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Superior orientation discrimination and increased peak gamma frequency in autism spectrum conditions

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Running Title: Orientation Discrimination & peak gamma frequency in ASC.

Abstract

While perception is recognised as being atypical in individuals with autism spectrum conditions (ASC), the underlying mechanisms for such atypicality are unclear. Here we test the hypothesis that individuals with ASC will show enhanced orientation discrimination compared to neurotypical observers. This prediction is based both on anecdotal report of superior discriminatory skills in ASC and also on evidence in the auditory domain that some individuals with ASC have superior pitch discrimination. In order to establish whether atypical perception might be mediated by an imbalance in the ratio of neural excitation and inhibition (E:I ratio) we also measured peak gamma frequency which provides an indication of neural inhibition levels. Using a rigorous thresholding method we found that orientation discrimination thresholds for obliquely oriented stimuli were significantly lower in participants with ASC. Using EEG to measure the visually induced gamma band response we also found that peak gamma frequency was higher in participants with ASC, relative to a well-matched control group. These novel results suggest that neural inhibition may be increased in the occipital cortex of individuals with ASC. Implications for existing theories of an imbalance in the E:I ratio of ASC are discussed.

Key words: autism; electroencephalography; gamma activity; perception; neural inhibition.

General scientific summary: This study found that one aspect of visual perception, orientation discrimination, is enhanced in autism. Peak gamma frequency was also found to be higher in individuals with autism. Together these findings suggest that neural inhibition is increased in autism.

Introduction

It is now widely acknowledged that atypical perception is part of the autism phenotype (APA, 2013). Empirical attempts to measure perception in autism spectrum conditions (ASC) have focussed on obtaining psychophysically derived discrimination and detection thresholds (e.g. Koh, Milne & Dobkins, 2010a; O'Riordan & Passetti, 2006). One of the more consistent findings from this body of work is evidence for superior auditory discrimination in ASC. To date, at least seven studies have demonstrated that individuals with ASC are more able to discriminate pure tone pitch than neurotypical controls (Bonnel, Mottron, Peretz, Trudel & Gallun, 2003; Bonnel et al. 2010; Heaton, Hudry, Ludlow & Hill, 2008; Jones et al. 2009; Meilleur, Berthiaume, Bertone & Mottron, 2014; O'Riordan & Passetti, 2006; Stanutz, Wapnick & Burack, 2014). However, it is unclear whether similarly enhanced discrimination abilities in ASC are seen in the visual domain.

Although anecdotal reports of fine-grained attention to detail in ASC and empirical evidence of superior visual search in ASC have led many to speculate that visual discrimination may be enhanced in ASC (e.g. O'Riordan & Plaisted 2001), little direct evidence supports this position. Indeed when visual discrimination in ASC has been measured directly, results indicate impaired discrimination for some stimuli, e.g. colour (Franklin, Sowden, Burley, Notman & Alder, 2008; Franklin et al. 2010; Heaton et al. 2008; Hurlbert, Loveridge, Ling, Kourkoulou & Leekam, 2011), or unremarkable discrimination for other stimuli such as luminance discrimination and contrast sensitivity (Behrmann, Thomas & Humphreys, 2006; De Jonge et al. 2007; Franklin et al. 2010; Koh, Milne & Dobkins, 2010b). **However, it has been found that individuals with ASC show a heightened ability to detect luminance-defined gratings, demonstrating that low level visual perception is altered (Bertone, Mottron, Jelenic & Faubert, 2005, Kéïta, Guy, Berthiaume, Mottron & Bertone, 2014).** Whilst the study from Bertone and colleagues is

often cited as an example of an orientation discrimination task in ASC, this study principally measures ability to detect either horizontal or vertical gratings under differing levels of contrast.

Nevertheless, orientation discrimination is a particularly relevant metric in ASC given the role that neural inhibition plays in shaping the tuning curves of orientation selective neurons (Hubel & Wiesel, 1968). 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, Yang, Liang, Xia & Zhou, 2008). Conversely, the application of GABA antagonists reduces orientation selectivity (Katzner, Busse & Carandini, 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, Muthukumaraswamy, Freeman & Singh, 2009).

