alpha and beta, as well as gamma power. Similar increases have been reported under eyes closed conditions (Cornew, Roberts, Blaskey & Edgar, 2012; van Diessen et al. 2014). Van Dissien et al (2014) report that relative power is increased in ASC, which Machado et al (2013) also reported in addition to absolute power.

In two studies which had large participant overlap Orekhova et al. (2007; 2008) found spontaneous EEG power (24.4-44Hz) to be higher in boys with ASC compared to typically developing boys at several in frontal, central and parietal regions. In addition to studying spontaneous gamma power, Orekhova et al (2008) also studied sensory responses to auditory stimuli in order to evaluate sensory gating in ASC. Sensory gating is the suppression of the processing of repetitive irrelevant sensory information. The P50 is a component of the auditory event related potential, the amplitude of which is said to reveal whether sensory gating has occurred. This is relevant to this thesis as P50 suppression in response to the repeated stimuli is said to indicate that sensory gating has occurred, and reflect typical inhibitory neuronal functioning (Nagamoto, Adler, Waldo & Freedman, 1989). Orekhova et al. (2008) found an association between higher gamma power and reduced P50 suppression. This indicates that the children with ASC demonstrate abnormal sensory gating, which the authors state indicates an abnormal E:I balance. However, it should be noted that typical P50 suppression has previously been found in children with ASC who have above average intelligence levels (Kemner, Oranje, Verbaten & van Engeland, 2002). As the children who participated in Orekhova and colleague’s (2008) study had low intelligence levels, the authors state that this abnormal sensory gating may be specific to children with developmental delay.

However, one study has found reduced gamma power. Maxwell et al. (2013) report reduced gamma power in right lateral electrodes, but found no difference in left lateral, frontal, central and parieto-occipital electrodes.

Most studies investigating spontaneous gamma power in ASC find it to be increased over several brain regions, regardless of whether eyes open, or eyes closed conditions are used. However, it needs to be noted that all of these studies are restricted to child participants. Therefore, these conclusions may not be accurate in adolescents, or adults with ASC. Rojas et al. (2014) point out that is of extreme importance to understand whether spontaneous gamma power is altered in ASC, as most gamma band power studies compare power changes relative to baseline. If baseline power is increased or decreased in subjects with ASC, this may affect estimates of normalised post stimulus power. In addition, both absolute and relative power should be reported, as absolute and relative power may differ for a given frequency band, and this could give us more insight into the neural dynamics which may be contributing to the abnormal gamma response (Cornew et al., 2012).

**Table 4.1** Studies measuring spontaneous gamma band activity in ASC.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study**  **(Technique)** | **Participants**  **Group - N, mean age (years)** | **Eyes open/Eyes Closed** | **Location** | **Main Finding** |
| **Orekhova et al. 2007 (EEG)** | ASC: N=40, 5.2.  TD: N=40, 5.3. | Eyes open; sustained visual attention. | Frontal, central & parietal (all midline) | Increased absolute gamma power in ASC (24.4-44Hz). |
| **Orekhova et al. 2008 (EEG)** | ASC: N=21, 5.9  TD: N=21, 5.9 | Eyes open; sustained visual attention. | Frontal, central & parietal (all midline) | Increased absolute gamma power in ASC (24.4-44Hz). |
| **Cornew et al. 2011**  **(MEG)** | ASC: N=27, 9.8, TD: N=21, 10.8 | Eyes closed. | Parietal, temporal, occipital. | Increased absolute gamma power (30-120Hz). |
| **Machado et al. 2013 (EEG)** | ASC: N=11, 5.9 TD: N=14, 5.6 | Eyes open; sustained visual attention. | Midline,  frontal, temporal, parietal, occipital | Increased absolute & relative (22-55Hz). |
| **Maxwell et al. 2013 (EEG)** | ASC: N=15, 15.1  TD: N=18, 14.2 | Eyes open, no stimulus | Right/left lateral, central, frontal and parieto-occipital | Decreased absolute power in right lateral electrodes in ASC (30-50Hz). |
| **van Diessen et al. 2014 (EEG)** | ASC: N=19, 10.6, TD: N=19, 10.1 | Eyes closed | Frontal, parietal, temporal | Increased relative gamma power in ASC (30-45Hz). |
| **Edgar et al. 2015**  **(MEG)** | ASC: N=105, 10.07  TD: N=36, 10.9 | Eyes open; Pre-auditory stimulus baseline | Superior temporal gyrus | Increased absolute power in ASC (20-80Hz) |
|  |  |  |  |  |

## 4.3 Evoked gamma band activity in ASC

As previously described, evoked activity is phase locked to the onset of a stimulus, and can therefore be extracted using conventional averaging procedures. Several studies have examined evoked gamma band activity in ASC in response to low level visual or auditory stimuli (see table 4.2). In the visual domain, Milne, Scope, Pascalis, Buckley & Makeig (2009) showed that evoked gamma band activity was modulated by the spatial frequency of Gabor patches. Whilst there were no group differences in evoked gamma power response, children with ASC showed less modulation of both evoked alpha and gamma power compared to control participants. Snijders, Milivojevic & Kemner (2013) also studied evoked gamma band elicited by Gabor patches in adults, but studied steady state response, rather than transient evoked power. Steady state response refers to when a stimulus is modulated over a certain timescale, and produces a corresponding entrainment of the EEG signal at the same frequency. For instance, flickering a visual stimuli at 40Hz will entrain the steady state visual evoked potential at the same frequency and elicit a robust steady state visual evoked potential at 40Hz (Muller et al., 1998). Snijders et al. (2013) found the 60Hz steady state response (in response to refresh rate of the screen) was reduced in power in ASC. In addition when the stimuli were altered (the orientation of components within stimuli were altered to be more or less homogenous), the ASC group showed less modulation of evoked power compared to control participants.

Other studies have used illusory stimuli, such as Kanisza figures, which require illusory closure in order to perceive the full figure. Both Baruth et al. (2010) and Stroganova et al. (2012) studied gamma power in response to Kanisza figures, with both studies finding evoked gamma power to be reduced in ASC. Baruth and colleagues (2010) report reduced evoked gamma over frontal and parietal areas in adolescents with ASC, whilst Stroganova and colleagues (2012) report reduced evoked gamma over occipital areas in children with ASC.

Sun et al. (2012) used MEG to study gamma band activity in adolescents with ASC during the presentation of upright and inverted Mooney faces. Participants with ASC showed elevated reaction times and reduced detection rates during the presentation of upright Mooney faces, whilst performance for inverted faces was not significantly different between participants with ASC and control participants. In addition, participants with ASC were found to exhibit a reduction in both the amplitude and phase locking of evoked gamma band activity over occipital-parietal areas in response to upright but not inverted faces. In fronto central regions, evoked gamma power was found to be increased in lower frequencies (25-60Hz), but decreased in higher frequencies (60-120Hz). Wright et al. (2012) also studied face stimuli using MEG. However, they found no group differences in evoked power in occipital regions in response to faces.

A similar reduction in gamma band power has also been found by studies employing auditory stimuli. Wilson, Rojas, Reite, Tele & Rogers (2007) examined auditory evoked responses to click trains at a frequency of 40Hz in children and adolescents with ASC using MEG. It was found that whilst control subjects showed an increase in the amplitude of gamma band responses, participants with ASC exhibited a marked reduction in evoked gamma band power, specifically in the left hemisphere. Similar results were reported by Rojas et al. (2008) who used EEG to demonstrate that whilst evoked power in the auditory cortex was reduced in response to pure tones, there was increased induced power. This pattern of results was also found in the parents of children with ASC, suggesting that dysfunctions in sensory driven gamma band activity may be a potential endophenotype.

Edgar et al. (2015) reported that evoked gamma and phase locking were reducing in ASC in response to pure tones in the superior temporal gyrus. It can be expected that a reduction in phase locking would also be reflected in reduced evoked power due to the nature of evoked activity, as was found in this study. In addition, whilst spontaneous pre stimuli power was associated with M100 latency, post stimulus evoked power was not related to M100 latency, suggesting that the abnormalities involved with these two processes are distinct. Gandal et al (2010) also studied gamma band activity in response to pure tones in children with ASC. There were no group differences in either evoked or induced gamma power. However, there was reduced phase locking in ASC which was not reflected by the absent group difference in evoked gamma activity.

**Table 4.2** Studies measuring evoked gamma band activity in ASC.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study (Technique)** | **Participants**  **Group - N, mean age (years)** | **Stimulus** | **Location** | **Main Finding** |
| **Wilson et al. 2007**  **(MEG)** | ASC: N=10, 12.4  TD: N=10, 12 | Auditory clicks. | Left auditory cortex. | Reduced evoked gamma power in ASC (40Hz) |
| **Rojas et al. 2008.**  **(MEG)** | ASC: N=11, 31.5  TD: N=16, 43.1.  Parents of children with ASC: N = 16, 42.6. | Pure tone | Superior temporal gyrus | Reduced evoked gamma power in ASC (40Hz). |
| **Milne et al. 2009**  **(EEG)** | ASC: N = 20, 12.2.  TD: N=20, 13.4. | Gabor Patches. | Occipital | No group difference but less stimulus modulation of evoked gamma power (30-40Hz) in ASC. |
| **Baruth et al. 2010**  **(EEG)** | ASC: N=25, 13.8  TD: N=20, 15.3 | Kanisza | Frontal and parietal | Reduced power (30-45Hz). |
| **Gandal et al. 2010**  **(MEG)** | ASC: N=25, 10.2  TD: N=17, 10.8 | Pure tone | Superior temporal gyrus | No group difference (30-50Hz) |
| **Stroganova et al. 2012**  **(EEG)** | ASC: N=23, 5  TD: N= 23, 5.11 | Kanisza square | Occipital | Reduced gamma power (25-48Hz) |
| **Sun et al., 2012**  **(MEG)** | ASC: N = 13, 30.3.  TD: N=16, 29.7. | Mooney Faces | Occipito-parietal | Reduced evoked gamma band power in ASC (in response to upright rather than inverted faces). (25-120Hz) |
| **Sun et al. 2012**  **(MEG)** | ASC: N = 13, 30.3.  TD: N=16, 29.7. | Mooney Faces | Fronto-central | Increased gamma power (25-60Hz), decreased gamma power (60-120Hz) |
| **Wright et al., 2012**  **(MEG)** | ASC: N = 13, 15.1  TD: N=13, 15.7. | Faces. | Occipital | No group difference (30-80Hz) |
| **Snijders et al. 2013**  **(EEG)** | ASC: N=12, 22  TD: N=12, 22 | Gabor patches | Occipito-parietal | Less evoked power in ASC (60Hz steady state response); less stimulus modulation of evoked power. |
| **Edgar et al. 2015**  **(MEG)** | ASC: N=105, 10.07  TD: N=36, 10.9 | Pure tone | Superior temporal gyrus | Reduced gamma power (40Hz) |

## 4.4 Induced gamma band activity in ASC

Induced activity is also of interest in ASC. As stated above, induced activity is not phase locked to the onset of a stimulus. Therefore this activity is extracted by performing time frequency analysis on each trial before averaging is carried out. Similarly to evoked activity, low level visual and auditory stimuli have been used to study the induced gamma response in ASC (see table 4.3). However, the results of these studies are more variable than those found for both spontaneous and evoked activity in ASC.

Wright et al. (2012) used MEG to measure the occipital gamma response in children and adolescents with ASC in response to faces. Whilst evoked responses were intact, the power of induced gamma responses was found to be decreased in individuals with ASC. However, lower band responses (3-30Hz) were similar between ASC and control participants. Sun et al. (2012) also found induced gamma band responses (25-60Hz) in response to mooney faces to be unaltered in individuals with ASC compared to controls, whilst activity in higher frequencies (60-120Hz) was decreased. However, Gross et al. (2013) also measured induced gamma activity in response to faces, and found it to be decreased in lower frequencies (35-45Hz).

Grice et al. (2001) also analysed induced gamma activity during the perception of faces, but in frontal regions. In control participants there was an increase in induced gamma band power in response to upright faces in contrast to inverted faces. However, there was no such difference in the ASC group, demonstrating abnormal induced gamma modulation.

Sokhadze et al (2009) used the Kanisza illusory figure test in which participants have to indicate the presence of target Kanisza squares amongst distracter Kanisza triangles and non-Kanisza figures. It was found that ASC participants did not differ from control participants in terms of reaction time, but they did make more errors. In addition, the power of induced gamma oscillations in response to non-target stimuli (both Kanisza and standard) was higher in the ASC participants compared to controls at left frontal, left and right parietal and occipital sites. In a similar study, Brown et al (2005) found that adolescents with ASC did not differ significantly in terms of either reaction time or accuracy from matched controls when indicating the presence or absence of an illusory Kanisza shape. However, there were significant task related differences in neural activity, as individuals with ASC showed increased induced gamma activity compared to subjects with moderate learning difficulties.

Induced gamma band activity has also been studied in response to auditory stimuli. Gandal et al. (2010) studied induced gamma band responses to pure tones, and found no differences between individuals with ASC and controls. However, Rojas et al. (2008) found increased induced gamma band activity in ASC in response to auditory clicks trains presented at 40Hz.

**Table 4.3** Description of studies measuring induced gamma band activity in ASC.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study (Technique)** | **Participants**  **Group - N, mean age (years)** | **Stimulus** | **Location** | **Main Finding** |
| **Grice et al. 2001 (EEG)** | ASC: N = 8, 36.3.  TD: N=8, 30.9. | Faces | Frontal | No difference in induced gamma power, but less stimulus (upright and inverted faces) modulation of gamma band power in ASC. (32-48Hz) |
| **Brown et al. 2005 (EEG)** | ASC: N = 6, age 14.7 Learning difficulties group: N = 8, 14 | Kanizsa Figures | Parietal | Increased induced power in ASC. (29.3 – 41.5Hz) |
| **Rojas et al., 2008. (MEG)** | ASC: N=11, 31.5  TD: N=16, 43.1  Parents of children with ASC: N = 16, 42.6 | Auditory clicks | Right and left auditory cortices. | Increased induced power in ASC and parent group. (40Hz) |
| **Sokhadze et al. 2009.**  **(EEG)** | ASC: N= 13, 17.2  TD: N=13, 18.6 | Kanisza figures | frontal | Increased induced power in ASC. (30-80Hz) |
| **Gandal et al. 2010 (MEG)** | ASC: N=25, 10.2  TD: N=17, 10.8 | Pure tones | Superior temporal gyrus | No differences (30-50Hz) |
| **Sun et al. 2012 (MEG)** | ASC: N = 13, 30.3  TD: N=16, 29.7 | Mooney faces | Occipito-parietal | Decreased induced gamma power in ASC (60-120Hz), no difference in low gamma (25-60Hz) |
| **Wright et al., 2012 (MEG)** | ASC: N = 13, 15.1  TD: N=13, 15.7. | Faces | Occipital | Decreased induced gamma power in ASC (30-80Hz) |
| **Gross et al (2013) (EEG)** | ASC: N=10, 14.1  TD: N=11, 14.8 | Faces | Parietal | Decreased induced gamma power in ASC (35-45Hz) |

## 4.5 Peak gamma band frequency

All the studies described in this chapter either report peak gamma power or ITPC in ASC. An additional metric of gamma oscillations is the frequency at which power peaks. Peak gamma frequency has not yet been studied in ASC, or in relation to autistic traits. Peak gamma frequency is said to be directly mediated by neural inhibition levels and has been associated with GABA levels, as MRS studies have revealed that higher levels of resting GABA are associated with a higher peak induced gamma frequency in typical observers (Edden et al. 2009; Muthukumaraswamy et al. 2009) and in schizophrenia (Chen et al. 2014). However, a large study by Cousijn and colleagues failed to replicate this finding (Cousijn et al., 2014).

Mathematical models also suggest that peak gamma frequency is set by the E:I ratio, and that higher levels of inhibition, or faster inhibition, lead to a higher peak gamma frequency (Brunel & Wang, 2003). Further support for the claim that peak gamma frequency provides an indication of E:I balance comes from work showing that peak gamma frequency and orientation discrimination thresholds are negatively correlated such that higher peak gamma frequency co-occurs with lower orientation discrimination thresholds (Edden et al., 2009).

In vitro and in vivo techniques in animal models have confirmed that the balance between excitation and inhibition modulates the gamma band oscillatory frequency, as manipulating inhibition levels in rat hippocampus instantaneously alters the peak gamma band frequency, whilst excitation levels modulate gamma band power (Atallah & Scanziani, 2009). This is also supported by the demonstration that optogenetically increasing excitation levels in mouse prefrontal cortex leads to increased power in the gamma range, but increasing inhibition does not exert the same effects (Yizhar et al., 2011).

In addition, Lally et al. (2014) measured dynamic glutamate levels in human participants using MRS and reported a trend towards higher levels of occipital glutamate being associated with lower evoked peak gamma frequency. It was also found that glutamate levels correlate with power, with higher levels of glutamate linked with higher evoked gamma band oscillatory power. They suggest that this adds weight to the idea that whilst the frequency of gamma activity is determined by the ratio of GABA and glutamate concentrations (Atallah & Scanziani, 2009), GABA does not contribute to power, and power is instead modulated by glutamate levels. This is supported by previous findings that GABA levels correlate with peak gamma frequency, but not gamma power (Edden et al., 2009; Muthukumaraswamy et al., 2009).

As gamma frequency and gamma power are unrelated, peak frequency cannot simply be inferred from previous investigations that have presented power changes alone (Jia, Xing & Kohn, 2013). Therefore, peak gamma frequency is a metric which could be used for studying the E:I balance in ASC

## 4.6 Conclusion

Gamma activity has been studied extensively in ASC, with several studies measuring spontaneous gamma activity, and also studying stimulus related evoked and induced activity. The results of these studies are variable, but there is general support for increased spontaneous gamma activity and reduced evoked power in ASC. However, the results of studies investigating induced gamma activity are more variable, with increased and decreased gamma power in ASC reported equally often, as well as several studies finding no group differences. All these studies have looked at peak gamma power. However, different studies have restricted the gamma band activity to specific frequencies within the gamma response, with some studies restricting themselves to quite a specific range (e.g. 30-50Hz; Gandal et al., 2010). Therefore, examining a wider range of frequencies within the gamma range (e.g. 30-90Hz) may reveal more about gamma activity in ASC and resolve some of the discrepancies between studies.

In addition, all of the studies described here report peak gamma power. Peak gamma frequency is an additional metric which can be measured in the gamma band, and may allow more specific predictions as to the E:I imbalance in ASC. Peak gamma frequency has not yet been studied either in individuals with ASC, or in relation to autistic traits. The next chapter will describe an investigation into peak gamma frequency in relation to both autistic traits (study three), and in ASC (study four).

# 5. Chapter five: peak gamma frequency in relation to autistic traits and in ASC

As discussed in chapter four, the indirect method of observing oscillatory activity in the gamma band (>30Hz) provides a way of investigating individual variation in E:I balance as gamma band activity emerges from the interaction of excitatory and inhibitory processes (Buzsáki & Wang, 2012). Peak gamma frequency provides an incisive way of inferring the E:I balance, as mathematical models suggest that higher levels of inhibition lead to a higher peak gamma frequency (Brunel & Wang, 2003). Further support for the claim that peak gamma frequency provides an indication of E:I balance comes from data showing that peak gamma frequency and orientation discrimination thresholds are negatively correlated such that higher peak gamma frequency co-occurs with lower orientation discrimination thresholds (Edden et al., 2009).

This relationship may be mediated by GABA as both orientation discrimination and peak gamma frequency are related to resting levels of GABA (Edden et al., 2009; Muthukumaraswarmy et al., 2009; Chen et al., 2014, however see Cousijn et al., 2014). This demonstrates that individual variability in E:I balance drives individual differences in sensory sensitivity such that higher levels of inhibition lead to enhanced ability to discriminate between visual stimuli of different orientations (Edden et al., 2009). Thus, as individuals with higher levels of autistic traits and individuals with a clinical diagnosis of ASC have lower orientation discrimination thresholds (chapter two) it may be the case that the presence of higher levels of autistic personality traits is associated with disruptions to the E:I balance. This may become apparent through measuring peak gamma frequency, which has not been studied previously either in relation to autistic traits, or in those with a clinical ASC diagnosis. Measuring peak gamma frequency as opposed to gamma power allows for more specific predictions to be made about the direction of any potential E:I imbalance.

Studies three and four of this thesis will measure peak gamma frequency in relation to autistic traits and in ASC, respectively. This will determine whether the enhanced orientation discrimination seen in both of these populations may be due to alterations in E:I balance.

## 5.1 Study three: the relationship between peak gamma frequency and autistic traits

Study one in this thesis demonstrated that individual differences in orientation discrimination are related to the presence of autistic personality traits, with higher levels of autistic traits associated with lower (superior) orientation discrimination thresholds (Dickinson et al., 2014). Here it is explored whether variability in E:I balance, as indexed by peak gamma frequency, is associated with variability within both of these domains. This will help elucidate the extent to which the relationship between autistic traits and orientation discrimination thresholds is mediated by variation in E:I balance.

Given that higher levels of autistic traits are associated with enhanced orientation discrimination, and enhanced orientation discrimination is associated with increased peak gamma frequency (Edden et al., 2009), it is predicted that peak gamma frequency may be increased in individuals with higher levels of autistic traits. No study has directly measured all three variables in the same participants, and the present study is the first to investigate whether individual differences in autistic traits are related to peak gamma frequency.

### 5.1.2 Method

*Participants*

Every participant in the current study had taken part in a previous study investigating the relationship between orientation discrimination thresholds and autistic personality traits (chapter two) in which all 116 participants were given the option of taking part in an additional testing session on the same day during which EEG would be recorded. Thirty-three neurotypical individuals (12 female) with normal or corrected to normal vision took part in the present study. Participants were all aged between 18 and 45 years (M=25, SD=6.63). The orientation discrimination data for these participants can be found in chapter two. The study received ethical approval from the Department of Psychology University of Sheffield ethics committee. Participants provided informed written consent, in accordance with the declaration of Helsinki.

*Questionnaire*

Participants completed the AQ, a 50 item self-report questionnaire which measures autistic traits in the general population (Baron-Cohen et al., 2001). The AQ is described in detail in chapter two.

*Orientation discrimination task*

Orientation discrimination thresholds were measured using a two-alternative forced choice adaptive staircase procedure based on that described by Edden and colleagues (2009) and used by Dickinson et al. (2014). The orientation discrimination task is described in chapter two.

*EEG Task*

*Apparatus*

EEG data were collected using the BioSemi ActiveTwo system (BioSemi, Amsterdam, The Netherlands). Recordings were taken from 128 electrodes at a sampling rate of 2048Hz. All EEG was filtered online with a band pass of 0.01 -140Hz and digitised using BioSemi ActiView software. Direct current offset voltages were kept below +/- 25mV. Recordings were carried out in an electrically shielded room. Stimuli were displayed on a linearised Viglen LCD monitor with a spatial resolution of 1280 x 1024 pixels and a temporal resolution of 60Hz. Stimuli were presented using the PsychToolbox set of functions (Brainard, 1997) in MATLAB (The MathWorks Inc., Natick, MA, 2000).

*Procedure*

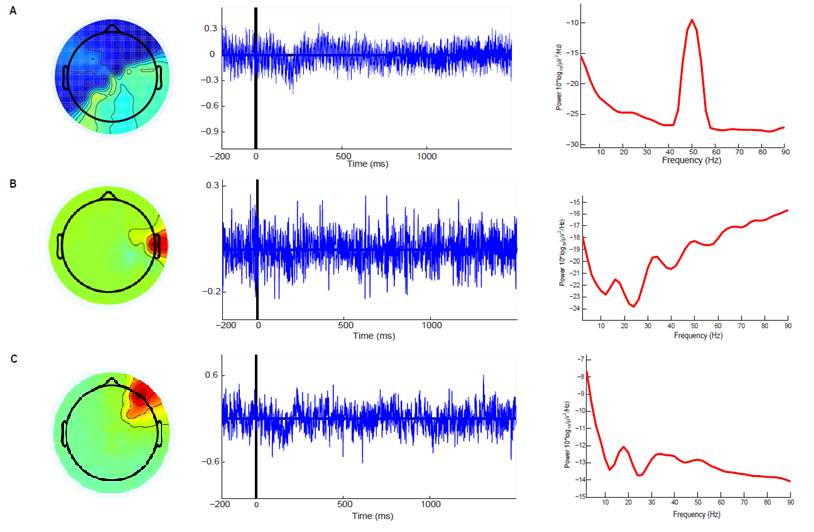
Participants were asked to sit comfortably and keep movement to a minimum. They were instructed to fixate on a red cross in the centre of the computer monitor throughout the experiment. In order to maintain attention, participants were asked to respond by pressing the spacebar when the stimulus (described below) disappeared from the screen and reaction time was recorded.