Neural 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. For example, applying a GABA antagonist to neurons in the primary auditory cortex of chinchillas increases the range of frequencies to which the neurons respond (Wang, Caspary & Salvi, 2000; Wang, Ding & Salvi, 2002). Given that pure-tone pitch discrimination is enhanced in ASC, and orientation discrimination thresholds are negatively correlated with autistic traits in the neurotypical population (Dickinson, Jones & Milne, 2014), it is possible that individuals with ASC may show superior orientation discrimination. To our knowledge only one study has measured orientation discrimination thresholds in ASC (Schwarzkopf, Anderson, de Haas, White & Rees, 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, the small sample size may not have been sufficient to reveal any differences in orientation discrimination in ASC. Therefore, here we used a more rigorous psychophysical task to measure orientation discrimination thresholds and collected data from a larger sample of individuals.

Given that neural inhibition mediates orientation discrimination (Li et al. 2008; Edden et al. 2009), a difference in the orientation thresholds of individuals with and without ASC would suggest an alteration in the balance of neural excitation and inhibition. Consequently our prediction that orientation discrimination may be enhanced in ASC implies that neural inhibition in visual areas will be increased in ASC. In order to investigate E:I balance in ASC, we also investigated the sustained gamma-band response elicited by the presentation of a visual stimulus. Gamma band activity, recorded by either MEG or EEG arises from the interaction of pyramidal cells and GABAergic inhibitory interneurons (Buzsáki and Wang, 2012), with E:I balance setting the oscillation frequency of the network. Specifically, higher levels of inhibition lead to higher peak gamma frequency (Brunel and Wang, 2003). Therefore peak frequency of the visually induced gamma response is considered to reflect E:I balance in human observers. The relationship between E:I balance and gamma frequency is further suggested by work which has found that increased resting GABA levels in the occipital cortex (Edden et al., 2009, Muthukumaraswamy, Edden, Jones, Swettenham & Singh, 2009) and decreased dynamic glutamate levels in the lateral occipital cortex (Lally et al. 2014) are related to higher peak gamma frequency. In addition, orientation discrimination thresholds are correlated with peak gamma frequency (Edden et al. 2009; Dickinson, Bruyns-Haylett, Jones & Milne, 2015) providing further support for the link between neural inhibition, peak gamma frequency and orientation discrimination Although many studies

have measured gamma *power* in ASC (e.g. Snijders, Milivojevic & Kemner, 2013), to the best of our knowledge, peak gamma frequency in ASC has not yet been reported.

In sum, the aim of this study was to measure orientation discrimination thresholds in ASC. Based on previous evidence for low level visual enhancements, and enhanced auditory discrimination in ASC (Meilleur, Berthiaume, Bertone & Mottron, 2014) we predicted that orientation discrimination would be enhanced in ASC. In order to establish whether superior orientation discrimination might reflect an imbalance of the E:I ratio in ASC we measured peak visually-induced gamma frequency, which has been identified as a correlate of neural inhibition in the occipital cortex

Method

Participants

Ninety-six volunteers, half of whom had a diagnosis of ASC were enrolled to this study. Participants with ASC were either recruited from our existing participant database, or through a local NHS neurodevelopmental service which provides adult autism spectrum diagnoses. Control participants, defined as individuals who did not have a diagnosis of an ASC nor a first degree relative with an ASC, were recruited from our existing database of research volunteers.

Data from twenty-nine participants were excluded from all analyses: six participants with ASC declined to take part in the EEG recording; ten further datasets (five ASC. five control) were excluded due to excessive EEG artifacts (see below). 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.