The stimuli used during the EEG recording session were based on that of Edden and colleagues (2009) who previously used these stimuli to measure gamma activity using MEG. A red cross (1° x 1°) located in the centre of the screen was constantly present throughout the experiment. A black and white square grating (4° x 4°; spatial frequency 3 cycles/degree; contrast 99.6%; mean luminance 39.33 cd/m2), located to the bottom left of the fixation cross, was repeatedly presented for between 1500 - 2500 milliseconds with an inter stimulus interval of 1500-2500ms. Stimuli were created in MATLAB (The MathWorks Inc., Natick, MA, 2000) using the PsychToolbox set of functions (Brainard, 1997). 200 trials were presented, separated into two blocks with a self-timed break in between. Participants were instructed to respond to the first half of the trials using their right hand, and the second half using their left hand. Participants sat 57cm away from the monitor, at this distance the stimuli subtended 4 degrees of visual angle.

*Problems of measuring gamma activity*

EEG recorded at the scalp is a linear mixture of several sources of neural activity, as well as several sources of non-neural artifact. Electrooculography (EOG) and electromyography (EMG) artifacts are highly prevalent in the EEG signal. In addition, there are also artifacts which are particularly problematic for the current investigation as they share a similar frequency range to the gamma band of interest. For instance power line interference causes artifacts throughout the EEG signal at 50Hz. In addition, there have been previous reports of EEG power changes in the gamma frequency range between 200 and 300ms post stimulus onset that are related to saccadic eye movements (Yuval-Greenberg, Tomer, Keren, Nelken & Deouell, 2008). Power line interference and the saccadic spike potential (SP) would therefore overlap with both the time and frequency range of interest here (>30Hz).

A solution to this problem is to use independent component analysis (ICA), a statistical blind source separation technique, to decompose the EEG recording into maximally independent components (Makeig, Jung, Bell, Ghahremani & Sejnowski, 1997) Analysing data from a single independent component for each participant which best represented the visual response to the stimuli allowed us to isolate the visual response and eliminate artifacts including EMG, EOG, the SP and the residual 50Hz power line interference that resisted shielding. These different artifacts can be clearly observed in different components and have characteristic properties which make them distinguishable from the activity of interest, which is more difficult when analysing channel data (Onton & Makeig, 2006). Figure 5.1 shows examples of the scalp topography, power spectra and time series of 50Hz line noise, EMG and EOG artifacts which could be excluded from the signal due to ICA.

****

**Figure 5.1. (A)** Scalp map, time series and power spectrum of a component identified as 50Hz line noise. **(B)** Scalp map, time series and power spectrum of a component identified as EMG artifact. **(C)** Scalp map, time series and power spectrum of a component identified as EOG artifact

*EEG Analysis*

Continuous EEG data were down-sampled from 2048Hz to 1024Hz using BioSemi DBF Decimator software. The rest of the offline data analysis was performed using EEGLAB (Delorme & Makeig, 2004), and in-house MATLAB scripts. Data were referenced to the vertex electrode and high pass filtered to remove frequencies below 1Hz, using a finite impulse response filter, as implemented in EEGLAB. Data were then visually screened and any artifactual channels or segments of data were removed. After removing artifactual channels an average of 117 channels (SD = 8.27, range = 91 - 127) remained for each participant.

Data were then segmented into epochs (-200 -1500 ms) corresponding to the presentation of the stimulus at 0ms. Any trials in which the participant did not respond within 1500ms following stimulus-offset were removed. After this process an average of 185 epochs per participant remained (SD = 11.58, range = 149 – 200).

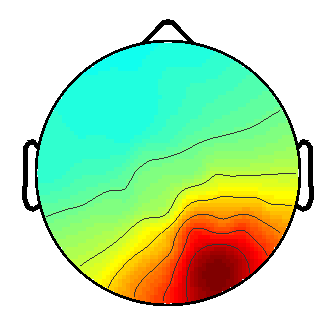
After epoching, extended infomax ICA was carried out using EEGLAB (Delorme & Makeig, 2004). Finally, the source location for each independent component was estimated using the DIPFIT function in EEGLAB. DIPFIT estimates the anatomical location using inverse source modelling by creating an equivalent current dipole model which best represents the scalp topography of each independent component, applied to a standard boundary head model (Oostendorp & Van Oosterom, 1989). A standardised process (described below) was then used to choose a single component for each participant for gamma-band analysis.

*Independent component selection*

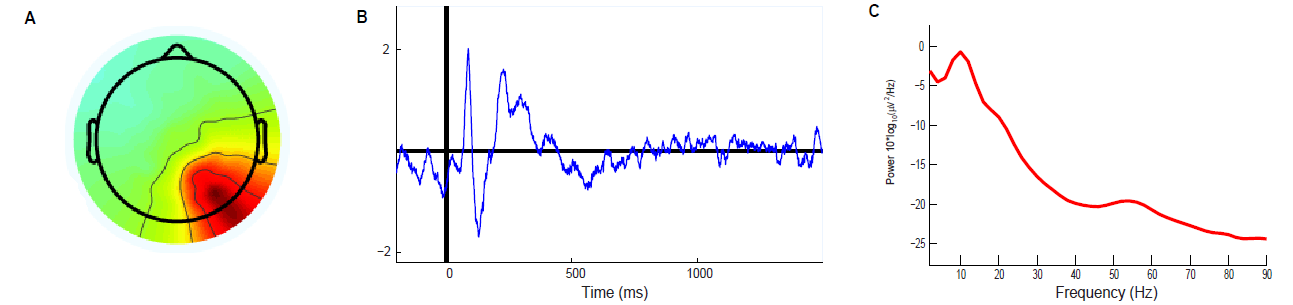
The scalp topography of each component was visually inspected. Any components which had focal activity projecting to posterior electrodes which was lateralised to the right hemisphere were initially selected. This led to up to 8 components being selected for each participant. The time course (ie. The ERP) of each of the selected components was used to exclude any components without a clear visual evoked potential. This led to up to 4 components being retained for each participant.

Time frequency analysis (described below) was then performed on each of the remaining components. Any components which did not show a stimulus elicited change in oscillatory gamma activity were excluded. The final component for each participant was selected on the grounds of the clearest sustained visually elicited change in gamma power. The final component was chosen out of a maximum of 3 components per participant.

To summarise, for each participant a single independent component was selected on the basis of it reflecting a source of activity in or near right occipital cortex and demonstrating visually-elicited neural activity, including an increase in post-stimulus gamma-band power. Component selection was carried out while the experimenter was blind to both the AQ score and orientation-discrimination threshold of the participant. See Figure 5.2 for the scalp topography of the average selected component for all participants. Figure 5.3 shows an example of the scalp topography, time series and power spectra of a selected component for one participant.



**Figure 5.2.** Scalp topography of the average selected component for all participants



**Figure 5.3. (A)** Scalp map **(B)** time series and **(C)** power spectrum of a selected component for one participant which is consistent with the elicited visual activity of interest.

*Time frequency analysis*

Frequency analyses, such as Fourier transform, are required in order to extract frequency information from a signal. However, a stimulus elicited signal measured by EEG is non-stationary as the properties of the signal, including frequency, change over time. Therefore Fourier transform is unsuitable for analysing frequency information in stimulus elicited EEG, as it does not localise frequency changes in time. Use of time frequency analyses such as short time Fourier transform (STFT) allows analysis of both time and frequency information. The time series is split into windows of a specific length, and a Fourier transform is performed on each window. However, this requires pre determining the window length, which involves a time/ frequency trade off. For instance, for lower frequency signals there will be fewer oscillations within a time window, compromising frequency localisation. However, for higher frequencies there will be more oscillations within a time window, and so time localisation is lost.

Wavelet transform enables analysis of a time series with variable window sizes for analysing the different frequency components within a signal (Daubechies, 1990). A wavelet is a waveform of limited duration that has an average value of zero and is able to identify frequency components concurrently with their location in time. This involves changing the location and scaling of a mother wavelet in order to capture both high and low frequency information in a signal simultaneously. Wavelet analyses are therefore more suited to non-stationary signals, as their flexibility allows the preservation of both time and frequency resolution. Therefore, wavelet transforms were chosen to analyse the time series of the selected independent component from each participant in the time-frequency domain.

There are different types of mother wavelets, one of which is the Morlet wavelet, a complex exponential modulated by a Gaussian, ω0= 6; where ω0 is nondimensional frequency. The Morlet wavelet was chosen as the function ψ0 because it provides a good balance between time and frequency localisation for feature extraction purposes (Grinsted, Moore & Jevrejeva, 2004; Müller et al., 2004). The complex Morlet wavelet is described by the following function:

|  |  |  |
| --- | --- | --- |
|  |  | **1** |

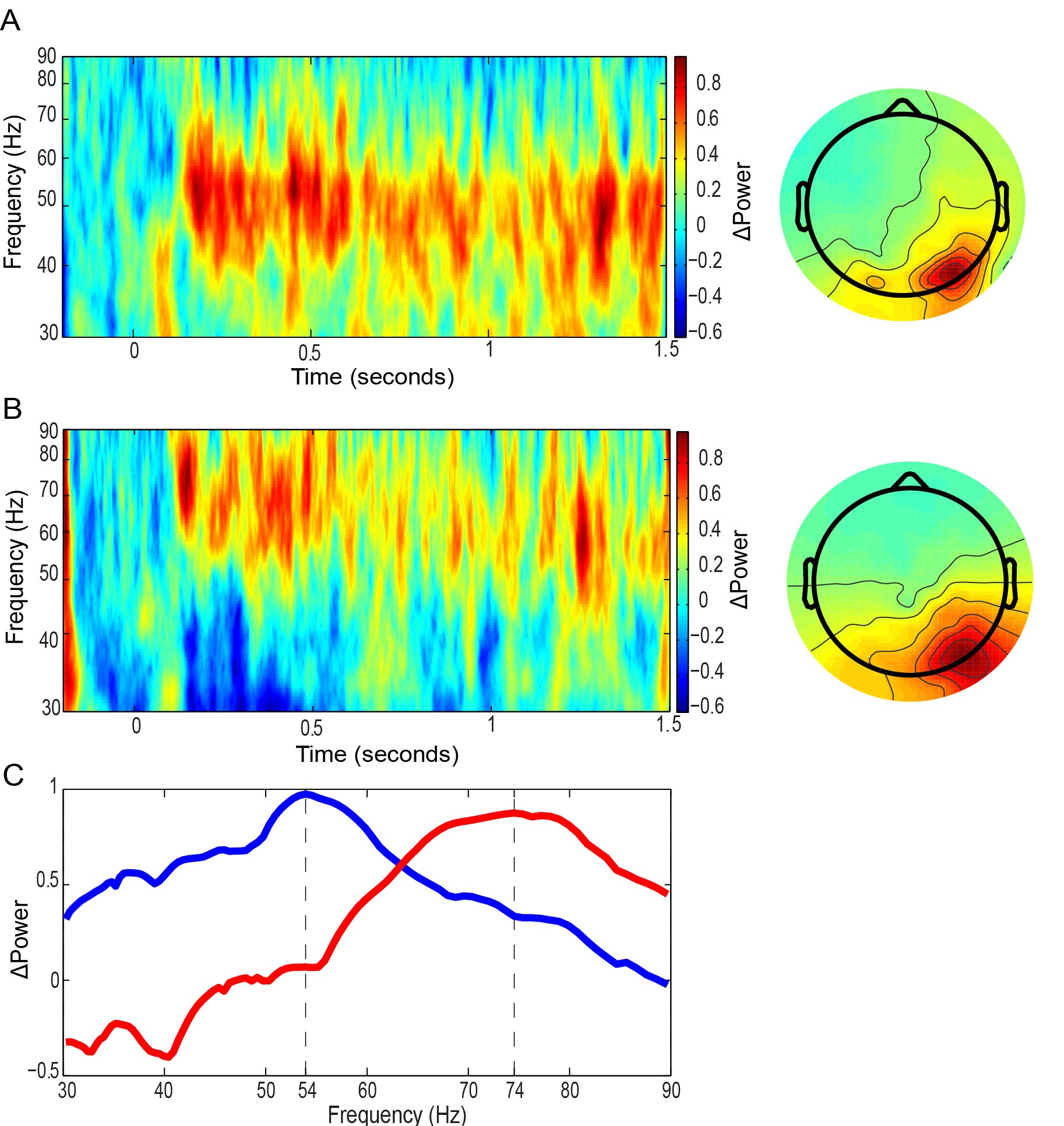
The wavelet transform is a complex quantity whose modulus expresses the amount of power in and whose angle represents the local phase localised in time and frequency (scale). Scale determines the temporal resolution of the analysis. The continuous wavelet transform of a time series of subsampled data points at equal time increments of (Kaiser, 2010), is defined as the convolution of with a scaled and translated version of :

|  |  |  |
| --- | --- | --- |
|  |  | **2** |

where is the complex conjugate of , is the time index and denotes the wavelet scale. The set of scales were chosen such that the number of octaves per scale was set at 1/60 which provided a sufficiently ‘smooth’ picture of wavelet power and resulted in sufficient spectral resolution in the gamma range for the purposes of the present investigation (<1Hz).

The time series of the selected component for each participant for each stimulus presentation trial (epoch) was analysed using this wavelet method. The mean values of power for each scale during the pre-stimulus period for each trial was considered to be baseline and was subtracted from the wavelet transforms. As such, data is presented as changes in power following stimulus presentation (see figure 5.4A and 5.4B). For each participant the wavelet transforms were performed on each trial and were then trial-averaged to estimate changes in induced power. The maxima of the subsequent matrix provided the maximum post-stimulus increase in power in the gamma range following stimulus presentation and the associated frequency at which it occurred (see figure 5.4C). The analysis was restricted to the gamma range, ie. frequencies between 30-90Hz ( Edden et al., 2009).

An additional time frequency analysis was also conducted in which the time series from each trial was averaged before undergoing wavelet transforms in order to estimate changes in evoked gamma power. Again, the maximum post-stimulus increase in power in the gamma range following stimulus presentation (and the frequency at which this occurred) was obtained.[[1]](#footnote-1)



**Figure 5.4.** **(A)** Time frequency decomposition and scalp map of the selected component of a subject with a low AQ score. **(B)** Time frequency decomposition and scalp map of the selected component of a subject with a high AQ score. **(C)** The total power change at each frequency for the low (plotted in blue) and high (plotted in red) subjects plotted in 5.4A and 5.4B.

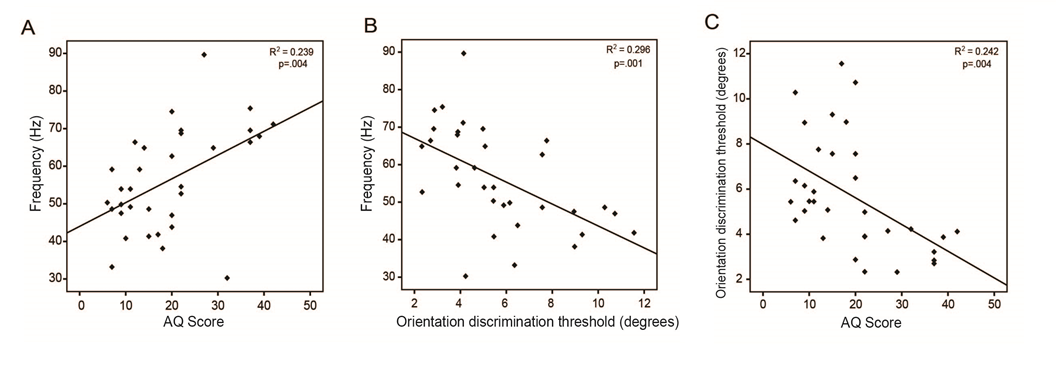
.

### 5.1.3. Results

The AQ scores in the present sample ranged from 6 to 42 (*M*= 19.3, *SD* = 10.5). As in the larger sample these participants were recruited from, this is the distribution of AQ scores we would expect to see in the general population (Baron-Cohen et al., 2001). Vertical orientation discrimination thresholds ranged from .44 – 5.41° (*M*=1.53, *SD*= 1.09). Oblique orientation discrimination thresholds ranged from 2.32 to11.56° (*M*=5.69, *SD*=2.52). Given that the oblique condition provides a more sensitive indication of orientation discrimination than the vertical condition (Dickinson et al., 2014) only oblique thresholds were used in further analyses.

Peak induced gamma frequency ranged from 30.27 to 89.66Hz (*M*=56.23, *SD*=13.57). As hypothesised, there was a significant correlation between peak induced gamma frequency and AQ score (*r*=.489, *p*=.004, see Figure 5.5A). There was also a significant correlation between oblique orientation discrimination thresholds and peak induced gamma frequency (*r*=-.544, *p*=.001, see Figure 5.5B).

As in study one (chapter two), there was a significant negative correlation between oblique orientation discrimination thresholds and AQ score (*r*=-.492, *p*=.004, see Figure 5.5C). Note that the data reported here represent a subset of a larger dataset reported elsewhere (Dickinson et al., 2014), therefore we highlight that a significant correlation between these two variables was still observed even in this restricted number of participants. All correlations remained consistent when using the more robust Spearman’s rho.

****

**Figure 5.5.** **(A)** Correlation between peak gamma frequency and AQ score (N=33) **(B)** Correlation between oblique orientation discrimination threshold and peak gamma frequency (N=33). **(C)** Correlation between oblique orientation discrimination threshold and AQ score (N=33).

There was no significant relationship between peak evoked frequency and oblique orientation discrimination threshold (*r*=.314, *p*=.08) or AQ score (*r*=-.27, *p*=.13). In addition there was no relationship between gamma power and level of autistic traits, or orientation discrimination thresholds. Peak induced power was not correlated with either oblique orientation discrimination thresholds (*r*= -.13, *p*=.48) or AQ scores (*r*= -.11, *p*=.53). Peak evoked gamma power was also not associated with either oblique orientation discrimination scores (*r*= -.04, *p*=.84) or AQ scores (*r*= -.13, *p*=.48). Peak induced frequency was also not correlated with peak induced power (*r*= -.26, *p*=.15).

Peak induced gamma frequency showed a significant correlation with the attention to detail (*r*=.609, *p*=<.001), and communication (*r*=.459, *p*=.007) subscales of the AQ, but not with the social skills (*r*=.326, *p*=.064) or attention switching (*r*=.242, *p*=.175) subscales.

In addition, there was no significant relationship between peak gamma frequency and age (*r*= -.064, *p*=.722).

Reaction times recorded during the EEG task ranged from 170 – 720ms (*M*=413, *SD*=130ms). Reaction times were not related to the presence of autistic traits (*r*=.08, *p*= .662).

### 

### 5.1.4. Discussion

This study reports that individual differences in peak gamma frequency are related to both autistic traits and oblique orientation discrimination thresholds. Peak gamma frequency has previously been shown to be related to orientation discrimination thresholds (Edden et al., 2009), which are lower in those with high levels of autistic traits (Dickinson et al., 2014). Therefore, it was predicted that peak gamma frequency would be associated with level of autistic traits. This prediction was supported by the data as this study provides the first empirical evidence for a relationship between peak gamma frequency and level of autistic traits. These data also replicate existing work by showing a significant negative correlation between orientation discrimination thresholds and peak gamma-frequency (Edden et al., 2009).

As previously discussed in chapter four, higher peak gamma frequency is associated with higher levels of neural inhibition. Modelling work demonstrates that the frequency of gamma-band oscillations is affected by the balance between excitatory and inhibitory processes. Both a higher E:I ratio, and faster inhibition than excitation have been said to lead to a higher peak gamma frequency (Brunel & Wang, 2003). Therefore it may be the case that the higher peak gamma frequency observed in those with a higher level of autistic traits indicates increased neural inhibition. Increased inhibition may be mediated through a number of means, including increased levels of GABA, reduced levels of glutamate, or atypical lateral connectivity. Bertone and colleagues (2005) postulated that higher levels of lateral inhibition exist in individuals with ASC due to atypical neural connectivity. However, this suggestion is at odds with a prominent theory suggesting that inhibition is reduced in ASC, leading to cortical hyperexcitability (Rubenstein & Merzenich, 2003).

Given that orientation discrimination has also been found to be enhanced in ASC (study two), and enhanced thresholds consistent with increased lateral inhibition have been reported in the auditory domain (Bonnel et al. 2010; Jones et al. 2009; Stanutz et al. 2014), it is highlighted here that it is important to revisit the assumption that ASC is associated with reduced levels of inhibition.

Further work is clearly needed to establish whether inhibitory or excitatory processes are altered in ASC, and if so, through which mechanisms. The current finding that high levels of autistic traits are associated with both lower orientation discrimination thresholds and higher peak gamma frequencies is not consistent with this theory as it suggests increased levels of inhibition. However, it needs to be taken into account that alterations in the neural profile of those with high levels of autistic traits may not represent those who have a clinical diagnosis. Also, whilst it was found that the communication subscale of the AQ was correlated with both peak gamma frequency and oblique orientation discrimination thresholds, the other three subscales of the AQ were not consistently correlated across both measures. For instance, although attention to detail was not related to oblique orientation discrimination thresholds, it was significantly correlated with peak gamma frequency. Therefore, it could be that different items in the AQ drive correlations with oblique orientation discrimination thresholds, and peak gamma frequency, respectively. This further highlights the need to ascertain whether this relationship is also seen in individuals who have a clinical ASC diagnosis.

In addition, it is important to distinguish between evoked and induced gamma band activity, as they are said to represent different types of neural processing (Pulvermüller, Birbaumer, Lutzenburger & Mohr, 1997; Tallon-Baudry & Bertrand, 1999), with evoked activity thought to reflect early attention and sensory processing and induced activity thought to reflect higher order processing (Tallon-Baudry, Bertrand, Delpuech & Pernier, 1996). When analysing peak gamma activity in the current study, analysis methods were adapted from Edden and colleagues (Edden et al., 2009). Whilst evoked activity was isolated in the signal, the way in which induced activity was analysed may not have eliminated all evoked activity. The fact that the peak frequency selected by these two analysis methods was different provides some assurance that induced and evoked activity were selected separately. This is further supported by the fact that peak induced frequency was associated with AQ score and oblique orientation discrimination threshold, but peak evoked gamma frequency was not correlated. However, future work should conduct further analyses which separate these two types of activity in the most stringent way possible.

Future studies should also screen for other participant factors, as the participants in this study were not screened for migraine, other clinical conditions, or medication. Any of these co-occurring factors could influence E:I balance, so it is important to control for them in future studies. Therefore, it is possible that E:I balance is influenced by certain medications or conditions that may affect both orientation discrimination thresholds, and peak gamma frequency. Future work should therefore screen for these factors so that they can be controlled for.

In addition, no measure of intelligence was obtained. It is assumed that all participants were high functioning as all participants were recruited from a similar population. However, it is possible that there are intelligence differences within the sample, which may affect results.

To conclude, this study reports that individual differences in autistic traits are associated with variability in both orientation discrimination thresholds and peak gamma frequency. This leads to the novel hypothesis that inhibition levels may also mediate levels of autistic traits. Specifically, it is suggested that a higher level of inhibition could be associated with the presence of autistic traits in sub-clinical individuals. This is the first study to measure peak gamma frequency in relation to autistic traits, and along with previously published work, suggests that measuring peak gamma frequency represents a promising technique for investigating a putative E:I imbalance in ASC.

## 5.2. Study four: peak gamma frequency in ASC

Study three of this thesis demonstrates that in addition to enhanced orientation discrimination; increased peak gamma frequency is also associated with higher levels of autistic traits. The present study will determine whether increased peak gamma frequency is also apparent in individuals with a clinical diagnosis of ASC.

As orientation discrimination performance is also superior in those with ASC (study two), it is predicted that peak gamma frequency will be elevated in this population. Although many studies have measured gamma power in ASC (e.g. Snijders et al*.* 2013), peak gamma frequency in ASC has not yet been reported.

### 5.2.1. Method

*Participants*

Ninety-six participants who took part in the previously reported study investigating orientation discrimination in ASC (study two) were invited to take part in the additional EEG recording on the same day in order to measure peak gamma frequency. However, 6 participants declined to take part in the EEG recording, resulting in 42 participants with ASC, and 48 control participants taking part in the current study. The orientation discrimination data for these participants are reported in study two (chapter 2).