Insert Table 1 about here please

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 the self-report version of the social responsiveness scale (SRS-2; Constantino & Gruber, 2012) were used to assess symptomology in the participants with ASC. The ADOS is a standardised, semi-structured assessment used by both clinicians and researchers to assess communication and social interaction in ASC. Participants engage in different social-communicative sequences with an examiner, all of which are designed to elicit a different combination of particular social behaviours. Participants are scored based on the presence of these behaviours, with a score of 10 or above on the combined communication and interaction subscales defined as the cut-off for the presence of ASC. The adult self-report version of the SRS-2 is a 65-item questionnaire which measures the severity of social impairment in ASC, with a higher score indicating severer ASC symptomology. A T-score of 60 or above indicates the cut-off for an autism spectrum diagnosis.

Due to time-limitations during testing, or participants being unable to return for a second testing session, ADOS scores were not obtained for seven participants. 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 it but obtained a below cut-off score of 52. Of the twenty-one participants with ASC who completed the ADOS, eighteen met cut-off for autism spectrum. Two of the three participants who did not meet the clinical cut-off score for autism spectrum 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. **In addition, analyses were repeated after removing these participants, and this had no impact on the results reported below.**

Non-verbal IQ was assessed in all participants using the matrix reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Mean age, matrix reasoning scores, ADOS and SRS scores are provided in Table 1. No participant had taken part in any of our previous research (Dickinson et al. 2014; Dickinson et al. 2015). The study received full ethical approval from the local research ethics committee. Participants provided informed written consent, in accordance with the declaration of Helsinki.

Orientation discrimination task

A two-alternative forced choice adaptive staircase procedure task was used to measure orientation discrimination thresholds. This task was adapted from Edden and colleagues (Edden et al. 2009), and was used by us in previous work (Dickinson et al. 2014; Dickinson et al. 2015). The task design is illustrated in Figure 1.

Each trial consisted of presentation of a reference grating, followed by a target grating. Both circular gratings (diameter 4°; spatial frequency 3 cycles/degree; contrast 99%; mean luminance 83 cd/m2) were displayed for 350ms each and were separated by 500ms of fixation. Stimuli were created in MatLab (The Mathworks, 2000) using the PsychToolbox set of functions (Brainard, 1997). 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.

On each trial, participants were asked to verbally report whether the target grating had been rotated clock-wise, or anti-clockwise, compared to the reference grating. The experimenter recorded each response using the keyboard.

There were two conditions, one in which the reference grating was oriented at 0 degrees (vertical) and one in which it was oriented at 45 degrees. Two staircases were used in each condition, one which presented clockwise transformations of the stimulus and the other presented the anti-clockwise transformations. Each staircase used a one-up three-down method which converged on 79% accuracy (Leek, 2001). The target grating was presented 5 degrees away from the reference grating on the first trial of each staircase. The initial step size was 1 degree and this was decreased by 75% after each reversal. The four staircases were randomly interleaved to form one run.

Participants were seated 57cm away from the monitor, in a completely dark room. The monitor had a circular aperture placed over it which obscured the edge of the screen, in order to remove any external orientation cues. Participants completed a practice run which continued until each of the staircases had completed 20 trials. Participants then completed one run, which finished when each of the four staircases had reached 8 reversals. After a short self-timed break (of around 2 minutes), participants completed a second run. Thresholds were computed by averaging the last 6 reversals of each staircase. We calculated separate thresholds for the oblique and vertical conditions, by averaging the two staircases used in each condition. We then averaged the oblique and vertical thresholds obtained from the first and second runs to get an overall oblique threshold, and an overall vertical threshold.