Ten datasets (five ASC, five control) were excluded from analysis due to excessive EEG artifacts. In addition, ten participants (eight ASC, two control) were taking medication which may affect E:I balance at the time of the study, therefore their data were also excluded. Finally, three participants (one ASC, two control) were excluded as their orientation discrimination thresholds were more than 2 standard deviations above the group mean. Data from the remaining 67 participants (28 ASC, 39 control) are reported below [[2]](#footnote-2). Participant information is provided in table 5.1.

Within the ASC sample, seven people were diagnosed with autism and 21 were diagnosed with Asperger syndrome. Three participants with ASC had an additional diagnosis of ADHD; one had an additional diagnosis of OCD. One participant in the control group had been diagnosed with ADHD.

Module four of the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2000) and social responsiveness scale (SRS-2; Constantino & Gruber, 2012) were used to assess symptomology in the participants with ASC. Both the ADOS and SRS-2 are described in more detail in chapter two.

Due to time limitations during testing, or participants being unable to return for a second testing session, seven participants did not complete the ADOS. Five of these participants did however score above the clinical cut-off for ASC on the SRS. One of these participants did not complete the SRS and the other completed but obtained a below cut-off score of 52. Of the twenty-one participants with ASC who completed the ADOS, 18 met cut-off for ASC. Two of the three participants who did not meet the clinical cut-off score for ASC on the ADOS, did however meet the cut-off on the SRS, the other did not complete the SRS. Thus, three participants with ASC did not meet the criteria on either ADOS or SRS score, either due to scoring below the clinical cut-off or due to missing data. We retained these participants in our analyses given that they all had a clinical diagnosis of ASC (c.f. Schwarzkopf et al. 2014).

Non-verbal intelligence was measured in all participants using the matrix reasoning subtest of the Wechsler abbreviated scale of intelligence. No participant (in either the ASC or control group) took part in previously described studies assessing orientation discrimination (study one, chapter two; Dickinson et al. 2014) and peak gamma frequency (study three, chapter five; Dickinson et al. 2015) in relation to autistic traits. As stated, all participants had taken part in study two of this thesis (chapter two). The study received full ethical approval from the local research ethics committee. Participants provided informed written consent, in accordance with the declaration of Helsinki.

**Table 5.1** Demographic variables of participants included in analyses (N=67).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Measure** | **Autism Spectrum Condition Group** | **Control Group** | **Group Comparison** | |
| Mean (*SD*),  Range or number (%) | Mean (*SD*),  Range or number (%) | Student’s *t* (or X2) | *P* Value |
| **Age (years)** | 30.11 (11.75),  18-55 | 28.77 (12.15),  18-65 | .45 | 0.65 |
| **Sex (N females)** | 9  (32.14%) | 10  (25.64%) | 0.34 | 0.59 |
| **Matrix reasoning raw score** | 30.63 (2.72),  25-35 | 29.32 (3.90),  16-34. | 1.51 | 0.14 |
| **Matrix reasoning T-score** | 61.52 (5.5),  51-72 | 58.95 (8.71),  29-70 | 1.35 | 0.18 |
| **ADOS Communication and Social Interaction Total** (N=21) | 8.98 (3.89), 3-16 |  |  |  |
| **SRS T-Score** (N=20) | 74 (9.12), 52-86 |  |  |  |

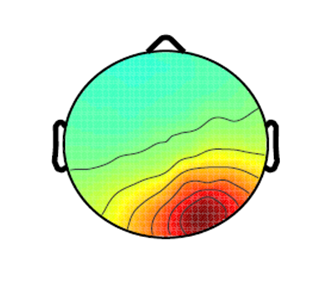
*Orientation discrimination task*

Orientation discrimination thresholds were measured using a two-alternative forced choice adaptive staircase procedure based on that described by Edden and colleagues (2009) and used in study two. The orientation discrimination task is described in study two (chapter two).

*EEG Task*

EEG was acquired using the exact same apparatus, procedure and stimuli described in study three (chapter five). The same methodology as the study three was used, as gamma band activity was successfully elicited and measured using this procedure.

In addition, due to the problems associated with measuring gamma activity described in study three (chapter five), again data were separated into maximally independent components using ICA. The same procedure described in study three was used for picking an occipital component which reflected a source of activity in or near right occipital cortex, and demonstrated visually elicited activity which included an increase in post-stimulus gamma-band power. The average scalp map of all selected independent components can be seen in figure 5.6.

**Figure 5.6.** Scalp topography of the average selected component for all participants

*Time-Frequency Analysis*

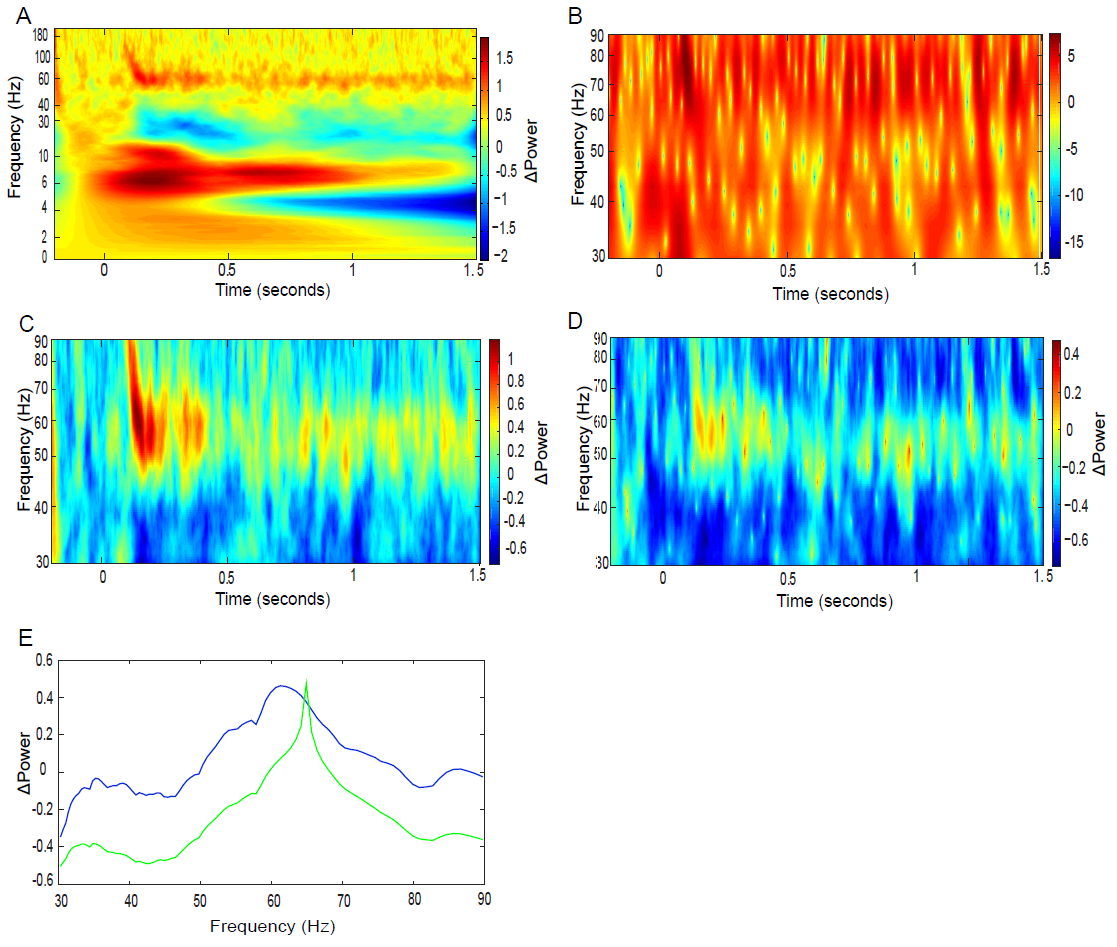
Morlet wavelet analysis was used to analyse data in the time frequency domain, as described in detail in study three (chapter five). However, in the present study additional analyses were performed in order to analyse gamma activity more thoroughly.

The time series of the selected component for each participant was analysed using the previously described wavelet analysis method to examine the two main types of stimulus related gamma activity: evoked and induced (Galambos, 1992). Evoked responses are phase locked to the onset of a stimulus, and occur at around 100msec post stimulus onset (Tallon-Baudry & Bertrand, 1999). Evoked activity can be detected by first averaging the time series of single trial responses and then subjecting them to time-frequency analysis. Induced gamma band activity typically occurs later than evoked activity, and consists of oscillatory bursts with variable onset latency from trial to trial. As such, induced gamma band responses cannot be observed by averaging data before time-frequency analyses, since they are not phase locked to the stimulus. Thus, induced gamma activity is inferred by performing time-frequency analyses on each trial and then averaging the power changes at each frequency. However this analysis will also contain the power changes of the evoked (phase-locked) gamma response. Therefore, a better estimate of induced activity can be obtained by subtracting the power changes at each frequency of the evoked response from these initial estimates of the induced activity (David, Kilner & Friston, 2006).

Thus, to estimate changes in induced gamma for each participant, the wavelet transforms were performed on each trial and were then subsequently averaged in order to obtain the full signal (see Figure 5.7C). The mean values of power for each scale during the pre-stimulus period were considered to be baseline and were subtracted from the wavelet transform. As such, data is presented as changes in power following stimulus presentation. In addition, separate analyses were also carried out in which each trial was averaged before undergoing wavelet transforms in order to analyse evoked gamma power (see figure 5.7B).

In order to remove the contribution of evoked gamma to the signal, the power changes for each frequency for the evoked response were subtracted from the full signal (see figure 5.7D). As the evoked wavelet transform had different magnitudes of power change to the full signal wavelet transform, the transforms were rescaled between zero and one before subtraction. After subtracting evoked activity from the full signal, the remaining power changes can be characterised as induced activity.

The maximum increase in post-stimulus increase power in the gamma range was obtained from both the evoked signal, and the induced signal for each participant using MATLAB (see figure 5.7E). As in study three, the gamma range was defined as 30-90Hz. The frequency at which this maximum increase in power was seen was also obtained for both the induced and evoked data.

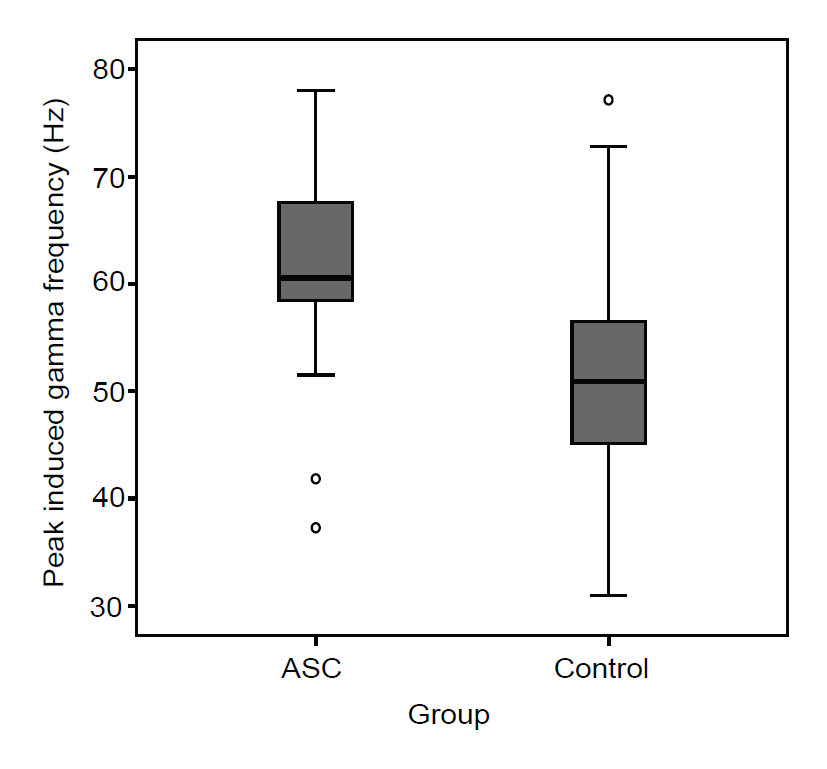


**Figure 5.7. (A)** Time frequency decomposition of all frequency bands (0-200Hz) for one participant. **(B)** Time frequency decomposition of evoked gamma activity signal for one participant. **(C)** Time frequency decomposition of full gamma activity signal, including evoked and induced activity for one participant. **(D)** Time frequency decomposition of induced gamma band response for one participant. **(E)** The total power change at each frequency in the full gamma signal (figure 5.7C; plotted in blue) and in the induced gamma signal (figure 5.7D; plotted in green) for one participant.

### 

### 5.2.2. Results

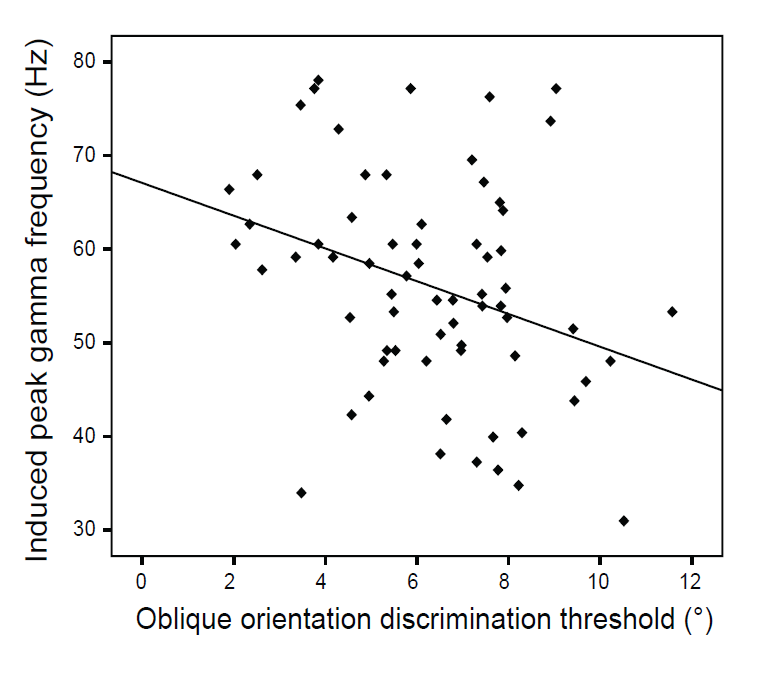
*Gamma activity*

**Peak induced gamma frequency ranged from 30.98 to 78.06Hz, with an overall mean of 56.03Hz (*SD*=11.64). As shown in figure 5.8, induced peak gamma frequency was significantly higher in individuals with ASC (*M*=62.19 Hz, *SD*=10.04 Hz) than controls (*M*=51.61Hz, *SD*=10.75Hz; *t*(65)=4.08, *p*=<.001). Analyses were repeated using different exclusion criteria, but this had no effect on the significance of group differences in peak gamma frequency (see table 5.2).

**Figure 5.8.** Box plot demonstrating peak induced gamma frequency for both ASC and control participants.

There was no difference in induced peak gamma power between individuals with ASC (*M*=.68, *SD*=.28) and control participants (*M*=.74, *SD*=.41; *t*(65)=-.653, *p*=.52). There was also no significant group difference in peak evoked gamma frequency between individuals with ASC (*M*=45.62, *SD*=15.38) and control participants (*M*= 45.97, *SD*= 17.95; *t*(65)=-.086, *p*=.93) or in peak evoked gamma power between individuals with ASC (*M*=5.51, *SD*=1.32) and control participants (*M*= 5.87, *SD*= 1.46; *t*(65)=-1.04, *p*=.3). Peak induced gamma frequency and peak induced gamma power were not correlated (*r*=.07, *p*=.60).

We also investigated the extent to which peak gamma frequency was correlated with orientation discrimination thresholds, and found, as expected, a significant negative correlation between these two variables (*r*=-.32, *p*=.008; see figure 5.9). Age was not correlated with peak gamma frequency (*r*= -.035, *p*=.78).

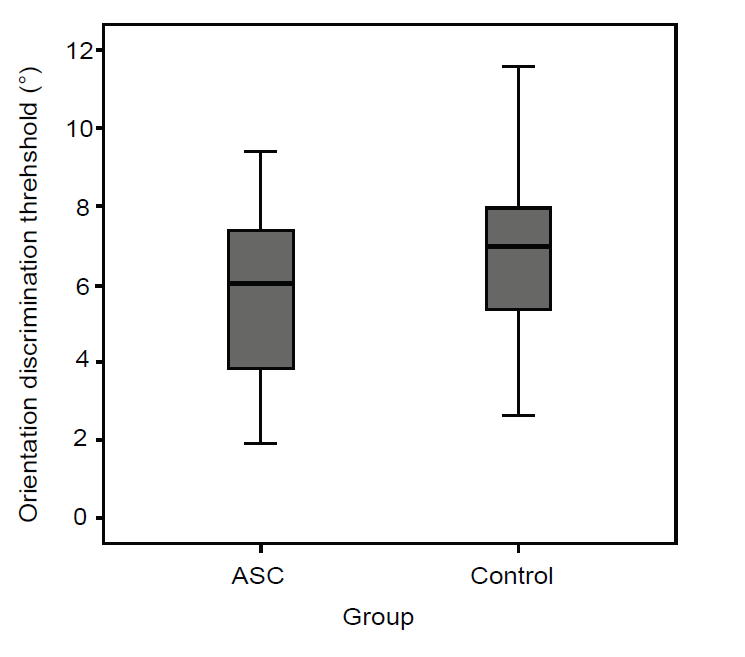


**Figure 5.9.** Correlation between oblique orientation discrimination threshold and induced peak gamma frequency. Each point represents an individual participant and the line represents linear regression.

Reaction times recorded during the EEG task ranged from 284 – 632ms (*M*=401, *SD*=73ms). There were no significant group differences in reaction times between those with ASC (*M*=*418*, *SD*=84ms) and control participants (*M*=389, *SD*=62ms; *t*(65)= 1.625, *p*=.109).

*Orientation Discrimination Thresholds*

In this restricted sample, a significant difference in orientation discrimination between the two groups was observed, as was reported for the larger sample in study two (chapter two). As expected, all participants showed an oblique effect with thresholds significantly higher in the oblique condition (*M*= 6.31°, *SD*=2.13°) than the vertical condition (*M*=1.35°, *SD*=.73°; *t*(66) = -22.07, *p*=<.001). A one-way ANOVA indicated that there was a significant effect of group on discrimination thresholds (*F*(1, 65) =488.55, *p*=<.001) and a significant interaction between group and orientation discrimination condition (*F*(1,65)=5.39, *p*=.02). Further analyses revealed that individuals with ASC had significantly lower oblique orientation discrimination thresholds (*M*=5.64°, *SD*=2.11°) than control participants (*M*=6.8°, *SD*=2.05°; *t*(65)=-2.25, *p*=.028), indicating superior orientation discrimination in the participants with ASC (see figure 5.10). However, there was no significant difference in vertical orientation discrimination thresholds between those with ASC (*M*=1.27°, *SD*=.63°) and controls (*M*= 1.41°, *SD*=.80°; *t*(65)=-.72, *p*=.47).



**Figure 5.10.** Box plot demonstrating oblique orientation discrimination thresholds for both ASC and control participants.

As there was a significant interaction between group and orientation discrimination threshold, the magnitude of the oblique effect was calculated by subtracting each individual’s vertical orientation discrimination threshold from their oblique orientation discrimination threshold. Participants with ASC had a significantly smaller oblique effect (*M*= 4.37°, *SD*=1.8°) than control participants (*M*=5.39°, *SD*=1.77°; *t*(65)=-2.32, *p*=.02).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sample** | **Peak Gamma Frequency** | | | | **Oblique Orientation Discrimination Threshold** | | | |
| **ASC Group** | **Control Group** | **Group difference** | | **ASC Group** | **Control Group** | **Group difference** | |
| Mean Frequency (*SD*) | Mean Frequency (*SD*) | Student’s *t* | *P* Value | Mean Threshold (*SD*) | Mean Threshold (*SD*) | Student’s *t* | *P* Value |
| **Full sample**  ASC N=37  Control N=43 | 60.68 (11.36) | 51.27 (11.35) | 3.7 | <.001 | 6.01 (2.35) | 7.01 (2.41) | -1.871 | .065 |
| **Outliers removed**  ASC N=36  Control N=41 | 60.78 (11.51) | 51.35 (10.88) | 3.693 | <.001 | 5.81 (2.02) | 6.89 (2.23) | -2.225 | .029 |
| **Participants taking medication removed**  ASC N=29  Control N=41 | 62.01 (9.91) | 51.44 (11.16) | 4.09 | <.001 | 5.91 (2.51) | 7.10 (2.43) | -2.00 | .049 |
| **Outliers and participants taking medication removed**  ASC N=28  Control N=39 | 62.19 (10.04) | 51.61 (10.75) | 4.08 | <.001 | 5.64 (2.11) | 6.80 (2.05) | -2.248 | .028 |

**Table 5.2** Group differences for the full sample (N=80) sample with outliers removed (N=70), full sample with participants taking medication removed (N=70), and both outliers and participants taking medication removed (N=67).

### 5.2.3 Discussion

This study reports the novel finding that the peak frequency of visually-induced gamma activity is higher in individuals with ASC. As higher peak gamma frequency is associated with higher levels of neural inhibition (Edden et al. 2009; Muthukumaraswamy et al. 2009), these results may indicate an increase in inhibition levels in ASC. This suggestion is in line with a previous claim that atypical neural connectivity in ASC leads to increased lateral inhibition (Bertone et al., 2005). Furthermore, as peak gamma frequency has specifically been linked to GABAergic inhibition (Chen et al. 2014; Edden et al. 2009; Muthukumaraswamy et al. 2009) this data may specifically indicate increased occipital GABA levels in ASC.

It is important to acknowledge that the suggestion of increased occipital neural inhibition in ASC is at odds with the theory of increased E:I ratio in ASC (Rubenstein and Merzenich, 2003). This highlights that the heterogeneity observed in ASC may also extend to its underlying neural mechanisms, and that one neural profile may not characterise the whole condition. The sample of participants recruited here was relatively homogeneous in the sense that all of the participants were high-functioning adults with ASC, and data from participants who had recently taken medication that may affect E:I balance, or a history of seizures was excluded. This is important as individuals with increased E:I ratio, as is seen in epilepsy and postulated in ASC, would be predicted to show decreased orientation discrimination – a claim which is supported by data showing that individuals with epilepsy have significantly higher tactile orientation discrimination thresholds than individuals without epilepsy (Grant, Henry, Fernandez, Hill & Sathian, 2005) Therefore, while increased E:I ratio may characterise some individuals with ASC, e.g. those with epilepsy, it may not necessarily apply to all individuals with ASC, e.g. those who show superior discrimination.

The suggestion of increased inhibition in ASC is also at odds with several studies that have found decreased GABA levels in ASC (Cochran et al. 2015; Gaetz et al. 2014; Harada et al. 2011; Rojas et al. 2014). However, these studies measured GABA levels in areas other than visual cortex (occipital), including somatosensory, auditory, motor and anterior cingulate cortex. Given that within-participant GABA levels are not consistent across cortical areas (Gao et al. 2013), it is entirely possible that GABA levels may be differentially altered throughout cortex in ASC. There is currently insufficient evidence to conclude that there is either a reduction of GABA levels in ASC – as predicted by the increased E:I ratio theory, or an increase in GABA levels in ASC – as implicated by the current findings. Rather the results presented here highlight discrepancies in the literature, and draw attention to the need for larger more comprehensive studies that use different approaches to measure neural inhibition across different areas of cortex.

To the author’s best knowledge, this study is the first to report peak gamma frequency in ASC, although numerous studies have measured gamma power in ASC. The results of previous studies investigating gamma band power are mixed (see chapter four for a full discussion). The present finding that neither evoked or induced gamma power were altered in those with high levels of autistic traits, or those with ASC is in line with data from Wright and colleagues (2012) and Gandal and colleagues (2010) who found no group differences in evoked or induced gamma band power, respectively.

In conclusion, here it is shown that in a group of high functioning adults with ASC the peak frequency of visually induced gamma activity was significantly higher compared to a well-matched control group. It is suggested that these results may indicate increased occipital inhibition in ASC, which may be mediated through increased GABA levels. This contrasts with the widely-held view that neural inhibition may be reduced in individuals with ASC. These data therefore highlight the possibility of different neural profiles in ASC. Crucially, this may be important in understanding the heterogeneity seen in response to clinical trials of drugs that attempt to modulate E:I balance in ASC(c.f. Erickson *et al*., 2014).

## 5.3 Chapter Discussion

Studies three and four of this thesis report that peak gamma frequency is higher in both individuals with higher levels of autistic traits, and individuals with ASC. This is the first study to measure peak gamma frequency in ASC, and the first to measure gamma activity in those with high levels of autistic traits.

These data demonstrate that in addition to correlating with the degree of autistic traits in members of the general population, increased peak gamma frequency also extends to those with a clinical ASC diagnosis. This suggests that along with autistic traits, the neural activity associated with ASC may also be present in the general population. This is consistent with work from Rojas et al. (2008) who studied gamma band activity in the parents of individuals with ASC, in addition to individuals with ASC. Parent of individuals with ASC are often found to demonstrate higher levels of autistic traits and are said to represent the ‘broader autism phenotype’ (Bishop et al., 2004; Robel et al., 2014). Rojas and colleagues found that, compared to control participants, both individuals with ASC, and parents of children with ASC showed increased induced and reduced evoked gamma band power. The similarly altered gamma band response in ASC and parents of children with ASC compared to controls suggests that atypical gamma band power may co-occur on a continuum, similarly to autistic traits (Constantino & Todd, 2002).

In studies three and four orientation discrimination was found to be enhanced in those with increased peak gamma frequency, and thus these findings are consistent with previous literature (Edden et al., 2009). It was also found that although differences in peak frequency are associated with both orientation discrimination threshold as well as the presence of autistic traits, or a clinical ASC diagnosis, no such relationship was found for gamma band power magnitude. The lack of relationship between gamma power magnitude and orientation discrimination was previously reported by Edden and colleagues (2009). Furthermore, in the current data sets, there was no significant relationship between peak gamma frequency and peak gamma-power, a finding which also concurs with previously reported existing data (Jia et al. 2013).

The question remains as to the underlying neurophysiological cause of variation in gamma band activity. One body of work suggests that it is variation in GABA levels specifically that may drive individual differences in peak gamma frequency (Chen et al., 2014; Muthukumaraswamy, et al., 2009; Edden et al., 2009). However, this claim has recently been put into question by a study which failed to find any relationship between peak gamma frequency and resting GABA levels measured using MRS (Cousijn et al., 2014). In addition, it is important to note that there are limitations to measuring GABA using MRS, which are discussed in detail in chapter three. Therefore, it is possible that that other causal factors may drive individual differences in peak gamma frequency, which will be discussed in chapter six.

Whilst these results replicate Edden and colleagues (2009), it is not entirely clear why there is an association between peak gamma frequency and autistic traits/ASC but not peak gamma power. One possible reason is that whilst peak gamma frequency is said to be determined by inhibitory as well as excitatory processes, gamma band power is said to be driven by excitatory processes alone (Atallah & Scanziani, 2009; Lally et al., 2014). This is consistent with the observation that peak gamma frequency, and now power is also associated with orientation discrimination thresholds. The present results may therefore indicate that there are specific atypicalities in inhibitory processes in ASC, a suggestion which is backed up by findings which show GABA levels specifically to be associated with peak gamma frequency, and not power (Edden et al., 2009; Muthukumaraswamy et al., 2009).

Although previous literature allows predictions as to why we see differences in peak gamma frequency, but not peak gamma power; interpreting why there is a difference in induced but not evoked peak gamma frequency is more difficult. One possibility is that these two types of activity represent different types of neural processing, with evoked activity said to reflect early sensory and attentional processing, and induced said to reflect higher order processes (Tallon-Baudry, Bertrand, Delpuech & Pernier, 1996).. Therefore the present results may reflect abnormalities in one specific type of neural processing.

Spontaneous gamma band power should also be studied as Yizhar and colleagues showed that optogenetically increasing excitation in the prefrontal cortex of mice led to increase in spontaneous gamma power (Yizhar et al., 2011). Therefore, it may be the case that spontaneous gamma power can also inform as to whether there is an E:I balance in ASC and could help support the current studies if so.

Future studies should also analyse ITPC as well as evoked power (Rojas et al., 2014). ITPC could inform about variability, which is said to be altered in ASC. Several studies have found reduced reliability of responses across trials in ASC using fMRI (Dinstein et al., 2010; 2012) and EEG (Milne et al., 2011) to auditory, visual and somatosensory stimuli. It has been suggested that imbalances in E:I may lead to lower reliability across trials. Poor response reliability may be an may be seen as an outcome of high E:I which leads to more excitable and noisy cortex. In EEG this may manifest as low ITPC, which would not necessarily be seen in response amplitude. Calculating ITPC may therefore reveal more about the E:I balance in ASC.

It should also be noted that peak gamma frequency was not found to decrease with age in either study three or four, as has been previously reported (Muthumumaraswarmy et al., 2009). This may be due to age range not being evenly distributed across the sample.

To conclude, here it is found that peak gamma frequency is increased in individuals with higher levels of autistic traits and those with a clinical ASC diagnosis. This mirrors findings presented in studies one and two of this thesis which found enhanced orientation discrimination in both of these populations. In the context of previous literature, both increased peak gamma frequency and enhanced orientation discrimination are consistent with increased levels of neural inhibition. This will be discussed in chapter six.

# Chapter 6: Discussion

## 6.1 Summary of findings

Atypical sensory perception has a large impact on the daily lives of many individuals with autism spectrum conditions (ASC). Whilst visuospatial tasks such as visual search, the EFT and the BDT reveal superior performance in ASC (Lockyear & Rutter, 1970; O’ Riordan, Plaisted, Driver & Baron-Cohen, 2001; Plaisted, O’Riordan, & Baron-Cohen, 1998; Shah & Frith, 1983; Shah & Frith, 1993), little is known about the basis of this atypical perception. As the visual system is well understood, this thesis sought to investigate low-level visual perception and its neural underpinnings in relation to autistic traits, and in those with ASC.

The first study in this thesis investigated orientation discrimination in relation to autistic traits. It was hypothesised that if differences in orientation discrimination ability did vary with autistic traits, they would be revealed through measuring oblique orientation discrimination thresholds, but not vertical thresholds, due to less inter participant variability when discriminating cardinal angles. Orientation discrimination thresholds were measured using an adaptive staircase procedure in participants without an ASC diagnosis, but with varying levels of self-reported autistic traits. A significant correlation was found between oblique orientation discrimination thresholds and autistic traits, with participants with higher levels of autistic traits demonstrating lower oblique orientation thresholds. However, there was no relationship with vertical orientation discrimination thresholds, confirming that this measure is not sensitive enough to probe inter participant variability in orientation discrimination.

Study two investigated whether this enhanced orientation discrimination ability was also present in individuals with a clinical diagnosis of ASC. High functioning adults with ASC took part in the same orientation discrimination task employed in study one. It was found that individuals with ASC had significantly enhanced oblique orientation discrimination ability, demonstrated through lower thresholds. Again, this superior performance was not found to extend to vertical orientation discrimination thresholds.

Given that the E:I balance has been posited to be disrupted in ASC, and that orientation discrimination thresholds are said to be mediated by lateral inhibition (Hubel & Wiesel, 1968; Edden et al., 2009); studies three and four of this thesis aimed to probe whether E:I balance was altered in the participants who demonstrated enhanced orientation discrimination. Peak gamma frequency was identified as a suitable metric to index this balance (discussed in chapter four). In study three, peak gamma frequency was measured using EEG in a subset of participants whose orientation discrimination data were reported in study one. It was found that higher peak gamma frequency was associated with higher levels of autistic traits, as well as lower orientation discrimination thresholds. This suggests that variability in these three factors may be mediated by a common neural mechanism.

In order to determine whether peak gamma frequency alterations were also present in individuals with a clinical diagnosis of ASC, study four (chapter five) measured peak gamma frequency in high functioning adults with ASC and matched controls whose data were reported in study two (chapter two). Peak gamma frequency was found to be higher in individuals with ASC compared to matched control participants, and also associated lower orientation discrimination thresholds.

It is well documented in the literature and has been highlighted throughout this thesis that orientation discrimination and peak gamma frequency are both associated with neural inhibition (Hubel & Wiesel, 1968; Edden et al., 2009; Muthukumaraswarmy et al., 2009). Therefore, it is possible that the results presented in this thesis indicate higher levels of inhibition in ASC, and those with high levels of autistic traits. This would account for both the enhanced orientation discrimination and increased peak gamma frequency reported in the two populations. This position, along with alternate explanations will be discussed in this chapter.

## 6.2 Increased inhibition in ASC

Whilst enhanced orientation discrimination and increased peak gamma frequency may implicate increased neural inhibition in the context of previous literature, it is important to consider how this account would fit in with other sensory atypicalities reported in ASC.

Enhanced auditory discrimination is a well replicated finding, with many studies reporting superior pure-tone pitch discrimination in ASC (Bonnel et al. 2010; Jones et al. 2009; Stanutz et al. 2014). Similarly to orientation discrimination, pitch discrimination is thought to be mediated by lateral inhibition (Houtgast, 1972). Akin to the effect on orientation selective neurons, applying a GABA antagonist to neurons in the primary auditory cortex of chinchillas increases the range of frequencies to which the neurons respond, making them less selective to a particular orientation (Wang, Caspary & Salvi, 2000; Wang, Ding & Salvi, 2002). Therefore, increased neural inhibition is consistent with findings of both enhanced orientation and pitch discrimination.

Whilst evidence of superior orientation discrimination in ASC concurs with work in the auditory domain, at first glance, this result appears to be inconsistent with current data in the visual domain. For example, there are a number of studies showing that hue-discrimination is impaired in ASC (Franklin et al. 2008; Franklin et al. 2010; Heaton et al. 2008; Hurlbert et al. 2011), whereas contrast sensitivity is unaltered (Franklin et al. 2010, Koh et al. 2010b). Therefore, at face value it is hard to see how disparate abilities in three low-level visual abilities can be reconciled with alterations in one neural mechanism.

However, all of these findings are entirely consistent with the suggestion that GABAergic inhibition may be increased in ASC. For instance, contrast sensitivity is unrelated to GABA levels (Yoon et al. 2010), therefore it would be expected that enhanced inhibition in ASC would not affect contrast discrimination. In addition, increases in GABAergic inhibition are associated with colour impairments such as those reported in ASC. Medication which increases GABA levels, such as vigabatrin, has been shown to lead to colour impairments in healthy individuals (Mecarelli, Rinalduzzi & Accornero, 2001). Therefore, increased GABA levels have previously been associated with enhanced orientation discrimination, impaired colour discrimination, and unaltered contrast sensitivity. This pattern of results thus reflects evidence for altered visual perception in ASC.

Whilst the results presented in this thesis are consistent with an increase in neural inhibition, they stand opposed to the majority of the literature which tends to discuss E:I imbalance in ASC from the standpoint of increased excitation. However, the results of studies which probe the E:I balance are more variable and equivocal than often interpreted. This evidence is discussed in detail in chapter four. MRS data will be discussed further here, as it is particularly interesting in light of the current results.

Measurements of GABA in many areas of ASC cortex using MRS support that inhibition is decreased in ASC (Cochran et al. 2015; Gaetz et al., 2014; Harada et al., 2011; Rojas, Singel, Steinmetz, Hepburn & Brown 2014). However, the one study to measure occipital GABA did not find it to be reduced (Gaetz et al. 2014). Gaetz and colleagues (2014) found an, albeit non-significant, increase in occipital GABA in individuals with ASC compared to matched controls. This is also consistent with the fact that occipital cortex is one of the cortical areas in ASC in which glutamate is decreased (De Vito et al., 2007). The pattern of MRS results is in-line with the suggestion that enhanced orientation discrimination and higher peak gamma frequency indicate increased neural inhibition in the visual cortex of individuals with ASC.

Whilst many studies have put forward evidence that refutes a GABA increase in ASC, one particularly compelling point which has not (to the authors best knowledge) previously been raised, is that increased GABAergic inhibition in ASC is inconsistent with the high prevalence of anxiety and depression in ASC (Howlin, 1997). GABA has been shown to play a major role in both of these conditions, with GABAergic deficits common in both anxiety and depression (see Möhler, 2012, for a thorough review). For instance, reductions in GABA transmission have been shown to induce anxiety (Horowski & Dorrow, 2002), whilst drug induced enhancement of GABA transmission reduces symptoms of anxiety (Baldwin et al, 2005; Durant, Christmas & Nutt, 2010; Rupprecht et al., 2009). GABA concentration is reduced in individuals with major depression, and this is countered by pharmacological depression treatments and electroconvulsive therapy (Sanacora et al., 1999; Sanacora, Mason, Rothman & Krystal, 2002; Sanacora, Rothman, Mason & Krystal, 2003). Drug induced enhancement of GABAergic activity is also an effective treatment used to alleviate symptoms of depression (Tyagarajan et al., 2011).

Therefore, it is difficult to reconcile a universal GABA increase with the observation that individuals with ASC often suffer from depression and anxiety. In addition, whilst studies two and four screened for clinical anxiety and depression, both anxiety and depression should have been assessed through a questionnaire. Having a measure of anxious and depressive traits would establish whether variability in these factors is also associated with peak gamma frequency or orientation discrimination thresholds.

It is clear that there are several factors which suggest that inhibition may not be increased in ASC, including that decreased GABA is associated with depression, anxiety and epilepsy, which are all prevalent in ASC. This suggests that heterogeneity in ASC needs to be considered when investigating its neural underpinnings, as any neural cause(s) are also likely to be heterogeneous.

## 6.3 Heterogeneity in ASC

As discussed in chapter four, there is direct and circumstantial evidence for increased excitation in ASC. However, given that evidence for increased excitation is not observed in everyone, and that the results presented in this thesis seem diametrically opposed to this position, it is important to consider why the present results conflict with previous data.

One possibility is that E:I balance is increased universally in ASC but at differing levels, resulting in a subtle excitation increase in some individuals which is hard to detect. For this to be accurate, inhibition cannot be leading to enhanced orientation discrimination and increased peak gamma frequency in ASC, and other factors must explain the current results.

Alternately, increases in neural excitation may not affect all areas of cortex and all individuals with ASC in the same way. This seems likely, given the heterogeneity of the condition. ASC are notoriously heterogeneous, with participants showing different patterns of symptoms, at different levels of severity. Within sensory symptoms alone, participants show varied symptom profiles. For instance, both hypo- and hyper-responsivity to different types of sensory stimuli, in different modalities are reported in ASC. Therefore, this would suggest that any underlying cause of sensory symptoms may not manifest in the same way in all individuals with ASC.

For instance, whilst this thesis has presented data which demonstrates that orientation discrimination thresholds are enhanced and peak gamma frequency is increased in ASC, this may not be the case for all individuals with the condition. A similar position has been put forward for findings in the auditory domain. Whilst enhanced pitch discrimination is a well replicated finding in ASC, Jones et al. (2009) put forward that it may actually only be present in 20% of individuals. Jones and colleagues also highlight that enhanced pitch discrimination tends to be present in those with higher levels of intelligence, and delayed language. Bonnel et al. (2010) also support this position as they find that enhanced pitch perception is present in individuals with autism, but not Asperger’s syndrome. This data suggests that enhanced pitch discrimination may be specifically associated with delayed language ability in ASC.

Therefore, it should be considered that enhanced orientation discrimination and increased peak gamma frequency may also not be seen across ASC, and therefore the implicated underlying mechanism of enhanced inhibition may not be present across the condition. For instance, increased inhibition may only be present in individuals who show enhanced orientation discrimination and increased peak gamma frequency, whereas increased excitation may be present in those who do not.

This also highlights the possibility that neural mechanisms may be altered differently across cortex, leading to intra participant variability in sensory symptoms and behaviour. It is entirely possible that E:I balance is not consistently altered across different brain areas, as GABA levels have been found to vary across cortical areas (e.g. Gao et al., 2013). Very few studies have examined multi modal discrimination thresholds in ASC. This would be an appropriate way to examine whether one neural mechanism could be responsible for alterations across different areas of cortex. One study carried out by Meilleur et al. (2014) studied pitch perception and contrast discrimination in adolescents and adults with ASC. It was found that whilst pitch discrimination was enhanced in ASC, contrast discrimination was not. Therefore, this study suggests that enhancements in low-level sensory perception can be limited to one modality. However, it should be noted that contrast discrimination has not been linked to GABAergic inhibition (Yoon et al. 2010), whereas pitch discrimination has (Wang et al. 2000; Wang et al. 2002), which may account for discrepancies between the findings.

A study of this nature which examined both inter and intra participant variability in sensory thresholds using tasks said to rely on the same neural mechanisms (such as pitch discrimination and orientation discrimination); as well as measuring neural inhibition levels in different areas of sensory cortex (ideally using both MRS and peak gamma frequency) would be an effective way to investigate this. Understanding the nature of both inter and intra-participant variation of perceptual sensitivity across modalities should reveal more about the potential neurological etiology of altered sensory discrimination in ASC.

In addition, it is important to consider how the current findings relate to sensory symptoms reported in ASC, as it is not currently known how low level differences in sensory processing impact the type of sensory experiences an individual reports. For instance, it is unknown whether participants who demonstrate enhanced orientation discrimination thresholds also have corresponding visual symptoms which effect their everyday lives, or if these are of a different nature to individuals who have average or impaired orientation discrimination ability. This is important, as it is tempting to assume that the hypersensitivity sometimes reported in ASC maps straight on to enhanced low-level visual perception. However this may not be the case. Future work will study this link by investigating how qualitative data regarding sensory experiences is related to low-level psychophysical measurements.

If it is the case that variable alterations in neural mechanisms are leading to different types of sensory symptoms, this raises the possibility that there are subtypes associated with different neural profiles in ASC. Crucially, this may be important in understanding the heterogeneity seen in response to clinical trials of drugs that attempt to modulate E:I balance in ASC(c.f. Erickson et al., 2014).

In addition, the current data also highlight that it is as important to study and interpret data that do not fit in with the current increased neural excitation theory of ASC, as it is to report those that do. Regardless of whether increased E:I ratio is an accurate description of the neural profile in ASC, understanding why results such as those presented in this thesis oppose this position will uncover more about ASC and improve our understanding.

Therefore, as well as conducting the more in depth studies that have been put forward in this discussion, alternative explanations for enhanced orientation discrimination and increased peak gamma frequency in ASC need to be considered. One reason may be that it is not increased neural inhibition which is leading to increased peak gamma frequency and enhanced orientation discrimination in the current data. Therefore, it is important to consider other factors, which could include high level differences in other cognitive factors including attention or decision making, or low-level differences in neural architecture.

## 6.4 Alternate explanations

### 6.4.1 Attenuated priors

Hypo-priors have previously been put forward as an explanation for atypical sensory processing in ASC (Pellicano and Burr, 2012; see chapter one for a discussion). It is stated that individuals with ASC are less affected by prior information when making a decision, leading to more accurate sensory judgements.

Rosenberg, Patterson and Angelaki (2013) put forward that a reduced oblique effect in ASC could be explained through hypo-priors. As cardinal angles are more present in natural scenes (Coppola et al., 1998), it is considered that the oblique effect can be seen as an example of prior information affecting a decision, as experience of cardinal angles in natural scenes indicates a stronger prior. As priors would facilitate responses to cardinal orientations, it is predicted that reduced priors would lead to less of a reliance on previous information, and manifest as a reduced oblique effect. Rosenberg et al. (2013) use simulations of a neural network model to demonstrate that a reduced oblique effect could be explained through reduced divisive normalisation (discussed in chapter three), which would therefore be indicative of reduced inhibition in ASC.

However, it seems likely that if the ASC group and controls differed in how they were utilising prior information, and it is prior information that mainly affects discrimination for cardinal angles, this would be seen in differences in vertical thresholds, rather than just changes in the magnitude of the oblique effect, as was reported in chapter five. Therefore, this suggests that hypo-priors do not underlie the reduced oblique effect observed in ASC, or enhanced oblique orientation discrimination.

### 

### 6.4.2 Attention

Whilst the orientation task employed in this thesis was chosen to provide a low level measurement of vision, the tasks used do not completely eradicate the effects of attention. Attention has been said to be altered in many different ways in ASC (for a review see Ames & Fletcher-Watson, 2010). If attention varied between individuals with ASC and those without, it might be expected to affect the orientation discrimination and peak gamma frequency differences reported here. As participants with ASC showed superior orientation discrimination, attention may have been improved in these participants. However, it is hard to predict how attention effect orientation discrimination performance, as paradigms using poor/full attention have shown that attention improves orientation discrimination performance (Lee, Kohn & Braun, 1997), whilst others find no impact of attention on orientation discrimination task performance (Bosworth, Petrich & Dobkins, 2012).

Spatial attention has been studied in ASC through measuring the spatial gradient of attention. This refers to how processing is greatest at an attended location and falls of gradually with distance (Downing & Pinker, 1985; Shulman Wilson & Sheehy, 1985). It has been shown that individuals with ASC show a sharper spatial gradient of attention (Roberston et al., 2013), meaning that there is a greater fall-off in performance with spatial distance from cue. Whilst this may be relevant to visual search superiorities, the orientation discrimination task employed in studies one and two required participants to maintain fixation throughout. Therefore, as participants were attending at fixation throughout experiment, it is likely that effects of spatial attention would be minimal.

In addition, studies which show an effect of attention on orientation discrimination (Lee, Kohn & Braum, 1997) and peak gamma frequency (Bosman et al., 2012) manipulate attention using a paradigm in which participants pay full attention, or no attention. All participants in the studies reported in this thesis were highly compliant, and were observed to be maintaining attention throughout experimental tasks. This is supported by the fact that the thresholds measured in the vertical condition were similar between groups.

An additional way to check attentional effects may be to look at the difference between thresholds obtained for the two runs, for both vertical and oblique thresholds. Consistent scores between the two runs would indicate that participants were paying a similar amount of attention throughout. There was no difference in the consistency between the two thresholds obtained for both vertical and oblique thresholds between individuals with ASC and control participants (reported in chapter two). The difference also did not correlate with level of autistic traits. This suggests that attention was not affecting orientation discrimination performance. However, another way to study this would be to measure reaction times. Heightened attention is often associated with reaction time decreases (e.g. Coull & Nobre, 1998). Therefore, any difference in reaction times between individuals with ASC and control participants may infer that the two groups were paying different levels of attention during the task.

In addition, peak gamma frequency has also been shown to be modulated by attention. Bosman et al. (2012) reported an increase in peak gamma frequency in macaque V1 for attended, versus unattended stimuli, with peak gamma frequency around 2-3hz higher for attended stimuli. Whilst gamma band activity in general has been shown to be modulated by attention in humans, the effects of attention on peak gamma frequency have not been studied. In addition, Bosman and colleagues again used a paradigm which explicitly manipulated attention under poor and full conditions. During EEG recording in studies three and four it was observed that all participants were attending. In addition, reaction times during the EEG task were not different between individuals with ASC and those without, and did not correlate with AQ scores in study one. This indicates that all participants were attending at a similar level.

### 

### 6.4.3 Decision making

Although additional data checks suggest that attention did not affect orientation discrimination performance, it cannot be ruled out that the decision making process used by participants varied. This would most likely only affect orientation discrimination results, as the EEG paradigm used to measure peak gamma frequency involved passive viewing and minimal decision making.

The orientation discrimination task involved making a decision based on sensory evidence. Decisions regarding sensory information are based on the gradual accumulation of evidence over time (Diederich, 1997). Therefore, if participants are subjected to a sensory stimulus for longer, their decisions tend to be more accurate (Britten, Shadlen, Newsome & Movshon, 1992). It has been found that even when a sensory stimulus is no longer presented, delaying a response can lead to evidence continuing to accumulate in short term memory, therefore improving accuracy (Vlassova & Pearson, 2013).

Delaying a response might therefore lead to enhanced orientation discrimination thresholds. In the context of the current results, this would indicate that individuals with ASC or higher levels of autistic traits may have delayed their response, resulting in orientation discrimination performance. This is possible, as there have been reports of longer reaction times in ASC (Inui, Yamanishi & Tada, 1995).

As responses in the orientation discrimination task were reported verbally to the experimenter, reaction times cannot be studied in order to determine whether individuals with ASC were showing longer reaction times. Therefore, future work will investigate sensory decision making in ASC using an orientation discrimination paradigm to study the effect of decision difficulty on reaction times. Fitting reaction time data with a drift diffusion model (DDM; Ratcliff, 1978) will allow insight into decision making processes in ASC, and whether they differ for low level visual decisions compared to control participants.