EEG Task

EEG data were collected from 128 electrodes using the BioSemi ActiveTwo system (Amsterdam, The Netherlands). EEG data were filtered online with a band pass of 0.01 - 140Hz and digitised using BioSemi ActiView software at a sampling rate of 2048Hz. All recordings were carried out in an electrically shielded room, and direct current offset voltages were kept below +/- 25mV. A linearised Viglen LCD monitor with a spatial resolution of 1280 x 1024 pixels and a temporal resolution of 60Hz was used to display the stimuli. Participants were seated 57cm from the monitor in a comfortable chair and were asked to remain as still and relaxed as possible in order to minimise muscle artifacts. Stimuli were identical to those that we previously used to measure peak gamma frequency (Dickinson et al. 2015) and were originally adapted from Edden and colleagues (Edden et al. 2009). A red cross (1° x 1°) was present in the centre of the screen throughout the experiment and participants were asked to fixate on this cross throughout Each trial consisted of a black and white square grating (4° x 4°; spatial frequency 3 cycles/degree; contrast 99.6%; mean luminance 39.33 cd/m2) presented to the bottom left of the fixation point. The grating was displayed for a jittered duration between 1500-2500ms, with a jittered inter stimulus interval of 1500-2500ms. Participants were asked to press the spacebar every time the grating disappeared. There were 200 trials, with a self-timed break half way through, at which point participants swapped the hand which they were using to respond.

Problems of measuring induced gamma activity

In general, electrooculography (EOG) and EMG artifacts are highly prevalent in any EEG signal. In addition, there are two specific EEG artifacts which are particularly problematic for the current investigation as they share a similar frequency range to the

gamma band of interest. These are: power line interference which causes artifacts throughout the EEG signal at 50Hz; and power changes in the gamma frequency range that are related to saccadic eye movements (Yuval-Greenberg, Tomer, Keren, Nelken & Deouell, 2008). One way to minimise the effects of these artifacts on the data 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 small amount of residual 50Hz power line interference that resisted electrical shielding. **The reliability of this technique has been demonstrated previously, as studies which use objective criteria, such as those used here (described below), reveal that similar independent components are present across different participants (Debener et al., 2007; Joyce, Gorodnitsky & Kutas, 2004; Onton, Delorme & Makeig, 2005).**

Off line EEG Analysis

The BioSemi DBF Decimator software was used to down-sample continuous EEG data from 2048Hz to 1024Hz. All additional data analysis was completed using EEGLAB (Delorme & Makeig, 2004), and in-house MATLAB scripts.

Data were referenced to the vertex electrode, and a finite impulse response filter was used to remove frequencies below 1Hz. Data were visually inspected, and any channels or segments of data which were clearly artifactual were removed. Data were segmented into epochs (-200 to 1500ms), with stimulus presentation at 0ms. Any trials which had a response time of over 1500ms following stimulus offset were removed.

Independent components were derived using the extended infomax algorithm within EEGLAB (Delorme & Makeig, 2004).There was no significant difference in the number of channels submitted to ICA between participants with ASC (M=114.82, SD=7.47) and control participants (M=116.38, SD=6.6; t(65)=-.91, p=.37). There was also no difference in the number of epochs (and therefore data points) submitted to ICA between those with ASC (M=181.18, SD=13.22) and control subjects (M=183.23, SD=11.7; t (65)=-.67, p=. 51). Once independent components had been derived, we used the DIPFIT function in EEGLAB, to estimate the anatomical source location of each component (Oostendorp & Oosterom, 1989).

Independent Component Selection

In order to identify the component reflecting visually-induced activity, we carried out an iterative process for each participant. Initially, we examined the scalp topography of all components, and retained all components which had focal activity lateralised to the right hemisphere in or near the occipital cortex. This led to up to eight components being selected for each individual. The time course of the ERP from each of the selected components was then inspected to find any components which had a clear visual evoked response. This led to up to two components being selected for each participant. Time frequency analysis (described below) was then performed on each of the selected components. In the case of the individuals who had more than one suitable component, we selected the component which showed the clearest sustained gamma response in the wavelet decomposition. Thus, one component that reflected the visual response was selected for each participant. The residual variance of the dipole model fit for each of the final selected components did not differ significantly between those with ASC (M=9.88, SD=9.13) and controls (M=7.44, SD=4.83; t (65)=.1.42, p=.16) indicating similar data quality between the groups. Component selection and wavelet

transform were carried out whilst the participant was blind to any participant details, including group and orientation discrimination thresholds.