### 6.4.4 Neuroarchitecture

As well as high-level cognitive differences, low-level neural differences other than enhanced inhibition may also explain the current findings. Variability in V1 surface area has previously been linked to differences in both perceptual discrimination and peak gamma frequency (Schwarzkopf, Robertson, Song, Barnes & Rees, 2012; Song Schwarzkopf, Kanai & Rees, 2015). Larger V1 surface area has been associated with better visual discrimination for spatial location, and narrower neural position tuning width (Song et al., 2015). Song et al. (2015) also highlight that cortical thickness and cortical surface area have different impacts on perceptual discrimination. Whilst larger V1 surface area is associated with enhanced perceptual discrimination, increased cortical thickness is associated with reduced perceptual discrimination. As both cortical surface area and cortical thickness contribute to total brain volume (Wiegand et al., 2004), it is hard to distinguish between these two factors in studies which report total brain volume. For instance brain volume has said to be increased in ASC in several studies (Aylward, Minshew, Field, Sparks & Singh, 2002; Carper, Moses, Tigue & Courchesne, 2002; Piven et al., 1995), but it is difficult to determine whether this is due to increased surface area, or cortical thickness. Therefore, it is important to study these two factors separately. Hardan, Muddasani, Vemulapalli, Keshavan and Minshew (2006) studied cortical thickness in ASC and found it to be increased, which was most pronounced in the temporal lobe.

Variability in V1 surface area has also been found to be associated with variability in peak gamma frequency. Individuals with a larger V1 surface area have higher peak gamma frequency (Schwarzkopf et al., 2012). This data, coupled with the present results would suggest that increased V1 surface area in ASC may explain the why peak gamma frequency is found to be higher.

However, Schwarzkopf, Anderson, de Haas, White and Rees (2014) measured V1 surface area in ASC and did not find it to be altered. Whilst Schwarzkopf and colleagues did not find V1 surface area to be altered in ASC, it is still possible that V1 size is confounding the present results. For instance, as previously described, peak gamma frequency might only be higher in some individuals with ASC, likewise for orientation discrimination. Therefore the results from Schwarzkopf et al (2012) would only predict that individuals with higher peak gamma frequency will have larger V1. Whilst Schwarzkopf et al. (2014) did not measure peak gamma frequency; orientation discrimination thresholds were measured and found to be unaltered in ASC. Consequently, we would not expect to see larger V1 surface area in these participants. Therefore, it should be investigated whether V1 size is altered in participants who show enhanced orientation discrimination and higher peak gamma frequency.

### 6.4.5 The effect of stimulus properties on peak gamma frequency

It also needs to be taken into account that other factors may be mediating peak gamma frequency differences in ASC. For instance, stimulus properties have also been found to modulate peak gamma frequency. Peak gamma frequency has been shown to be affected by contrast in monkey V1 (Ray and Maunsell, 2010) and position in space in animal models and humans (Lima, Singer, Chen & Neuenschwander, 2010; van Pelt and Fries, 2013), with stimuli closer to the fovea eliciting a higher peak gamma band frequency. Moving stimuli have also been shown to induce higher peak gamma frequency in animal models and human observers (Friedman-Hill, Maldonado, & Gray, 2000; Muthukumaraswamy and Singh, 2013; Swettenham, Muthukumaraswamy & Singh, 2009; van Pelt & Fries, 2013). Stimulus size has also been shown to be related to peak gamma frequency with a smaller stimulus size in animals (Gieselmann and Thiele, 2008; Ray and Maunsell, 2011) and in humans (van Pelt & Fries, 2013) leading to higher peak gamma frequency (However, see Perry, Hamandi, Brindley, Muthukumaraswamy & Singh, 2013).

In line with the suggestion from Bosman et al. (2012) that attended stimuli lead to a higher peak gamma frequency than non-attended stimuli, Van Pelt and Fries (2013) put forward the suggestion that all of the stimulus factors that affect peak gamma frequency exert their effects by manipulating the salience of stimuli. They state that stimulus factors such as higher contrast, a position closer to the fovea, and increased motion would all increase stimulus salience, and therefore attract more attention, and increase peak gamma frequency. Bosman and colleagues also state that whilst the finding of larger stimuli sizes leading to lower peak gamma frequency may seem counterintuitive to this position, smaller stimuli may actually be more salient as larger stimuli may start to be seen as background information.

Whilst the stimulus properties were kept constant across groups and would therefore not impact on the group difference in peak gamma frequency reported here; it is possible that as well as varying in baseline peak gamma frequency, that we will also see inter participant variability in the modulations caused by stimulus factors. For instance, Schwarzkopf et al. (2012) predict that individuals with a larger V1 will shower a slower decrease in peak gamma frequency as stimulus size increases. This would be interesting to study in ASC.

Peak gamma frequency is also said to be affected by other inter individual differences such as age (Gaetz et al., 2012). However, there was no significant decrease in peak gamma frequency with age seen in this data. This may be because the age of the participant sample did not have enough variability in order to study the effects of age.

Peak gamma frequency has also been found to have a strong genetic determination, with a heritability of around 91% (van Pelt, Boosma & Fries, 2012). The fact that peak gamma frequency is highly heritable suggests that it could be a potential biomarker and endophenotype in ASC. A biomarker is an objective measurable indicator that could indicate the presence of a condition, or define sub-groups within a condition. An endophenotype is defined as a familial, heritable and quantitative trait associated with a condition (Persico & Sacco, 2014). Persico and Sacco (2014) review autism endophenotypes (but do not cover gamma activity) and explain that all endophenotypes are biomarkers, but not all biomarkers are endophenotypes. Peak gamma frequency therefore could represent both an endophenotype and a biomarker. Identifying biomarkers that are endophenotypes is said to increase the power of genetic studies (Gottesman & Gould, 2003).

## 6.5 Future Directions

As discussed, an important future study will involve investigating sensory discrimination across modalities, and inhibition levels across different areas of cortex in a large sample to assess both intra and inter participant variability. This work should also be carried out in a wider sample than that currently employed – including both children and lower functioning adults, and as described in chapter two, should use psychophysical procedures which have been adapted appropriately.

Obtaining converging within-participant results using these different methodologies, in addition to anatomical correlates such as V1 size (c.f. Schwarzkopf et al. 2012), would provide much clearer insight into E:I balance within individuals and would also provide vitally important evidence regarding heterogeneity in neural profiles within ASC.

The motivation for the work presented in this thesis was the diverse and prevalent sensory symptoms reported in ASC. Efforts to elucidate the link between psychophysical tasks and high level sensory symptoms would improve understanding of the relationship between neural mechanisms, low-level sensory perception and the sensory symptoms that affect the day to day lives of individuals with ASC.

## 6.6 Conclusion

Two novel results are reported here: first, individuals with ASC and those with high levels of autistic traits have lower (superior) orientation discrimination thresholds; second the peak frequency of visually-induced gamma activity is higher in ASC and in those with high levels of autistic traits. Both of these findings suggest increased levels of neural inhibition in ASC. While this suggestion is in-line with a previous claim that ASC may be associated with increased lateral inhibition (Bertone et al., 2005), it is at odds with the major neurological theory that postulates increased excitation in ASC (Rubenstein & Merzenich, 2003).

Considering these findings in the context of existing work it is highlighted that inhibition levels may not be altered universally across all areas of the cortex, nor in all individuals with ASC. This is not a position currently taken in the ASC literature, which tends to look for a universal mechanism altered consistently across ASC. The suggestion is put forward that data such as these which indicate that the altered neural profile is not as straightforward and consistent as has previously been suggested will be crucial to understanding the neural underpinnings of ASC and its heterogeneity.

# References

Almeida, R. A., Dickinson, J. E., Maybery, M. T., Badcock, J. C., & Badcock, D. R. (2013). Visual search targeting either local or global perceptual processes differs as a function of autistic-like traits in the typically developing population. *Journal of autism and developmental disorders, 43*(6), 1272-1286.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Ames, C., & Fletcher-Watson, S. (2010). A review of methods in the study of attention in autism. *Developmental Review*, *30*(1), 52-73.

Appelle, S. (1972). Perception and discrimination as a function of stimulus orientation: the" oblique effect" in man and animals. *Psychological bulletin*,*78*(4), 266.

Ashwin, E., Ashwin, C., Rhydderch, D., Howells, J., & Baron-Cohen, S. (2009). Eagle-eyed visual acuity: an experimental investigation of enhanced perception in autism. *Biological psychiatry, 65*(1), 17-21.

Asperger, H. (1944) ‘Die “autistischen Psychopathen”. *Kindesalter Archives fur Psychiatri und Nervenkrankenheiten 117:* 76–136.

Atallah, B. V., & Scanziani, M. (2009). Instantaneous modulation of gamma oscillation frequency by balancing excitation with inhibition. *Neuron*, *62*(4), 566-577.

Austin, E. J. (2005). Personality correlates of the broader autism phenotype as assessed by the Autism Spectrum Quotient (AQ). *Personality and Individual Differences*, *38*(2), 451-460.

Auyeung, B., Baron-Cohen, S., Wheelwright, S., & Allison, C. (2008). The autism spectrum quotient: Children’s version (AQ-Child). *Journal of autism and developmental disorders*, *38*(7), 1230-1240.

Aylward, E. H., Minshew, N. J., Field, K., Sparks, B. F., & Singh, N. (2002). Effects of age on brain volume and head circumference in autism. *Neurology*,*59*(2), 175-183.

Bach, M., & Dakin, S. C. (2009). Regarding “Eagle-Eyed visual acuity: An experimental investigation of enhanced perception in autism”. *Biological Psychiatry, 66*(10), e19-e20.

Baird, G., Charman, T., Baron-Cohen, S., Cox, A., Swettenham, J., Wheelwright, S., & Drew, A. (2000). A screening instrument for autism at 18 months of age: a 6-year follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry, 39*(6), 694-702.

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., & Charman, T. (2006). Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *The lancet, 368*(9531), 210-215.

Baldwin, D. S., Anderson, I. M., Nutt, D. J., Bandelow, B., Bond, A., Davidson, J. R., ... & Wittchen, H. U. (2005). Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*,*19*(6), 567-596.

Baranek, G. T. (2002). Efficacy of sensory and motor interventions for children with autism. *Journal of autism and developmental disorders, 32*(5), 397-422.

Baranek, G. T., David, F. J., Poe, M. D., Stone, W. L., & Watson, L. R. (2006). Sensory Experiences Questionnaire: Discriminating sensory features in young children with autism, developmental delays, and typical development. *Journal of Child Psychology and Psychiatry, 47*(6), 591-601.

Baron-Cohen, S. (2002). The extreme male brain theory of autism. *Trends in cognitive sciences, 6*(6), 248-254.

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a “theory of mind”?. *Cognition, 21*(1), 37-46.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of autism and developmental disorders, 31*(1), 5-17.

Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature reviews neuroscience*, *8*(1), 45-56.

Baruth, J. M., Casanova, M. F., El-Baz, A., Horrell, T., Mathai, G., Sears, L., & Sokhadze, E. (2010). Low-frequency repetitive transcranial magnetic stimulation modulates evoked-gamma frequency oscillations in autism spectrum disorder. *Journal of neurotherapy*, *14*(3), 179-194.

Bastiaansen, J. A., Meffert, H., Hein, S., Huizinga, P., Ketelaars, C., Pijnenborg, M., ... & de Bildt, A. (2011). Diagnosing autism spectrum disorders in adults: the use of Autism Diagnostic Observation Schedule (ADOS) module 4. *Journal of autism and developmental disorders*, *41*(9), 1256-1266.

Bauer, M., Oostenveld, R., Peeters, M., & Fries, P. (2006). Tactile spatial attention enhances gamma-band activity in somatosensory cortex and reduces low-frequency activity in parieto-occipital areas. *The Journal of Neuroscience*, *26*(2), 490-501.

Behrmann, M., Thomas, C., & Humphreys, K. (2006). Seeing it differently: visual processing in autism. *Trends in cognitive sciences, 10*(6), 258-264.

Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S. A., Engel-Yeger, B., & Gal, E. (2009). A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. *Journal of autism and developmental disorders, 39*(1), 1-11.

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2003). Motion perception in autism: a “complex” issue. *Journal of Cognitive Neuroscience, 15*(2), 218-225.

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain, 128*(10), 2430-2441.

Bertrand, O., & Tallon-Baudry, C. (2000). Oscillatory gamma activity in humans: a possible role for object representation. *International Journal of Psychophysiology*, *38*(3), 211-223.

BioSemi, Amsterdam, The Netherlands.

Bishop, D. V., Maybery, M., Maley, A., Wong, D., Hill, W., & Hallmayer, J. (2004). Using self‐report to identify the broad phenotype in parents of children with autistic spectrum disorders: a study using the Autism‐Spectrum Quotient.*Journal of child psychology and psychiatry*, *45*(8), 1431-1436.

Blakemore, S. J., Tavassoli, T., Calò, S., Thomas, R. M., Catmur, C., Frith, U., & Haggard, P. (2006). Tactile sensitivity in Asperger syndrome. *Brain and cognition, 61*(1), 5-13.

Blatt, G. J., Fitzgerald, C. M., Guptill, J. T., Booker, A. B., Kemper, T. L., & Bauman, M. L. (2001). Density and distribution of hippocampal neurotransmitter receptors in autism: an autoradiographic study. *Journal of autism and developmental disorders, 31*(6), 537-543.

Blundell, J., Blaiss, C. A., Etherton, M. R., Espinosa, F., Tabuchi, K., Walz, C., ... & Powell, C. M. (2010). Neuroligin-1 deletion results in impaired spatial memory and increased repetitive behavior. *The Journal of Neuroscience, 30*(6), 2115-2129.

Bogdashina, O. (2003). *Sensory perceptual issues in autism and Asperger Syndrome: different sensory experiences, different perceptual worlds.* London: Jessica Kingsley.

Bölte, S. (2012). Brief report: the social responsiveness scale for adults (SRS-A): initial results in a German cohort. *Journal of autism and developmental disorders*, *42*(9), 1998-1999.

Bölte, S., Holtmann, M., Poustka, F., Scheurich, A., & Schmidt, L. (2007). Gestalt perception and local-global processing in high-functioning autism. *Journal of autism and developmental disorders, 37*(8), 1493-1504.

Bölte, S., Hubl, D., Dierks, T., Holtmann, M., & Poustka, F. (2008). An fMRI-study of locally oriented perception in autism: altered early visual processing of the block design test. *Journal of Neural Transmission, 115*(3), 545-552.

Bölte, S., Schlitt, S., Gapp, V., Hainz, D., Schirman, S., Poustka, F., ... & Walter, H. (2012). A close eye on the eagle-eyed visual acuity hypothesis of autism. *Journal of autism and developmental disorders, 42*(5), 726-733.

Bonnel, A. M., Mottron, L., Peretz, I., Trudel, M., & Gallun, E. (2003). Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. *Journal of Cognitive Neuroscience, 15*(2), 226-235.

Bonnel, A., McAdams, S., Smith, B., Berthiaume, C., Bertone, A., Ciocca, V., ... & Mottron, L. (2010). Enhanced pure-tone pitch discrimination among persons with autism but not Asperger syndrome. *Neuropsychologia, 48*(9), 2465-2475.

Bosman, C. A., Schoffelen, J. M., Brunet, N., Oostenveld, R., Bastos, A. M., Womelsdorf, T., ... & Fries, P. (2012). Attentional stimulus selection through selective synchronization between monkey visual areas. *Neuron*, *75*(5), 875-888.

Bosworth, R. G., Petrich, J. A., & Dobkins, K. R. (2013). Effects of attention and laterality on motion and orientation discrimination in deaf signers. *Brain and cognition*, *82*(1), 117-126.

Bowery, N. G. (1983). *Classification of GABA receptors.* In The GABA receptors (pp. 177-213). Humana Press Clifton, NJ.

Brainard, D. H. (1997). The psychophysics toolbox. *Spatial vision*, *10*, 433-436.

Brian, J. A., & Bryson, S. E. (1996). Disembedding performance and recognition memory in autism/PDD. *Journal of Child Psychology and Psychiatry, 37*(7), 865-872.

Britten, K. H., Shadlen, M. N., Newsome, W. T., & Movshon, J. A. (1992). The analysis of visual motion: a comparison of neuronal and psychophysical performance. *The Journal of Neuroscience*, *12*(12), 4745-4765.

Brock, J., Brown, C. C., Boucher, J., & Rippon, G. (2002). The temporal binding deficit hypothesis of autism. *Development and psychopathology*, *14*(02), 209-224.

Brock, J., Xu, J. Y., & Brooks, K. R. (2011). Individual differences in visual search: relationship to autistic traits, discrimination thresholds, and speed of processing. *Perception-London, 40*(6), 739.

Brosch, M., Bauer, R., Schanze, T., & Eckhorn, R. (1991). Stimulus-induced oscillatory events and their spatial correlation profiles in cat visual cortex. *Eur. J. Neurosci, 54,* 1235.

Brovelli, A., Lachaux, J. P., Kahane, P., & Boussaoud, D. (2005). High gamma frequency oscillatory activity dissociates attention from intention in the human premotor cortex. *Neuroimage*, *28*(1), 154-164.

Brown, C., Gruber, T., Boucher, J., Rippon, G., & Brock, J. (2005). Gamma abnormalities during perception of illusory figures in autism. *Cortex*, *41*(3), 364-376.

Brown, M. S., Singel, D., Hepburn, S., & Rojas, D. C. (2013). Increased Glutamate Concentration in the Auditory Cortex of Persons With Autism and First‐Degree Relatives: A 1H‐MRS Study. *Autism Research, 6*(1), 1-10.

Brugha, T., McManus, S., Meltzer, H., Smith, J., Scott, F. J., Purdon, S., ... & Bankart, J. (2009). Autism spectrum disorders in adults living in households throughout England: Report from the adult psychiatric morbidity survey 2007. *Leeds: The NHS Information Centre for Health and Social Care.*

Brunel, N., & Wang, X. J. (2003). What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation-inhibition balance. *Journal of neurophysiology*, *90*(1), 415-430.

Bryson, S. E., Clark, B. S., & Smith, I. M. (1988). First report of a Canadian epidemiological study of autistic syndromes. *Journal of Child Psychology and Psychiatry, 29*(4), 433-445.

Burnette, C. P., Mundy, P. C., Meyer, J. A., Sutton, S. K., Vaughan, A. E., & Charak, D. (2005). Weak central coherence and its relations to theory of mind and anxiety in autism. *Journal of autism and developmental disorders, 35*(1), 63-73.

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *science*, *315*(5820), 1860-1862.

Buxhoeveden, D. P., Semendeferi, K., Buckwalter, J., Schenker, N., Switzer, R., & Courchesne, E. (2006). Reduced minicolumns in the frontal cortex of patients with autism. *Neuropathology and applied neurobiology, 32*(5), 483-491.

Buxhoeveden, D. P., Switala, A. E., Litaker, M., Roy, E., & Casanova, M. F. (2001). Lateralization of minicolumns in human planum temporale is absent in nonhuman primate cortex. *Brain, Behavior and Evolution, 57*(6), 349-358.

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *science*, *304*(5679), 1926-1929.

Buzsáki, G., & Wang, X. J. (2012). Mechanisms of gamma oscillations. *Annual review of neuroscience*, *35*, 203.

Canitano, R. (2007). Epilepsy in autism spectrum disorders. *European child & adolescent psychiatry, 16*(1), 61-66.

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., ... & Moore, C. I. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*, *459*(7247), 663-667.

Caron, M. J., Mottron, L., Berthiaume, C., & Dawson, M. (2006). Cognitive mechanisms, specificity and neural underpinnings of visuospatial peaks in autism. *Brain, 129*(7), 1789-1802.

Caron, M. J., Mottron, L., Rainville, C., & Chouinard, S. (2004). Do high functioning persons with autism present superior spatial abilities?. *Neuropsychologia, 42*(4), 467-481.

Carper, R. A., Moses, P., Tigue, Z. D., & Courchesne, E. (2002). Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage*, *16*(4), 1038-1051.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002a). Minicolumnar pathology in autism. *Neurology, 58*(3), 428-432.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002b). Asperger's syndrome and cortical neuropathology. *Journal of Child Neurology, 17*(2), 142-145.

Casanova, M. F., Buxhoeveden, D., & Gomez, J. (2003). Disruption in the inhibitory architecture of the cell minicolumn: implications for autisim. *The Neuroscientist, 9*(6), 496-507.

Casanova, M. F., van Kooten, I. A., Switala, A. E., van Engeland, H., Heinsen, H., Steinbusch, H. W., ... & Schmitz, C. (2006). *Minicolumnar abnormalities in autism. Acta neuropathologica, 112*(3), 287-303.

Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K. A., & Essick, G. (2008). Tactile perception in adults with autism: a multidimensional psychophysical study. *Journal of autism and developmental disorders, 38*(1), 127-137.

Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K. A., & Essick, G. (2008). Tactile perception in adults with autism: a multidimensional psychophysical study. *Journal of autism and developmental disorders, 38*(1), 127-137.

Chakrabarti, S., & Fombonne, E. (2001). Pervasive developmental disorders in preschool children. *Jama, 285*(24), 3093-3099.

Chen, C. M. A., Stanford, A. D., Mao, X., Abi-Dargham, A., Shungu, D. C., Lisanby, S. H., ... & Kegeles, L. S. (2014). GABA level, gamma oscillation, and working memory performance in schizophrenia. *NeuroImage: Clinical*, *4*, 531-539.

Chen, F., Lemonnier, E., Lazartigues, A., & Planche, P. (2008). Non-superior disembedding performance in children with high-functioning autism and its cognitive style account. *Research in Autism Spectrum Disorders, 2*(4), 739-752.

Chez, M. G., Chang, M., Krasne, V., Coughlan, C., Kominsky, M., & Schwartz, A. (2006). Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy & Behavior, 8(*1), 267-271.

Coghlan, S., Horder, J., Inkster, B., Mendez, M. A., Murphy, D. G., & Nutt, D. J. (2012). GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neuroscience & Biobehavioral Reviews, 36*(9), 2044-2055.

Coghlan, S., Horder, J., Inkster, B., Mendez, M. A., Murphy, D. G., & Nutt, D. J. (2012). GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neuroscience & Biobehavioral Reviews, 36*(9), 2044-2055.

Constantino, J.N., & Gruber, C.P. (2012). *The Social Responsiveness Scale Manual, Second Edition (SRS-2).* Los Angeles, CA: Western Psychological Services.

Constantino, J. N., & Todd, R. D. (2003). Autistic traits in the general population: a twin study. *Archives of general psychiatry, 60*(5), 524-530.

Constantino, J. N., Przybeck, T., Friesen, D., & Todd, R. D. (2000). Reciprocal social behavior in children with and without pervasive developmental disorders. *Journal of Developmental & Behavioral Pediatrics, 21*(1), 2-11.

Coppola, D. M., Purves, H. R., McCoy, A. N., & Purves, D. (1998). The distribution of oriented contours in the real world. *Proceedings of the National Academy of Sciences*, *95*(7), 4002-4006.

Cornew, L., Roberts, T. P., Blaskey, L., & Edgar, J. C. (2012). Resting-state oscillatory activity in autism spectrum disorders. *Journal of autism and developmental disorders*, *42*(9), 1884-1894.

Cosbey, J., Johnston, S. S., & Dunn, M. L. (2010). Sensory processing disorders and social participation. *American Journal of Occupational Therapy, 64*(3), 462-473.

Coull, J. T., & Nobre, A. C. (1998). Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *The Journal of Neuroscience*, *18*(18), 7426-7435.

Courtney, S.M., & Ungerleider, L.G. (1997). What fMRI has taught us about human vision. *Current Opinion in Neurobiology, 7*(4), 554-61.

Cousijn, H., Haegens, S., Wallis, G., Near, J., Stokes, M. G., Harrison, P. J., & Nobre, A. C. (2014). Resting GABA and glutamate concentrations do not predict visual gamma frequency or amplitude. *Proceedings of the National Academy of Sciences*, *111*(25), 9301-9306.

Crabbe, J. C., Wahlsten, D., & Dudek, B. C. (1999). Genetics of mouse behavior: interactions with laboratory environment. *Science, 284*(5420), 1670-1672.

Crawley, J. N. (2012). Translational animal models of autism and neurodevelopmental disorders. *Dialogues in clinical neuroscience, 14*(3), 293.

Crewther, D. P., & Sutherland, A. (2009). The more he looked inside, the more piglet wasn't there: is autism really blessed with visual hyperacuity?. *Biological Psychiatry, 66*(10), e21-e22.

Damarla, S. R., Keller, T. A., Kana, R. K., Cherkassky, V. L., Williams, D. L., Minshew, N. J., & Just, M. A. (2010). Cortical underconnectivity coupled with preserved visuospatial cognition in autism: evidence from an fMRI study of an embedded figures task. *Autism Research, 3*(5), 273-279.

Damasio, A. R. (1989). The brain binds entities and events by multiregional activation from convergence zones. *Neural Computation, 1*(1), 123-132.

Daubechies, I. (1990). The wavelet transform, time-frequency localization and signal analysis. *Information Theory, IEEE Transactions on*, *36*(5), 961-1005.

David, O., Kilner, J.M., & Friston, K.J. (2006). Mechanisms of evoked and induced responses in MEG/EEG. Neuroimage, 31, 1580-1591.

De Bildt, A., Sytema, S., Ketelaars, C., Kraijer, D., Mulder, E., Volkmar, F., & Minderaa, R. (2004). Interrelationship between autism diagnostic observation schedule-generic (ADOS-G), autism diagnostic interview-revised (ADI-R), and the diagnostic and statistical manual of mental disorders (DSM-IV-TR) classification in children and adolescents with mental retardation. *Journal of autism and developmental disorders*, *34*(2), 129-137.

de Jonge, M. V., Kemner, C., & van Engeland, H. (2006). Superior disembedding performance of high-functioning individuals with autism spectrum disorders and their parents: The need for subtle measures. *Journal of autism and developmental disorders*, *36*(5), 677-683.

de Jonge, M. V., Kemner, C., De Haan, E. H., Coppens, J. E., Van den Berg, T. J. T. P., & Van Engeland, H. (2007). Visual information processing in high-functioning individuals with autism spectrum disorders and their parents. *Neuropsychology, 21*(1), 65.

Debener, S., Herrmann, C. S., Kranczioch, C., Gembris, D., & Engel, A. K. (2003). Top-down attentional processing enhances auditory evoked gamma band activity. *Neuroreport*, *14*(5), 683-686.

DeFelipe, J. (1999). Chandelier cells and epilepsy. *Brain, 122*(10), 1807-1822.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of neuroscience methods*, *134*(1), 9-21.

DeVito, T. J., Drost, D. J., Neufeld, R. W., Rajakumar, N., Pavlosky, W., Williamson, P., & Nicolson, R. (2007). Evidence for cortical dysfunction in autism: a proton magnetic resonance spectroscopic imaging study. *Biological psychiatry, 61*(4), 465-473.

Dhossche, D., Applegate, H., Abraham, A., Maertens, P., Bland, L., Bencsath, A., & Martinez, J. (2002). Elevated plasma gamma-aminobutyric acid (GABA) levels in autistic youngsters: stimulus for a GABA hypothesis of autism. *Medical Science and Technology, 8*(8), PR1-PR6.

Dickinson, A., Jones, M., & Milne, E. (2014). Oblique orientation discrimination thresholds are superior in those with a high level of autistic traits. *Journal of autism and developmental disorders*, *44*(11), 2844-2850.

Diederich, A. (1997). Dynamic stochastic models for decision making under time constraints. *Journal of Mathematical Psychology*, *41*(3), 260-274.

Dinstein, I., Heeger, D. J., Lorenzi, L., Minshew, N. J., Malach, R., & Behrmann, M. (2012). Unreliable evoked responses in autism. *Neuron*, *75*(6), 981-991.

Dinstein, I., Thomas, C., Humphreys, K., Minshew, N., Behrmann, M., & Heeger, D. J. (2010). Normal movement selectivity in autism. *Neuron*, *66*(3), 461-469.

Dohn, A., Garza-Villarreal, E. A., Heaton, P., & Vuust, P. (2012). Do musicians with perfect pitch have more autism traits than musicians without perfect pitch? An empirical study. *PLoS One*, *7*(5), e37961.

Downing, C. J., & Pinker, S. (1985). The spatial structure of visual attention. In M. I. Posner & O. S. M. Marin (Eds.), Attention & Performance XI: Mechanisms of Attention. Hillsdale, NJ: Erlbaum.

Durant, C., Christmas, D., & Nutt, D. (2010). The pharmacology of anxiety. In*Behavioral Neurobiology of Anxiety and Its Treatment* (pp. 303-330). Springer Berlin Heidelberg.

Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M., & Reitboeck, H. J. (1988). Coherent oscillations: A mechanism of feature linking in the visual cortex?. *Biological cybernetics, 60(*2), 121-130.

Eckhorn, R., Frien, A., Bauer, R., Woelbern, T., & Kehr, H. (1993). High frequency (60-90 Hz) oscillations in primary visual cortex of awake monkey. *Neuroreport, 4*(3), 243-246.

Edden, R. A., Muthukumaraswamy, S. D., Freeman, T. C., & Singh, K. D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *The Journal of Neuroscience, 29*(50), 15721-15726.

Edgar, J. C., Heiken, K., Chen, Y. H., Herrington, J. D., Chow, V., Liu, S., ... & Roberts, T. P. (2015). Resting-state alpha in autism spectrum disorder and alpha associations with thalamic volume. *Journal of autism and developmental disorders*, *45*(3), 795-804.

Edgin, J. O., & Pennington, B. F. (2005). Spatial cognition in autism spectrum disorders: Superior, impaired, or just intact?. *Journal of autism and developmental disorders, 35*(6), 729-745.

Elliott, C. D., & Murray, D. & Pearson, LS (1979). *British Ability Scales.* Windsor, England: National Foundation for Educational Research.

Engel, A. K., König, P., Kreiter, A. K., & Singer, W. (1991). Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science, 252*(5009), 1177-1179.

Engel, J. (1996). Introduction to temporal lobe epilepsy. *Epilepsy research, 26*(1), 141-150.

Erickson, C.A., Veenstra-Vanderweele, J.M., Melmed, R.D., McCracken, J.T., Ginsberg, L.D., Sikich, L., Scahill, L., Cherubini, M., Zarevics, P., Walton-Bowen, K., et al. (2014). STX209 (arbaclofen) for autism spectrum disorders: an 8-week open-label study. Journal of autism and developmental disorders, 44, 958-964.

Fagiolini, M., & Hensch, T. K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. *Nature, 404*(6774), 183-186.

Falkmer, M., Stuart, G. W., Danielsson, H., Bram, S., Lönebrink, M., & Falkmer, T. (2011). Visual acuity in adults with asperger’s syndrome: No evidence for “eagle-eyed” vision. *Biological Psychiatry, 70*(9), 812-816.

Falter, C. M., Plaisted, K. C., & Davis, G. (2008). Visuo-spatial processing in autism—testing the predictions of extreme male brain theory. *Journal of autism and developmental disorders, 38*(3), 507-515.

Fatemi, S. H., Folsom, T. D., Reutiman, T. J., & Thuras, P. D. (2009a). Expression of GABAB receptors is altered in brains of subjects with autism. *The Cerebellum, 8*(1), 64-69.

Fatemi, S. H., Halt, A. R., Stary, J. M., Kanodia, R., Schulz, S. C., & Realmuto, G. R. (2002). Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biological psychiatry, 52*(8), 805-810.

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., & Thuras, P. D. (2009b). GABAA receptor downregulation in brains of subjects with autism. *Journal of autism and developmental disorders, 39*(2), 223-230.

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., Rustan, O. G., Rooney, R. J., & Thuras, P. D. (2014). Downregulation of GABAA Receptor Protein Subunits α6, β2, δ, ε, γ2, θ, and ρ2 in Superior Frontal Cortex of Subjects with Autism. *Journal of autism and developmental disorders, 44*(8), 1833-1845.

Favorov, O. V., & Kelly, D. G. (1994). Minicolumnar organization within somatosensory cortical segregates: I. Development of afferent connections. *Cerebral Cortex, 4*(4), 408-427.

Favorov, O. V., Diamond, M. E., & Whitsel, B. L. (1987). Evidence for a mosaic representation of the body surface in area 3b of the somatic cortex of cat. *Proceedings of the National Academy of Sciences, 84*(18), 6606-6610.

Fombonne, E. (2009). Epidemiology of pervasive developmental disorders. *Pediatric research, 65*(6), 591-598.

Foss-Feig, J. H., Tadin, D., Schauder, K. B., & Cascio, C. J. (2013). A substantial and unexpected enhancement of motion perception in autism. *The Journal of Neuroscience*, *33*(19), 8243-8249.

Franklin, A., Sowden, P., Burley, R., Notman, L., & Alder, E. (2008). Color perception in children with autism. *Journal of Autism and Developmental Disorders, 38*(10), 1837-1847.

Franklin, A., Sowden, P., Notman, L., Gonzalez‐Dixon, M., West, D., Alexander, I., ... & White, A. (2010). Reduced chromatic discrimination in children with autism spectrum disorders. *Developmental science, 13*(1), 188-200.

Freitag, C. M. (2007). The genetics of autistic disorders and its clinical relevance: a review of the literature. *Molecular psychiatry, 12*(1), 2-22.

Freiwald, W. A., Kreiter, A. K., & Singer, W. (1995). Stimulus dependent intercolumnar synchronization of single unit responses in cat area 17. *Neuroreport, 6(*17), 2348-2352.

Friedman-Hill, S., Maldonado, P. E., & Gray, C. M. (2000). Dynamics of striate cortical activity in the alert macaque: I. Incidence and stimulus-dependence of gamma-band neuronal oscillations. *Cerebral Cortex*, *10*(11), 1105-1116.

Frien, A., Eckhorn, R., Bauer, R., Woelbern, T., & Kehr, H. (1994). Stimulus-specific fast oscillations at zero phase between visual areas V1 and V2 of awake monkey. *Neuroreport, 5*(17), 2273-2277.

Friston, K. J., Lawson, R., & Frith, C. D. (2013). On hyperpriors and hypopriors: comment on Pellicano and Burr. *Trends Cogn. Sci, 17*(1), 10-1016.

Frith, U. (1989). *Autism: Explaining the enigma.* Oxford: Blackwell.

Gaetz, W., Bloy, L., Wang, D. J., Port, R. G., Blaskey, L., Levy, S. E., & Roberts, T. P. L. (2014). GABA estimation in the brains of children on the autism spectrum: measurement precision and regional cortical variation. *Neuroimage, 86*, 1-9.

Gail, A., Brinksmeyer, H. J., & Eckhorn, R. (2000). Contour decouples gamma activity across texture representation in monkey striate cortex. *Cerebral Cortex, 10*(9), 840-850.

Galambos, R. (1992). A comparison of certain gamma band (40-Hz) brain rhythms in cat and man. In *Induced rhythms in the brain* (pp. 201-216). Birkhäuser Boston.

Gandal, M. J., Edgar, J. C., Ehrlichman, R. S., Mehta, M., Roberts, T. P., & Siegel, S. J. (2010). Validating γ oscillations and delayed auditory responses as translational biomarkers of autism. *Biological psychiatry*, *68*(12), 1100-1106.

Gao, F., Edden, R. A., Li, M., Puts, N. A., Wang, G., Liu, C., ... & Barker, P. B. (2013). Edited magnetic resonance spectroscopy detects an age-related decline in brain GABA levels. *Neuroimage, 78*, 75-82.

Gieselmann, M. A., & Thiele, A. (2008). Comparison of spatial integration and surround suppression characteristics in spiking activity and the local field potential in macaque V1. *European Journal of Neuroscience*, *28*(3), 447-459.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry*,*160*(4), 636-645.

Gould, J., & Ashton-Smith, J. (2011). Missed diagnosis or misdiagnosis? Girls and women on the autism spectrum. *Good Autism Practice (GAP), 12*(1), 34-41.

Grandin, T. (2009). How does visual thinking work in the mind of a person with autism? A personal account. *Philosophical Transactions of the Royal Society B: Biological Sciences, 364*(1522), 1437-1442.

Grant, A. C., Henry, T. R., Fernandez, R., Hill, M. A., & Sathian, K. (2005). Somatosensory processing is impaired in temporal lobe epilepsy. *Epilepsia*,*46*(4), 534-539.

Gray, C. M., König, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature, 338*(6213), 334-337.

Gray, K. M., Tonge, B. J., & Sweeney, D. J. (2008). Using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule with young children with developmental delay: evaluating diagnostic validity.*Journal of autism and developmental disorders*, *38*(4), 657-667.

Gregory, B. L., & Plaisted-Grant, K. C. (2013). The autism-spectrum quotient and visual search: shallow and deep autistic endophenotypes. *Journal of autism and developmental disorders, 1-10.*

Grice, S. J., Spratling, M. W., Karmiloff-Smith, A., Halit, H., Csibra, G., de Haan, M., & Johnson, M. H. (2001). Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. *Neuroreport*, *12*(12), 2697-2700.

Grinsted, A., Moore, J. C., & Jevrejeva, S. (2004). Application of the cross wavelet transform and wavelet coherence to geophysical time series. *Nonlinear processes in geophysics*, *11*(5/6), 561-566.

Grinter, E. J., Maybery, M. T., Van Beek, P. L., Pellicano, E., Badcock, J. C., & Badcock, D. R. (2009). Global visual processing and self-rated autistic-like traits. *Journal of autism and developmental disorders, 39*(9), 1278-1290.

Grinter, E. J., Van Beek, P. L., Maybery, M. T., & Badcock, D. R. (2009). Brief report: Visuospatial analysis and self-rated autistic-like traits. *Journal of autism and developmental disorders, 39*(4), 670-677.

Gruber, T., Müller, M. M., Keil, A., & Elbert, T. (1999). Selective visual-spatial attention alters induced gamma band responses in the human EEG. *Clinical neurophysiology*, *110*(12), 2074-2085.

Güçlü, B., Tanidir, C., Mukaddes, N. M., & Ünal, F. (2007). Tactile sensitivity of normal and autistic children. *Somatosensory & motor research, 24*(1-2), 21-33.

Gustafsson, L. (1997a). Inadequate cortical feature maps: A neural circuit theory of autism. *Biological psychiatry, 42*(12), 1138-1147.

Gustafsson, L. (1997b). Excessive lateral feedback synaptic inhibition may cause autistic characteristics. *Journal of Autism and Developmental Disorders, 27*, 219-20.

Haesen, B., Boets, B., & Wagemans, J. (2011). A review of behavioural and electrophysiological studies on auditory processing and speech perception in autism spectrum disorders. *Research in Autism Spectrum Disorders, 5*(2), 701-714.

Haesen, B., Boets, B., & Wagemans, J. (2011). A review of behavioural and electrophysiological studies on auditory processing and speech perception in autism spectrum disorders. *Research in Autism Spectrum Disorders, 5*(2), 701-714.

Haesen, B., Boets, B., & Wagemans, J. (2011). A review of behavioural and electrophysiological studies on auditory processing and speech perception in autism spectrum disorders. *Research in Autism Spectrum Disorders, 5*(2), 701-714.

Haider, B., Häusser, M., & Carandini, M. (2013). Inhibition dominates sensory responses in the awake cortex. *Nature, 493*(7430), 97-100.

Haig, A. R., Gordon, E., De Pascalis, V., Meares, R. A., Bahramali, H., & Harris, A. (2000). Gamma activity in schizophrenia: evidence of impaired network binding?. *Clinical Neurophysiology*, *111*(8), 1461-1468.

Happé, F. G. (1994). An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *Journal of autism and Developmental disorders, 24*(2), 129-154.

Happé, F. G. (1996). Studying weak central coherence at low levels: children with autism do not succumb to visual illusions. A research note. *Journal of Child Psychology and Psychiatry, 37*(7), 873-877.

Happé, F., & Frith, U. (2006). The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *Journal of autism and developmental disorders, 36*(1), 5-25.

Harada, M., Taki, M. M., Nose, A., Kubo, H., Mori, K., Nishitani, H., & Matsuda, T. (2011). Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 tesla instrument. *Journal of autism and developmental disorders, 41*(4), 447-454.

Hardan, A. Y., Muddasani, S., Vemulapalli, M., Keshavan, M. S., & Minshew, N. J. (2006). An MRI study of increased cortical thickness in autism. *American Journal of Psychiatry*, *163*(7), 1290-1292.

Harrison, J., & Hare, D. J. (2004). Brief report: assessment of sensory abnormalities in people with autistic spectrum disorders. *Journal of Autism and Developmental Disorders, 34*(6), 727-730.

Hassan, T. H., Abdelrahman, H. M., Fattah, N. R. A., El-Masry, N. M., Hashim, H. M., El-Gerby, K. M., & Fattah, N. R. A. (2013). Blood and brain glutamate levels in children with autistic disorder. *Research in Autism Spectrum Disorders, 7*(4), 541-548.

Havenith, M. N., Yu, S., Biederlack, J., Chen, N. H., Singer, W., & Nikolić, D. (2011). Synchrony makes neurons fire in sequence, and stimulus properties determine who is ahead. *The Journal of Neuroscience*, *31*(23), 8570-8584.

Heaton, P., Hermelin, B., & Pring, L. (1998). Autism and pitch processing: A precursor for savant musical ability?. *Music perception,* 291-305.

Heaton, P., Hudry, K., Ludlow, A., & Hill, E. (2008). Superior discrimination of speech pitch and its relationship to verbal ability in autism spectrum disorders. *Cognitive neuropsychology, 25*(6), 771-782.

Heaton, P., Ludlow, A., & Roberson, D. (2008). When less is more: Poor discrimination but good colour memory in autism. *Research in Autism Spectrum Disorders, 2*(1), 147-156.

Hensch, T. K. (2005). Critical period mechanisms in developing visual cortex. *Current topics in developmental biology, 69*, 215-237.

Hensch, T. K., & Stryker, M. P. (2004). Columnar architecture sculpted by GABA circuits in developing cat visual cortex. *Science, 303*(5664), 1678-1681.

Herrmann, C. S., & Mecklinger, A. (2001). Gamma activity in human EEG is related to highspeed memory comparisons during object selective attention.*Visual Cognition*, *8*(3-5), 593-608.

Herrmann, C. S., Mecklinger, A., & Pfeifer, E. (1999). Gamma responses and ERPs in a visual classification task. *Clinical Neurophysiology*, *110*(4), 636-642.

Herrmann, C. S., Munk, M. H., & Engel, A. K. (2004). Cognitive functions of gamma-band activity: memory match and utilization. *Trends in cognitive sciences*, *8*(8), 347-355.

Hillyard, S. A., & Picton, T. W. (1987). Electrophysiology of cognition. *Comprehensive Physiology*.

Hoekstra, R. A., Bartels, M., Cath, D. C., & Boomsma, D. I. (2008). Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): a study in Dutch population and patient groups. *Journal of autism and developmental disorders*, *38*(8), 1555-1566.

Horder, J., Wilson, C. E., Mendez, M. A., & Murphy, D. G. (2014). Autistic traits and abnormal sensory experiences in adults. *Journal of autism and developmental disorders, 44*(6), 1461-1469.

Horlin, C., Albrecht, M. A., Falkmer, M., Leung, D., Ordqvist, A., Tan, T., ... & Falkmer, T. (2014). Visual search strategies of children with and without autism spectrum disorders during an embedded figures task. *Research in Autism Spectrum Disorders, 8*(5), 463-471.

Horowski, R., & Dorow, R. (2002). Anxiogenic, not psychotogenic, properties of the partial inverse benzodiazepine receptor agonist FG 7142 in man.*Psychopharmacology*, *162*(2), 223-224.

Houtgast, T. (1972). Psychophysical evidence for lateral inhibition in hearing. *The Journal of the Acoustical Society of America, 51*(6B), 1885-1894.

Howlin, P. (1997). *Autism. Preparing for adulthood.* London: Routledge

Hoy, J. A., Hatton, C., & Hare, D. (2004). Weak central coherence: a cross-domain phenomenon specific to autism?. *Autism, 8*(3), 267-281.

Hubel, D. H., & Wiesel, T. N. (1968). Receptive fields and functional architecture of monkey striate cortex. *The Journal of physiology, 195*(1), 215-243.

Hughes, J. R., & Melyn, M. (2005). EEG and seizures in autistic children and adolescents: further findings with therapeutic implications. *Clinical EEG and Neuroscience, 36*(1), 15-20.

Hurlbert, A., Loveridge, C., Ling, Y., Kourkoulou, A., & Leekam, S. (2011). Color discrimination and preference in autism spectrum disorder. *Journal of Vision, 11*(11), 429-429.

Hussman, J. P. (2001). Letters to the editor: suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *Journal of autism and developmental disorders, 31*(2), 247-248.

Iarocci, G., & Armstrong, K. (2014). Age‐Related Changes in Conjunctive Visual Search in Children with and without ASD. *Autism Research, 7*(2), 229-236.

Inui, N., Yamanishi, M., & Tada, S. (1995). Simple reaction times and timing of serial reactions of adolescents with mental retardation, autism, and Down syndrome. *Perceptual and motor skills*, *81*(3), 739-745.

Jarrold, C., Gilchrist, I. D., & Bender, A. (2005). Embedded figures detection in autism and typical development: Preliminary evidence of a double dissociation in relationships with visual search. *Developmental science, 8*(4), 344-351.

Jia, X., Xing, D., & Kohn, A. (2013). No consistent relationship between gamma power and peak frequency in macaque primary visual cortex. *The Journal of Neuroscience*, *33*(1), 17-25.

Jolliffe, T., & Baron-Cohen, S. (1997). Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test?. *Journal of Child Psychology and Psychiatry, 38*(5), 527-534.

Jones, C. R., Happé, F., Baird, G., Simonoff, E., Marsden, A. J., Tregay, J., ... & Charman, T. (2009). Auditory discrimination and auditory sensory behaviours in autism spectrum disorders. *Neuropsychologia, 47*(13), 2850-2858.

Jones, R., Quigney, C., & Huws, J. (2003). First-hand accounts of sensory perceptual experiences in autism: A qualitative analysis. *Journal of Intellectual and Developmental Disability, 28*(2), 112-121.

Joseph, R. M., Keehn, B., Connolly, C., Wolfe, J. M., & Horowitz, T. S. (2009). Why is visual search superior in autism spectrum disorder?. *Developmental science, 12*(6), 1083-1096.

Kaiser, G. (2010). *A friendly guide to wavelets*. Springer Science & Business Media.

Kaiser, J., & Lutzenberger, W. (2005). Human gamma-band activity: a window to cognitive processing. *Neuroreport*, *16*(3), 207-211.

Kaland, N., Mortensen, E. L., & Smith, L. (2007). Disembedding performance in children and adolescents with Asperger syndrome or high-functioning autism. *Autism, 11*(1), 81-92.

Kaldy, Z., Kraper, C., Carter, A. S., & Blaser, E. (2011). Toddlers with autism spectrum disorder are more successful at visual search than typically developing toddlers. *Developmental science, 14*(5), 980-988.

Kanner, L. (1943). *Autistic disturbances of affective contact* (pp. 217-250). publisher not identified.

Katzner, S., Busse, L., & Carandini, M. (2011). GABAA inhibition controls response gain in visual cortex. *The Journal of neuroscience, 31*(16), 5931-5941.

Keehn, B., Brenner, L. A., Ramos, A. I., Lincoln, A. J., Marshall, S. P., & Müller, R. A. (2009). Brief report: eye-movement patterns during an embedded figures test in children with ASD. *Journal of autism and developmental disorders, 39*(2), 383-387.

Keehn, B., Brenner, L., Palmer, E., Lincoln, A. J., & Müller, R. A. (2008). Functional brain organization for visual search in ASD. *Journal of the International Neuropsychological Society, 14*(06), 990-1003.

Keehn, B., Shih, P., Brenner, L. A., Townsend, J., & Müller, R. A. (2013). Functional connectivity for an “Island of sparing” in autism spectrum disorder: an fMRI study of visual search. *Human brain mapping, 34*(10), 2524-2537.

Kéïta, L., Mottron, L., & Bertone, A. (2010). Far visual acuity is unremarkable in autism: Do we need to focus on crowding?. *Autism Research, 3*(6), 333-341.

Kéïta, L., Mottron, L., Dawson, M., & Bertone, A. (2011). Atypical lateral connectivity: a neural basis for altered visuospatial processing in autism. Biological psychiatry, 70(9), 806-811.

Kemner, C., Oranje, B., Verbaten, M. N., & van Engeland, H. (2002). Normal P50 gating in children with autism. *The Journal of clinical psychiatry*, *63*(3), 214-217.

Kemner, C., Van Ewijk, L., Van Engeland, H., & Hooge, I. (2008). Brief report: Eye movements during visual search tasks indicate enhanced stimulus discriminability in subjects with PDD. *Journal of Autism and Developmental Disorders, 38*(3), 553-557.

Kern, J. K., Trivedi, M. H., Grannemann, B. D., Garver, C. R., Johnson, D. G., Andrews, A. A., ... & Schroeder, J. L. (2007). Sensory correlations in autism. *Autism, 11*(2), 123-134.

Khalfa, S., Bruneau, N., Rogé, B., Georgieff, N., Veuillet, E., Adrien, J. L., ... & Collet, L. (2004). Increased perception of loudness in autism. *Hearing research, 198*(1), 87-92.

Koh, H. C., Milne, E., & Dobkins, K. (2010a). Spatial contrast sensitivity in adolescents with autism spectrum disorders. *Journal of autism and developmental disorders, 40*(8), 978-987.

Koh, H. C., Milne, E., & Dobkins, K. (2010b). Contrast sensitivity for motion detection and direction discrimination in adolescents with autism spectrum disorders and their siblings. *Neuropsychologia, 48*(14), 4046-4056.

Kreiter, A. K., & Singer, W. (1992). Oscillatory neuronal responses in the visual cortex of the awake macaque monkey. *European Journal of Neuroscience*,*4*(4), 369-375.

Lally, N., Mullins, P. G., Roberts, M. V., Price, D., Gruber, T., & Haenschel, C. (2014). Glutamatergic correlates of gamma-band oscillatory activity during cognition: a concurrent ER-MRS and EEG study. *Neuroimage*, *85*, 823-833.

Landrigan, P. J. (2010). What causes autism? Exploring the environmental contribution. *Current opinion in pediatrics*, *22*(2), 219-225.

Lee, D. K., Koch, C., & Braun, J. (1997). Spatial vision thresholds in the near absence of attention. *Vision research*, *37*(17), 2409-2418.

Lee, K. H., Williams, L., Haig, A., & Gordon, E. (2003). " Gamma (40 Hz) phase synchronicity" and symptom dimensions in schizophrenia. *Cognitive Neuropsychiatry*, *8*(1), 57-71.

Lee, P. S., Foss-Feig, J., Henderson, J. G., Kenworthy, L. E., Gilotty, L., Gaillard, W. D., & Vaidya, C. J. (2007). Atypical neural substrates of Embedded Figures Task performance in children with Autism Spectrum Disorder. *Neuroimage, 38*(1), 184-193.

Leek, M. R. (2001). Adaptive procedures in psychophysical research.*Perception & psychophysics*, *63*(8), 1279-1292.

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *Journal of autism and developmental disorders, 37*(5), 894-910.

Lewis, D. A., Cho, R. Y., Carter, C. S., Eklund, K., Forster, S., Kelly, M. A., & Montrose, D. (2008). Subunit-selective modulation of GABA type A receptor neurotransmission and cognition in schizophrenia. *The American journal of psychiatry*, *165*(12), 1585-1593.

Li, G., Yang, Y., Liang, Z., Xia, J., & Zhou, Y. (2008). GABA-mediated inhibition correlates with orientation selectivity in primary visual cortex of cat. *Neuroscience, 155*(3), 914-922.

Light, G. A., Hsu, J. L., Hsieh, M. H., Meyer-Gomes, K., Sprock, J., Swerdlow, N. R., & Braff, D. L. (2006). Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biological psychiatry*,*60*(11), 1231-1240.

Lima, B., Singer, W., Chen, N. H., & Neuenschwander, S. (2010). Synchronization dynamics in response to plaid stimuli in monkey V1. *Cerebral cortex*, *20*(7), 1556-1573.

Lockyer, L., & Rutter, M. (1970). A Five‐to Fifteen‐Year Follow‐up Study of Infantile Psychosis: IV. Patterns of Cognitive Ability. *British Journal of Social and Clinical Psychology, 9*(2), 152-163.

Lord, C., Risi, S., Lambrecht, L., Cook Jr, E. H., Leventhal, B. L., DiLavore, P. C., ... & Rutter, M. (2000). The Autism Diagnostic Observation Schedule—Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of autism and developmental disorders, 30*(3), 205-223.

Lord, C., Risi, S., Lambrecht, L., Cook Jr, E. H., Leventhal, B. L., DiLavore, P. C., ... & Rutter, M. (2000). The Autism Diagnostic Observation Schedule—Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of autism and developmental disorders*,*30*(3), 205-223.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of autism and developmental disorders, 24*(5), 659-685.

Machado, C., Estevez, M., Melillo, R., Leisman, G., Carrick, F. R., Machado, A., ... & Carballo, M. (2013). QUANTITATIVE RESTING EEG IN THE AUTISTIC SPECTRUM DISORDER. *International Journal of Child Health and Human Development*, *6*(4), 511.

Makeig, S., Jung, T. P., Bell, A. J., Ghahremani, D., & Sejnowski, T. J. (1997). Blind separation of auditory event-related brain responses into independent components. *Proceedings of the National Academy of Sciences*, *94*(20), 10979-10984.

Maldonado, P. E., Friedman-Hill, S., & Gray, C. M. (2000). Dynamics of striate cortical activity in the alert macaque: II. Fast time scale synchronization. *Cerebral Cortex, 10*(11), 1117-1131.

Manjaly, Z. M., Bruning, N., Neufang, S., Stephan, K. E., Brieber, S., Marshall, J. C., ... & Fink, G. R. (2007). Neurophysiological correlates of relatively enhanced local visual search in autistic adolescents. *Neuroimage, 35*(1), 283-291.

Markram, H., Rinaldi, T., & Markram, K. (2007). The intense world syndrome–an alternative hypothesis for autism. *Frontiers in Neuroscience, 1*(1), 77.

Markram, K., Rinaldi, T., La Mendola, D., Sandi, C., & Markram, H. (2008). Abnormal fear conditioning and amygdala processing in an animal model of autism. *Neuropsychopharmacology, 33*(4), 901-912.

MATLAB, 6.1, The MathWorks Inc., Natick, MA, 2000.

Maxwell, C. R., Villalobos, M. E., Schultz, R. T., Herpertz-Dahlmann, B., Konrad, K., & Kohls, G. (2013). Atypical laterality of resting gamma oscillations in autism spectrum disorders. *Journal of autism and developmental disorders*,*45*(2), 292-297.

McIntosh, D. N., Miller, L. J., & Shyu, V. (1999). Development and validation of the Short Sensory Profile. In W. Dunn (Ed.), *Sensory Profile manual* (pp. 59–73). San Antonio, TX: Psychological Corporation.

McKavanagh, R., Buckley, E., & Chance, S. A. (2015). Wider minicolumns in autism: a neural basis for altered processing?. *Brain.*

McVicar, K. A., Ballaban-Gil, K., Rapin, I., Moshe, S. L., & Shinnar, S. (2005). Epileptiform EEG abnormalities in children with language regression. *Neurology, 65*(1), 129-131.

Mecarelli, O., Rinalduzzi, S., & Accornero, N. (2001). Changes in color vision after a single dose of vigabatrin or carbamazepine in healthy volunteers.*Clinical neuropharmacology*, *24*(1), 23-26.

Meilleur, A. A. S., Berthiaume, C., Bertone, A., & Mottron, L. (2014). Autism-specific covariation in perceptual performances:“g” or “p” factor?.

Merzenich, M. M. (2001). Cortical plasticity contributing to child development. Mechanisms of cognitive development: *Behavioral and neural perspectives,* 67-95.

Merzenich, M.M., Saunders, G., Jenkins, W.M., S.L., Peterson, B.E., & Tallal, P. (1999). Pervasive Developmental Disorders: Listening Training and Language Abilities. In S.H. Broman & J.M. Fletcher (Eds.), *The Changing Nervous System: Neurobehavioral Consequences of Early Brain Disorders.* (pp. 365-385). Oxford: Oxford University Press.

Milne, E. (2011). Increased intra-participant variability in children with autistic spectrum disorders: evidence from single-trial analysis of evoked EEG.*Frontiers in psychology*, *2*.

Milne, E., & Scope, A. (2008). Are children with autistic spectrum disorders susceptible to contour illusions?. *British Journal of Developmental Psychology, 26*(1), 91-102.

Milne, E., Dunn, S. A., Freeth, M., & Rosas-Martinez, L. (2013). Visual search performance is predicted by the degree to which selective attention to features modulates the ERP between 350 and 600ms. *Neuropsychologia, 51*(6), 1109-1118.

Milne, E., Scope, A., Pascalis, O., Buckley, D., & Makeig, S. (2009). Independent component analysis reveals atypical electroencephalographic activity during visual perception in individuals with autism. *Biological psychiatry*,*65*(1), 22-30.

Milne, E., Swettenham, J., Hansen, P., Campbell, R., Jeffries, H., & Plaisted, K. (2002). High motion coherence thresholds in children with autism. J*ournal of Child Psychology and Psychiatry, 43*(2), 255-263.

Milner, P. M. (1974). A model for visual shape recognition. *Psychological review, 81*(6), 521.

Mitzdorf, U., & Singer, W. (1979). Excitatory synaptic ensemble properties in the visual cortex of the macaque monkey: a current source density analysis of electrically evoked potentials. *Journal of Comparative Neurology*, *187*(1), 71-83.

Möhler, H. (2012). The GABA system in anxiety and depression and its therapeutic potential. *Neuropharmacology*, *62*(1), 42-53.

Mottron, l., & Burack, J.A. (2001). Enhanced Perceptual Functioning in theDevelopment of Autism. In J.A. Burack, T. Charman., N. Yirmiya & P.R. Zelazo (Eds.), *The Development of Autism: Perspectives from Theory and Research* (pp. 131–48). Mahwah, NJ: Erlbaum.

Mottron, L., Burack, J. A., Iarocci, G., Belleville, S., & Enns, J. T. (2003). Locally oriented perception with intact global processing among adolescents with high‐functioning autism: evidence from multiple paradigms. *Journal of Child Psychology and Psychiatry, 44*(6), 904-913.

Mottron, L., Burack, J. A., Stauder, J. E., & Robaey, P. (1999). Perceptual processing among high-functioning persons with autism. *Journal of Child Psychology and Psychiatry, 40*(02), 203-211.

Mottron, L., Dawson, M., Soulieres, I., Hubert, B., & Burack, J. (2006). Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *Journal of autism and developmental disorders, 36*(1), 27-43.

Mottron, L., Peretz, I., & Menard, E. (2000). Local and Global Processing of Music in High‐functioning Persons with Autism: Beyond Central Coherence?. *Journal of Child Psychology and Psychiatry, 41*(8), 1057-1065.

Mountcastle, V. B. (1997). The columnar organization of the neocortex. *Brain, 120*(4), 701-722.

Müller, K., Lohmann, G., Neumann, J., Grigutsch, M., Mildner, T., & von Cramon, D. Y. (2004). Investigating the wavelet coherence phase of the BOLD signal. *Journal of Magnetic Resonance Imaging*, *20*(1), 145-152.

Müller, M. M., Bosch, J., Elbert, T., Kreiter, A., Sosa, M. V., Sosa, P. V., & Rockstroh, B. (1996). Visually induced gamma-band responses in human electroencephalographic activity—a link to animal studies. *Experimental Brain Research*, *112*(1), 96-102.

Müller, M. M., Gruber, T., & Keil, A. (2000). Modulation of induced gamma band activity in the human EEG by attention and visual information processing. *International Journal of Psychophysiology*, *38*(3), 283-299.

Müller, M. M., Junghöfer, M., Elbert, T., & Rochstroh, B. (1997). Visually induced gamma-band responses to coherent and incoherent motion: a replication study. *NeuroReport*, *8*(11), 2575-2579.

Muthukumaraswamy, S. D., & Singh, K. D. (2009). Functional decoupling of BOLD and gamma-band amplitudes in human primary visual cortex. *Human brain mapping*, *30*(7), 2000-2007.

Nagamoto, H. T., Adler, L. E., Waldo, M. C., & Freedman, R. (1989). Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. *Biological psychiatry*, *25*(5), 549-561.

O'Riordan, M. A., Plaisted, K. C., Driver, J., & Baron-Cohen, S. (2001). Superior visual search in autism. *Journal of Experimental Psychology: Human Perception and Performance, 27*(3), 719.

O'Riordan, M., & Plaisted, K. (2001). Enhanced discrimination in autism. *The Quarterly Journal of Experimental Psychology: Section A, 54*(4), 961-979.

O’riordan, M. A. (2004). Superior visual search in adults with autism. *Autism, 8*(3), 229-248.

O’Riordan, M., & Passetti, F. (2006). Discrimination in autism within different sensory modalities. *Journal of autism and developmental disorders, 36*(5), 665-675.

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2010). Decreased GABAB receptors in the cingulate cortex and fusiform gyrus in autism. *Journal of neurochemistry, 114*(5), 1414-1423.

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2011). Reduced GABA A receptors and benzodiazepine binding sites in the posterior cingulate cortex and fusiform gyrus in autism. *Brain research, 1380*, 218-228.

Oblak, A., Gibbs, T. T., & Blatt, G. J. (2009). Decreased GABAA receptors and benzodiazepine binding sites in the anterior cingulate cortex in autism. *Autism Research, 2*(4), 205-219.

Onton, J., & Makeig, S. (2006). Information-based modeling of event-related brain dynamics. *Progress in brain research*, *159*, 99-120.

Oostendorp, T. F., & Van Oosterom, A. (1989). Source parameter estimation in inhomogeneous volume conductors of arbitrary shape. *Biomedical Engineering, IEEE Transactions on*, *36*(3), 382-391.

Orekhova, E. V., Stroganova, T. A., Nygren, G., Tsetlin, M. M., Posikera, I. N., Gillberg, C., & Elam, M. (2007). Excess of high frequency electroencephalogram oscillations in boys with autism. *Biological psychiatry*,*62*(9), 1022-1029.

Orekhova, E. V., Stroganova, T. A., Prokofyev, A. O., Nygren, G., Gillberg, C., & Elam, M. (2008). Sensory gating in young children with autism: relation to age, IQ, and EEG gamma oscillations. *Neuroscience letters*, *434*(2), 218-223.

Ozonoff, S., Pennington, B. F., & Rogers, S. J. (1991). Executive function deficits in high-functioning autistic individuals: Relationship to theory of mind. *Journal of child Psychology and Psychiatry, 32*(7), 1081-1105.

Ozonoff, S., Strayer, D. L., McMahon, W. M., & Filloux, F. (1994). Executive function abilities in autism and Tourette syndrome: An information processing approach. *Journal of child Psychology and Psychiatry, 35*(6), 1015-1032.

Ozonoff, S., Young, G. S., Carter, A., Messinger, D., Yirmiya, N., Zwaigenbaum, L., ... & Stone, W. L. (2011). Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics, 128*(3), e488-e495.

Pantev, C. (1995). Evoked and induced gamma-band activity of the human cortex. *Brain topography*, *7*(4), 321-330.

Papanikolaou, K., Paliokosta, E., Houliaras, G., Vgenopoulou, S., Giouroukou, E., Pehlivanidis, A., ... & Tsiantis, I. (2009). Using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-Generic for the diagnosis of autism spectrum disorders in a Greek sample with a wide range of intellectual abilities. *Journal of autism and developmental disorders*,*39*(3), 414-420.

Pellicano, E., & Burr, D. (2012). When the world becomes ‘too real’: a Bayesian explanation of autistic perception. *Trends in cognitive sciences, 16*(10), 504-510.

Pellicano, E., Gibson, L., Maybery, M., Durkin, K., & Badcock, D. R. (2005). Abnormal global processing along the dorsal visual pathway in autism: a possible mechanism for weak visuospatial coherence?. *Neuropsychologia, 43*(7), 1044-1053.

Pellicano, E., Gibson, L., Maybery, M., Durkin, K., & Badcock, D. R. (2005). Abnormal global processing along the dorsal visual pathway in autism: a possible mechanism for weak visuospatial coherence?. *Neuropsychologia, 43*(7), 1044-1053.

Pellicano, E., Jeffery, L., Burr, D., & Rhodes, G. (2007). Abnormal adaptive face-coding mechanisms in children with autism spectrum disorder. *Current Biology, 17(*17), 1508-1512.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of child psychology and psychiatry, 37*(1), 51-87.

Perreault, A., Gurnsey, R., Dawson, M., Mottron, L., & Bertone, A. (2011). Increased sensitivity to mirror symmetry in autism. *PLoS One, 6*(4), e19519-e19519.

Perry, G., Hamandi, K., Brindley, L. M., Muthukumaraswamy, S. D., & Singh, K. D. (2013). The properties of induced gamma oscillations in human visual cortex show individual variability in their dependence on stimulus size. *Neuroimage*,*68*, 83-92.

Persico, A. M., & Sacco, R. (2014). Endophenotypes in Autism Spectrum Disorders. In *Comprehensive Guide to Autism* (pp. 77-95). Springer New York.

Piven, J., Arndt, S., Bailey, J., Havercamp, S., Andreasen, N. C., & Palmer, P. (1995). An MRI study of brain size in autism. *American Journal of Psychiatry*,*152*(8), 1145-1149.

Piven, J., Palmer, P., Jacobi, D., Childress, D., & Arndt, S. (1997). Broader autism phenotype: evidence from a family history study of multiple-incidence autism families. *American Journal of Psychiatry, 154*(2), 185-190.

Pizzarelli, R., & Cherubini, E. (2011). Alterations of GABAergic signaling in autism spectrum disorders. *Neural plasticity,* 2011.

Plaisted, K. C. (2001). Reduced generalization in autism: An alternative to weak central coherence. In J.A. Burack, T. Charman., N. Yirmiya & P.R. Zelazo (Eds.),

Plaisted, K., O'Riordan, M., & Baron-Cohen, S. (1998b). Enhanced visual search for a conjunctive target in autism: A research note. *Journal of Child Psychology and Psychiatry, 39*(05), 777-783.

Plaisted, K., O'Riordan, M., & Baron-Cohen, S. (1998a). Enhanced discrimination of novel, highly similar stimuli by adults with autism during a perceptual learning task. *Journal of Child Psychology and Psychiatry, 39*(5), 765-775.

Plaisted, K., Swettenham, J., & Rees, L. (1999). Children with autism show local precedence in a divided attention task and global precedence in a selective attention task. *Journal of child psychology and psychiatry, 40*(05), 733-742.

Posner, M. I., & Raichle, M. E. (1994). *Images of mind.* Scientific American Library/Scientific American Books.

Pulvermüller, F., Birbaumer, N., Lutzenberger, W., & Mohr, B. (1997). High-frequency brain activity: its possible role in attention, perception and language processing. *Progress in neurobiology*, *52*(5), 427-445.

Purcell, A. E., Jeon, O. H., Zimmerman, A. W., Blue, M. E., & Pevsner, J. (2001). Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. *Neurology, 57*(9), 1618-1628.

Puts, N. A., & Edden, R. A. (2012). In vivo magnetic resonance spectroscopy of GABA: a methodological review. *Progress in nuclear magnetic resonance spectroscopy, 60,* 29-41.

Puts, N. A., Wodka, E. L., Tommerdahl, M., Mostofsky, S. H., & Edden, R. A. (2014). Impaired tactile processing in children with autism spectrum disorder. Journal of neurophysiology, 111(9), 1803-1811.

Ratcliff, R. (1978). A theory of memory retrieval. *Psychological review*, *85*(2), 59.

Ray, S., & Maunsell, J. H. (2010). Differences in gamma frequencies across visual cortex restrict their possible use in computation. *Neuron*, *67*(5), 885-896.

Ray, S., & Maunsell, J. H. (2011). Different origins of gamma rhythm and high-gamma activity in macaque visual cortex. *PLoS Biol*, *9*(4), e1000610.

Ribary, U., Ioannides, A. A., Singh, K. D., Hasson, R., Bolton, J. P., Lado, F., ... & Llinas, R. (1991). Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans. *Proceedings of the National Academy of Sciences*,*88*(24), 11037-11041.

Ring, H. A., Baron-Cohen, S., Wheelwright, S., Williams, S. C., Brammer, M., Andrew, C., & Bullmore, E. T. (1999). Cerebral correlates of preserved cognitive skills in autism. *Brain, 122*(7), 1305-1315.

Robel, L., Rousselot-Pailley, B., Fortin, C., Levy-Rueff, M., Golse, B., & Falissard, B. (2014). Subthreshold traits of the broad autistic spectrum are distributed across different subgroups in parents, but not siblings, of probands with autism. *European child & adolescent psychiatry*, *23*(4), 225-233.

Robertson, A. E., & Simmons, D. R. (2012). The relationship between sensory sensitivity and autistic traits in the general population. *Journal of Autism and Developmental Disorders, 43*(4), 775-784.

Robertson, C. E., Kravitz, D. J., Freyberg, J., Baron-Cohen, S., & Baker, C. I. (2013). Slower rate of binocular rivalry in autism. *The Journal of Neuroscience, 33*(43), 16983-16991.

Rodriguez, E., George, N., Lachaux, J. P., Martinerie, J., Renault, B., & Varela, F. J. (1999). Perception's shadow: long-distance synchronization of human brain activity. *Nature, 397*(6718), 430-433.

Rogers, S. J. (1998). Empirically supported comprehensive treatments for young children with autism. *Journal of clinical child psychology, 27*(2), 168-179.

Rojas, D. C., & Wilson, L. B. (2014). γ-band abnormalities as markers of autism spectrum disorders. *Biomarkers in medicine*, *8*(3), 353-368.

Rojas, D. C., Becker, K. M., & Wilson, L. B. (2015). Magnetic Resonance Spectroscopy Studies of Glutamate and GABA in Autism: Implications for Excitation-Inhibition Imbalance Theory. *Current Developmental Disorders Reports, 2*(1), 46-57.

Rojas, D. C., Maharajh, K., Teale, P., & Rogers, S. J. (2008). Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism. *BMC psychiatry*, *8*(1), 66.

Rojas, D. C., Singel, D., Steinmetz, S., Hepburn, S., & Brown, M. S. (2014). Decreased left perisylvian GABA concentration in children with autism and unaffected siblings. *Neuroimage, 86,* 28-34.

Rolf, L. H., Haarmann, F. Y., Grotemeyer, K. H., & Kehrer, H. (1993). Serotonin and amino acid content in platelets of autistic children. *Acta Psychiatrica Scandinavica, 87(*5), 312-316.

Ropar, D., & Mitchell, P. (1999). Are individuals with autism and Asperger's syndrome susceptible to visual illusions?. *Journal of child psychology and psychiatry, 40*(08), 1283-1293.

Ropar, D., & Mitchell, P. (2001). Susceptibility to illusions and performance on visuospatial tasks in individuals with autism. *Journal of Child Psychology and Psychiatry, 42*(04), 539-549.

Ropar, D., & Mitchell, P. (2001). Susceptibility to illusions and performance on visuospatial tasks in individuals with autism. *Journal of Child Psychology and Psychiatry, 42*(04), 539-549.

Rosenberg, A., Patterson, J. S., & Angelaki, D. E. (2015). A computational perspective on autism. *Proceedings of the National Academy of Sciences*,*112*(30), 9158-9165.

Rosenhall, U., Johansson, E., & Gillberg, C. (1988). Oculomotor findings in autistic children. *The Journal of Laryngology & Otology, 102*(05), 435-439.

Rossi, P. G., Parmeggiani, A., Bach, V., Santucci, M., & Visconti, P. (1995). EEG features and epilepsy in patients with autism. *Brain and Development, 17*(3), 169-174.

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior, 2*(5), 255-267.

Rupprecht, R., Rammes, G., Eser, D., Baghai, T. C., Schüle, C., Nothdurfter, C., ... & Kucher, K. (2009). Translocator protein (18 kD) as target for anxiolytics without benzodiazepine-like side effects. *Science*, *325*(5939), 490-493.

Russell, J. E. (1997). *Autism as an executive disorder.* Oxford University Press.

Said, C. P., Egan, R. D., Minshew, N. J., Behrmann, M., & Heeger, D. J. (2013). Normal binocular rivalry in autism: implications for the excitation/inhibition imbalance hypothesis. *Vision research, 77,* 59-66.

Samson, F., Mottron, L., Soulieres, I., & Zeffiro, T. A. (2012). Enhanced visual functioning in autism: An ALE meta‐analysis. *Human brain mapping, 33*(7), 1553-1581.

Sanacora, G., Mason, G. F., Rothman, D. L., & Krystal, J. H. (2002). Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *American Journal of Psychiatry*, *159*(4), 663-665.

Sanacora, G., Mason, G. F., Rothman, D. L., Behar, K. L., Hyder, F., Petroff, O. A., ... & Krystal, J. H. (1999). Reduced cortical γ-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy.*Archives of general psychiatry*, *56*(11), 1043-1047.

Sanacora, G., Rothman, D. L., Mason, G., & Krystal, J. H. (2003). Clinical studies implementing glutamate neurotransmission in mood disorders. *Annals of the New York Academy of Sciences*, *1003*(1), 292-308.

Schlooz, W. A., Hulstijn, W., van den Broek, P. J., van der Pijll, A. C., Gabreëls, F., van der Gaag, R. J., & Rotteveel, J. J. (2006). Fragmented visuospatial processing in children with pervasive developmental disorder. *Journal of Autism and Developmental Disorders, 36*(8), 1025-1037.

Schwarzkopf, D. S., Anderson, E. J., de Haas, B., White, S. J., & Rees, G. (2014). Larger extrastriate population receptive fields in autism spectrum disorders. *The Journal of Neuroscience, 34*(7), 2713-2724.

Schwarzkopf, D. S., Robertson, D. J., Song, C., Barnes, G. R., & Rees, G. (2012). The frequency of visually induced gamma-band oscillations depends on the size of early human visual cortex. *The Journal of Neuroscience*, *32*(4), 1507-1512.

Shah, A., & Frith, U. (1983). An islet of ability in autistic children: A research note. *Journal of child Psychology and Psychiatry, 24*(4), 613-620.

Shah, A., & Frith, U. (1993). Why do autistic individuals show superior performance on the block design task?. *Journal of Child Psychology and Psychiatry, 34*(8), 1351-1364.

Shimmura, C., Suzuki, K., Iwata, Y., Tsuchiya, K. J., Ohno, K., Matsuzaki, H., ... & Mori, N. (2013). Enzymes in the glutamate-glutamine cycle in the anterior cingulate cortex in postmortem brain of subjects with autism. *Mol Autism, 4*(1), 6.

Shulman, G. L., Wilson, J., & Sheehy, J. B. (1985). Spatial determinants of the distribution of attention. *Perception & Psychophysics*, *37*(1), 59-65.

Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *Journal of autism and developmental disorders, 26*(4), 389-406.

Sillito, A. M. (1975). The effectiveness of bicuculline as an antagonist of GABA and visually evoked inhibition in the cat's striate cortex. *The Journal of physiology, 250(*2), 287-304.

Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision research, 49*(22), 2705-2739.

Singer, W., & Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annual review of neuroscience, 18*(1), 555-586.

Skuse, D. H. (2000). Imprinting, the X-chromosome, and the male brain: explaining sex differences in the liability to autism. *Pediatric Research, 47*(1), 9-9.

Snijders, T. M., Milivojevic, B., & Kemner, C. (2013). Atypical excitation–inhibition balance in autism captured by the gamma response to contextual modulation. *Neuroimage: Clinical*, *3*, 65-72.

Sokhadze, E. M., El-Baz, A., Baruth, J., Mathai, G., Sears, L., & Casanova, M. F. (2009). Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. *Journal of autism and developmental disorders, 39*(4), 619-634.

Sokhadze, E. M., El-Baz, A., Baruth, J., Mathai, G., Sears, L., & Casanova, M. F. (2009). Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. *Journal of autism and developmental disorders*, *39*(4), 619-634.

Sokolov, A., Pavlova, M., Lutzenberger, W., & Birbaumer, N. (2004). Reciprocal modulation of neuromagnetic induced gamma activity by attention in the human visual and auditory cortex. *Neuroimage*, *22*(2), 521-529.

Song, C., Schwarzkopf, D. S., Kanai, R., & Rees, G. (2015). Neural Population Tuning Links Visual Cortical Anatomy to Human Visual Perception. *Neuron*,*85*(3), 641-656.

Spencer, J., O'Brien, J., Riggs, K., Braddick, O., Atkinson, J., & Wattam-Bell, J. (2000). Motion processing in autism: evidence for a dorsal stream deficiency. *Neuroreport, 11*(12), 2765-2767.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., & McCarley, R. W. (2003). Abnormal neural synchrony in schizophrenia.*The Journal of Neuroscience*, *23*(19), 7407-7411.

Spencer, M. D., Holt, R. J., Chura, L. R., Calder, A. J., Suckling, J., Bullmore, E. T., & Baron-Cohen, S. (2012). Atypical activation during the Embedded Figures Task as a functional magnetic resonance imaging endophenotype of autism. *Brain, 135*(11), 3469-3480.

Stagg, C. J., Bachtiar, V., & Johansen-Berg, H. (2011). What are we measuring with GABA magnetic resonance spectroscopy? *Communicative & Integrative Biology*, *4*(5), 573–575.

Stam, C. J., van Walsum, A. M. V. C., Pijnenburg, Y. A., Berendse, H. W., de Munck, J. C., Scheltens, P., & van Dijk, B. W. (2002). Generalized synchronization of MEG recordings in Alzheimer’s disease: evidence for involvement of the gamma band. *Journal of Clinical Neurophysiology*, *19*(6), 562-574.

Stanutz, S., Wapnick, J., & Burack, J. A. (2014). Pitch discrimination and melodic memory in children with autism spectrum disorders. Autism, 18(2), 137-147.

Stewart, M. E., Watson, J., Allcock, A. J., & Yaqoob, T. (2009). Autistic traits predict performance on the block design. *Autism, 13*(2), 133-142.

Stroganova, T. A., Orekhova, E. V., Prokofyev, A. O., Tsetlin, M. M., Gratchev, V. V., Morozov, A. A., & Obukhov, Y. V. (2012). High-frequency oscillatory response to illusory contour in typically developing boys and boys with autism spectrum disorders. *Cortex*, *48*(6), 701-717.

Sun, L., Grützner, C., Bölte, S., Wibral, M., Tozman, T., Schlitt, S., ... & Uhlhaas, P. J. (2012). Impaired gamma-band activity during perceptual organization in adults with autism spectrum disorders: evidence for dysfunctional network activity in frontal-posterior cortices. *The Journal of Neuroscience*, *32*(28), 9563-9573.

Swettenham, J. B., Muthukumaraswamy, S. D., & Singh, K. D. (2009). Spectral properties of induced and evoked gamma oscillations in human early visual cortex to moving and stationary stimuli. *Journal of neurophysiology*, *102*(2), 1241-1253.

Tabuchi, K., Blundell, J., Etherton, M. R., Hammer, R. E., Liu, X., Powell, C. M., & Südhof, T. C. (2007). A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. *Science, 318*(5847), 71-76.

Takarae, Y., Minshew, N. J., Luna, B., & Sweeney, J. A. (2004). Oculomotor abnormalities parallel cerebellar histopathology in autism. *Journal of Neurology, Neurosurgery & Psychiatry, 75(*9), 1359-1361.

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in cognitive sciences*, *3*(4), 151-162.

Tallon-Baudry, C., Bertrand, O., Delpuech, C., & Pernier, J. (1996). Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *The Journal of Neuroscience*, *16*(13), 4240-4249.

Tavassoli, T., Latham, K., Bach, M., Dakin, S. C., & Baron-Cohen, S. (2011). Psychophysical measures of visual acuity in autism spectrum conditions. *Vision research, 51(*15), 1778-1780.

Tibber, M. S., Guedes, A., & Shepherd, A. J. (2006). Orientation discrimination and contrast detection thresholds in migraine for cardinal and oblique angles.*Investigative Ophthalmology and Visual Science*, *47*(12), 5599.

Tiitinen, H. T., Sinkkonen, J., Reinikainen, K., Alho, K., Lavikainen, J., & Näätänen, R. (1993). Selective attention enhances the auditory 40-Hz transient response in humans.

Tomchek, S. D., & Dunn, W. (2007). Sensory processing in children with and without autism: a comparative study using the short sensory profile. *American Journal of occupational therapy, 61*(2), 190-200.

Traub, R. D., Spruston, N., Soltesz, I., Konnerth, A., Whittington, M. A., & Jefferys, J. G. (1998). Gamma-frequency oscillations: a neuronal population phenomenon, regulated by synaptic and intrinsic cellular processes, and inducing synaptic plasticity. *Progress in neurobiology*, *55*(6), 563-575.

Turi, M., Burr, D. C., Igliozzi, R., Aagten-Murphy, D., Muratori, F., & Pellicano, E. (2015). Children with autism spectrum disorder show reduced adaptation to number. *Proceedings of the National Academy of Sciences, 112*(25), 7868-7872.

Tyagarajan, S. K., Ghosh, H., Yévenes, G. E., Nikonenko, I., Ebeling, C., Schwerdel, C., ... & Fritschy, J. M. (2011). Regulation of GABAergic synapse formation and plasticity by GSK3β-dependent phosphorylation of gephyrin.*Proceedings of the National Academy of Sciences*, *108*(1), 379-384.

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*, *52*(1), 155-168.

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*, *52*(1), 155-168.

Uhlhaas, P. J., & Singer, W. (2007). What do disturbances in neural synchrony tell us about autism?. *Biological psychiatry*, *62*(3), 190-191.

Uhlhaas, P., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolić, D., & Singer, W. (2009). Neural synchrony in cortical networks: history, concept and current status. *Frontiers in integrative neuroscience*, *3*, 17.

van Boxtel, J. J., & Lu, H. (2013). A predictive coding perspective on autism spectrum disorders. *Frontiers in psychology, 4.*

van Diessen, E., Senders, J., Jansen, F. E., Boersma, M., & Bruining, H. (2014). Increased power of resting-state gamma oscillations in autism spectrum disorder detected by routine electroencephalography. *European archives of psychiatry and clinical neuroscience*, 1-4.

van Elst, L. T., Pick, M., Biscaldi, M., Fangmeier, T., & Riedel, A. (2013). High-functioning autism spectrum disorder as a basic disorder in adult psychiatry and psychotherapy: psychopathological presentation, clinical relevance and therapeutic concepts. *European archives of psychiatry and clinical neuroscience, 263*(2), 189-196.

van Lang, N. D., Bouma, A., Sytema, S., Kraijer, D. W., & Minderaa, R. B. (2006). A comparison of central coherence skills between adolescents with an intellectual disability with and without comorbid autism spectrum disorder. *Research in developmental disabilities, 27*(2), 217-226.

van Loon, A. M., Knapen, T., Scholte, H. S., John-Saaltink, E. S., Donner, T. H., & Lamme, V. A. (2013). GABA shapes the dynamics of bistable perception. *Current Biology, 23*(9), 823-827.

van Pelt, S., & Fries, P. (2013). Visual stimulus eccentricity affects human gamma peak frequency. *Neuroimage*, *78*, 439-447.

van Pelt, S., Boomsma, D. I., & Fries, P. (2012). Magnetoencephalography in twins reveals a strong genetic determination of the peak frequency of visually induced gamma-band synchronization. *The Journal of Neuroscience*, *32*(10), 3388-3392.

Vandenbroucke, M. W., Scholte, H. S., van Engeland, H., Lamme, V. A., & Kemner, C. (2008). A neural substrate for atypical low-level visual processing in autism spectrum disorder. *Brain, 131*(4), 1013-1024.

Vattikuti, S., & Chow, C. C. (2010). A computational model for cerebral cortical dysfunction in autism spectrum disorders. *Biological psychiatry, 67*(7), 672-678.

Vlassova, A., & Pearson, J. (2013). Look Before You Leap Sensory Memory Improves Decision Making. *Psychological science*, 0956797612474321.

Von Der Malsburg, C. (1994). *The correlation theory of brain function* (pp. 95-119). Springer New York.

Von der Malsburg, C., & Schneider, W. (1986). A neural cocktail-party processor. *Biological cybernetics, 54*(1), 29-40.

Walter, E., Dassonville, P., & Bochsler, T. M. (2009). A specific autistic trait that modulates visuospatial illusion susceptibility. *Journal of Autism and Developmental Disorders, 39*(2), 339-349.

Wang, J., Barstein, J., Ethridge, L. E., Mosconi, M. W., Takarae, Y., & Sweeney, J. A. (2013). Resting state EEG abnormalities in autism spectrum disorders. *J Neurodev Disord*, *5*(1), 24.

Wang, J., Caspary, D., & Salvi, R. J. (2000). GABA‐A antagonist causes dramatic expansion of tuning in primary auditory cortex. *Neuroreport, 11*(5), 1137-1140.

Wang, J., Caspary, D., & Salvi, R. J. (2000). GABA‐A antagonist causes dramatic expansion of tuning in primary auditory cortex. *Neuroreport*, *11*(5), 1137-1140.

Wang, J., Ding, D., & Salvi, R. J. (2002). Functional reorganization in chinchilla inferior colliculus associated with chronic and acute cochlear damage. *Hearing research, 168*(1), 238-249.

Wang, J., Ding, D., & Salvi, R. J. (2002). Functional reorganization in chinchilla inferior colliculus associated with chronic and acute cochlear damage. *Hearing research*, *168*(1), 238-249.

Wechsler, D. (1974). *Manual for the Wechsler Intelligence Scale for Children—Revised.* New York: Psychological Corporation.

Westheimer, G., & Beard, B. L. (1998). Orientation dependency for foveal line stimuli: detection and intensity discrimination, resolution, orientation discrimination and vernier acuity. *Vision Research*, *38*(8), 1097-1103.

Wheatstone, C. (1838). Contributions to the physiology of vision.--Part the first. On some remarkable, and hitherto unobserved, phenomena of binocular vision. *Philosophical transactions of the Royal Society of London,* 371-394.

White, S. J., & Saldaña, D. (2011). Performance of children with autism on the Embedded Figures Test: a closer look at a popular task. *Journal of autism and developmental disorders, 41*(11), 1565-1572.

White, S., O’Reilly, H., & Frith, U. (2009). Big heads, small details and autism. *Neuropsychologia, 47*(5), 1274-1281.

Whittington, M. A., & Traub, R. D. (2003). Interneuron diversity series: inhibitory interneurons and network oscillations in vitro. *Trends in neurosciences*, *26*(12), 676-682.

Whittington, M. A., Traub, R. D., Kopell, N., Ermentrout, B., & Buhl, E. H. (2000). Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *International journal of psychophysiology*, *38*(3), 315-336.

Wiegand, L. C., Warfield, S. K., Levitt, J. J., Hirayasu, Y., Salisbury, D. F., Heckers, S., ... & Shenton, M. E. (2004). Prefrontal cortical thickness in first-episode psychosis: a magnetic resonance imaging study. *Biological psychiatry*,*55*(2), 131-140.

Williams, J. H., Whiten, A., Suddendorf, T., & Perrett, D. I. (2001). Imitation, mirror neurons and autism. *Neuroscience & Biobehavioral Reviews, 25*(4), 287-295.

Willoughby, J. O., Fitzgibbon, S. P., Pope, K. J., Mackenzie, L., Medvedev, A. V., Clark, C. R., ... & Wilcox, R. A. (2003). Persistent abnormality detected in the non-ictal electroencephalogram in primary generalised epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*(1), 51-55.

Wilson, H. R. (2003). Computational evidence for a rivalry hierarchy in vision. *Proceedings of the National Academy of Sciences, 100*(24), 14499-14503.

Wilson, T. W., Rojas, D. C., Reite, M. L., Teale, P. D., & Rogers, S. J. (2007). Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biological psychiatry*, *62*(3), 192-197.

Wing, L. (1988). The continuum of autistic characteristics. In *Diagnosis and assessment in autism* (pp. 91-110). Springer US.

Wing, L., Leekam, S. R., Libby, S. J., Gould, J., & Larcombe, M. (2002). The diagnostic interview for social and communication disorders: Background, inter‐rater reliability and clinical use. *Journal of Child Psychology and Psychiatry, 43*(3), 307-325.

Witkin, H. A., Oltman, P. K., Raskin, E., & Karp, S. A. (1971). *Manual for embedded figures test, children’s embedded figures test, and group embedded figures test.* Palo Alto, CA: Consulting Psychologists Press, Inc.

Wright, B., Alderson-Day, B., Prendergast, G., Bennett, S., Jordan, J., Whitton, C., ... & Green, G. (2012). Gamma activation in young people with autism spectrum disorders and typically-developing controls when viewing emotions on faces. *PLoS One*, *7*(7), e41326.

Yasuhara, A. (2010). Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). *Brain and Development, 32*(10), 791-798.

Yip, J., Soghomonian, J. J., & Blatt, G. J. (2007). Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications. *Acta neuropathologica, 113*(5), 559-568.

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O’Shea, D. J., ... & Deisseroth, K. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature, 477*(7363), 171-178.

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O’Shea, D. J., ... & Deisseroth, K. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, *477*(7363), 171-178.

Yoon, J. H., Maddock, R. J., Rokem, A., Silver, M. A., Minzenberg, M. J., Ragland, J. D., & Carter, C. S. (2010). GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *The Journal of Neuroscience*, *30*(10), 3777-3781.

Yordanova, J., Kolev, V., & Demiralp, T. (1997). The phase‐locking of auditory gamma band responses in humans is sensitive to task processing.*NeuroReport*, *8*(18), 3999-4004.

Yuval-Greenberg, S., Tomer, O., Keren, A. S., Nelken, I., & Deouell, L. Y. (2008). Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron*, *58*(3), 429-441.

**Appendices**

**Appendix 1.**

**Table 1.** Demographic variables of participants included in sub sample analyses. Participants taking medication removed, ASC N=37 Control N=45

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Measure | Autism Spectrum Condition Group (N=37) | Control Group (N=45) | Group Comparison | |
| **Mean (SD),**  **Range or number (%)** | Mean (SD),  Range or number (%) | Student’s t (or X2) | P-Value |
| Age (years) | 29.51 (11.27), 18-55 | 28.16 (11.89), 18-65 | .53 | .6 |
| Sex (N females) | 11 (29.73%) | 12 (26.67%) | .09 | .76 |
| Matrix reasoning raw score | 30.42 (2.86), 24-35 | 29.32 (3.82), 16-34. | 1.43 | .16 |
| Matrix reasoning T-score | 61.08 (5.76), 47-72 | 58.73 (8.43), 29-70 | 1.43 | .16 |
| ADOS Communication and Social Interaction Total (N=29) | 9 (4), 0-16 |  |  |  |
| SRS T-Score (N=24) | 101.96 (30.10), 38-143 |  |  |  |

**Table 2.** Demographic variables of participants included in sub sample analyses. Outliers removed, ASC N=47 Control N=46

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Measure | Autism Spectrum Condition Group (N=47) | Control Group (N=46) | Group Comparison | |
| **Mean (SD),**  **Range or number (%)** | Mean (SD),  Range or number (%) | Student’s t (or X2) | P-Value |
| Age (years) | 31.02 (12.90), 18-67 | 27.30 (11.71), 18-65 | 1.45 | .149 |
| Sex (N females) | 13 (27.66%) | 12 (26.09%) | .03 | .86 |
| Matrix reasoning raw score | 30.48 (2.67), 24-35 | 29.44 (3.81), 16-34. | 1.50 | .14 |
| Matrix reasoning T-score | 61.67 (5.77), 47-72 | 58.78 (8.44), 29-70 | 1.92 | .06 |
| ADOS Communication and Social Interaction Total (N=29) | 9.66 (4.58), 0-18 |  |  |  |
| SRS T-Score (N=24) | 104.90 (29.66), 38-159 |  |  |  |

**Table 3.** Demographic variables of participants included in sub sample analyses. Medication & Outliers removed, ASC N=36 Control N=43

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Measure | Autism Spectrum Condition Group (N=36) | Control Group (N=43) | Group Comparison | |
| **Mean (SD),**  **Range or number (%)** | Mean (SD),  Range or number (%) | Student’s t (or X2) | P-Value |
| Age (years) | 29.44 (11.42), 18-55 | 27.79 (11.97), 18-65 | .625 | .534 |
| Sex (N females) | 10 (27.77%) | 10(23.26%) | .21 | .65 |
| Matrix reasoning raw score | 30.54 (2.80), 24-35 | 29.38 (3.84), 16-34. | 1.49 | .14 |
| Matrix reasoning T-score | 61.29 (5.71), 47-72 | 58.76 (8.52), 29-70 | 1.49 | .14 |
| ADOS Communication and Social Interaction Total (N=29) | 9.07 (4.06), 0-16 |  |  |  |
| SRS T-Score (N=24) | 101.17 (30.53), 38-143 |  |  |  |

**Appendix 2.**

**Table 4.** Demographic variables of participants included in sub sample analyses. Full sample ASC N=37 Control N=43

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Measure | Autism Spectrum Condition Group (N=37) | Control Group (N=43) | Group Comparison | |
| **Mean (SD),**  **Range or number (%)** | Mean (SD),  Range or number (%) | Student’s t (or X2) | P-Value |
| Age (years) | 31.70 (12.77), 18-67 | 28.70 (11.90), 18-65 | 1.09 | .28 |
| Sex (N females) | 11 (29.73%) | 14 (32.56%) | .07 | .79 |
| Matrix reasoning raw score | 30.28 (2.72), 25-35 | 29.24 (3.84), 16-34. | 1.36 | .18 |
| Matrix reasoning T-score | 61.42 (5.65), 51-72 | 58.76 (8.54), 29-70 | 1.59 | .12 |
| ADOS Communication and Social Interaction Total (N=30) | 9.73 (4.30), 2-18 |  |  |  |
| SRS T-Score (N=26) | 108.35 (25.64), 47-159 |  |  |  |

**Table 5.** Demographic variables of participants included in sub sample analyses. Outliers removed ASC N=36 Control N=41

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Measure | Autism Spectrum Condition Group (N=36) | Control Group (N=41) | Group Comparison | |
| **Mean (SD),**  **Range or number (%)** | Mean (SD),  Range or number (%) | Student’s t (or X2) | P-Value |
| Age (years) | 31.70 (12.95), 18-67 | 27.49 (10.48), 18-56 | 1.58 | .12 |
| Sex (N females) | 10 (27.77%) | 13 (30.23%) | .14 | .71 |
| Matrix reasoning raw score | 30.40 (2.66), 25-35 | 29.35 (3.87), 16-34. | 1.35 | .18 |
| Matrix reasoning T-score | 61.63 (5.59), 51-72 | 58.68 (8.54), 29-70 | 1.75 | .09 |
| ADOS Communication and Social Interaction Total (N=29) | 9.83 (4.34), 2-18 |  |  |  |
| SRS T-Score (N=25) | 108.92 (26.08), 47-159 |  |  |  |

**Table 6.** Demographic variables of participants included in sub sample analyses. Individuals taking medication removed N=29 Control N=41

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Measure | Autism Spectrum Condition Group (N=29) | Control Group (N=41) | Group Comparison | |
| **Mean (SD),**  **Range or number (%)** | Mean (SD),  Range or number (%) | Student’s t (or X2) | P-Value |
| Age (years) | 30.17 (11.54), 18-55 | 29.12 (12.03), 18-65 | .37 | .72 |
| Sex (N females) | 10 (27.77%) | 12 (29.27%) | .21 | .64 |
| Matrix reasoning raw score | 30.46 (2.81), 25-35 | 29.25 (3.87), 16-34. | 1.42 | .16 |
| Matrix reasoning T-score | 61.25 (5.58), 51-72 | 58.90 (8.60), 29-70 | 1.27 | .21 |
| ADOS Communication and Social Interaction Total (N=22) | 8.86 (3.82), 3-16 |  |  |  |
| SRS T-Score (N=21) | 106.76 (25.56), 47-143 |  |  |  |

1. An additional method to select the maximum peak was also used in which a curve was fitted to the spectra at the time point associated with the maximum increase in gamma power following stimulus presentation using non-linear least squares. The single frequency associated with the maximum of this fitted curve was taken as the metric of peak gamma frequency for each subject. However, the values selected using this curve-fitting method were not significantly different to those obtained by picking the maxima. [↑](#footnote-ref-1)
2. However, in addition to this restricted sample (N=67) results are reported for the full sample (N=80), as well as with outliers removed (N=77), and participants taking medication removed (N=70). Group differences in peak gamma frequency remained consistent in all samples. In all of the described group comparisons, age, sex, matrix reasoning scores and age corrected matrix reasoning t scores were comparable between the two groups, see appendix 2. [↑](#footnote-ref-2)