In summary, for each participant we selected one component which reflected a source in or near right occipital cortex, which clearly demonstrated visually elicited neural activity identified as a sustained response in wavelet decomposition.

Time Frequency Analysis

The time series of the selected independent component from each subject was then analysed in the time-frequency domain using wavelet transforms. The complex Morlet wavelet (a complex exponential modulated by a Gaussian, ω0= 6; where ω0 is nondimensional frequency) 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:

$$\psi_0(\eta) = \pi^{-1/4} e^{i\omega_0\eta} e^{-\eta^2/2} \qquad \mathbf{1}$$

The wavelet transform $W^x(n,s)$ is a complex quantity whose modulus expresses the amount of power in x 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 x_n of N subsampled data points at equal time increments of δt (Kaiser, 2010), is defined as the convolution of x_n with a scaled and translated version of ψ_0:

$$W^x(n,s) = \sqrt{\frac{\delta t}{s}} \sum_{n'-1}^{N} x_{n'} \psi_0^* \left[\frac{(n'-n)\delta t}{s}\right] \qquad \mathbf{2}$$

where ψ_0^* is the complex conjugate of ψ_0, n is the time index and s 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 subject was analysed using this wavelet 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. Thus, to estimate changes in evoked gamma (phase-locked), data were trial averaged and then subject to the wavelet transform. 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. The maxima of the subsequent matrix provided the maximum post-stimulus increase in evoked power in the gamma range following stimulus presentation and the associated frequency at which it occurred. The analysis was restricted to the gamma range, ie. frequencies between 30-90Hz (Edden et al., 2009).

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 subject, the wavelet transforms were performed on each trial and were then subsequently averaged (see Figure 2A & 2C); to remove the remaining 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 2D). As the induced wavelet transform had different magnitudes of power change to the full signal wavelet transform, the transforms were rescaled between zero and unity before subtraction. The maxima of the subsequent matrix was selected, providing the maximum post-stimulus increase in induced power in the gamma range following stimulus presentation and the associated frequency at which it occurred.

Results

Orientation Discrimination Thresholds

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, *d*=.56), indicating superior orientation discrimination in the participants with ASC (See Figure 3A). 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, *d*=.19; see Figure 3B).

As there was a significant interaction between group and orientation discrimination threshold, we calculated the magnitude of the oblique effect 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, *d*=.57).

Peak Gamma Frequency

As shown in Figure 3B, 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, *d*=1.02). 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, *d*=0.17). Pearson's correlation coefficient indicated that peak induced gamma frequency and peak induced gamma power were not related (r=.07, p=.60).

There was no significant group difference in peak evoked gamma frequency between individuals with ASC (*M*=45.62 Hz, *SD*=15.38) and control participants (*M*= 45.97 Hz, *SD*= 17.95; *t*(65)=-.086, *p*=.93, *d*=.02). There was also no significant difference 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, *d*=.2).

We further investigated the extent to which induced 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). Pearson's correlation coefficient indicated that peak induced gamma power (r=-.05, p=.72), peak evoked gamma frequency (r=-0.5, p=.69) and peak evoked gamma power (r=.14, p=.26) were not correlated with orientation discrimination thresholds.

Neither induced peak gamma frequency (r= -.04, p=.78), or oblique orientation discrimination thresholds (r=.01, p=.92) were correlated with age. WASI T-scores were correlated with oblique orientation discrimination thresholds (r=-.362, p=.003), but not induced peak gamma frequency (r=.11, p=.39).

Discussion

Here, for the first time, we report that individuals with ASC have superior orientation discrimination thresholds compared to matched controls. Both oblique thresholds and the oblique effect are significantly reduced in ASC, whilst vertical thresholds do not differ. **This echoes the results of previous work demonstrating that whilst oblique orientation discrimination thresholds are linked to autistic traits in the general population, this relationship is not seen for vertical discrimination thresholds (Dickinson et al., 2014). Given that performance for vertical stimuli is superior than that for cardinal stimuli (Appelle, 1972), it is likely that vertical orientation discrimination thresholds may lead to ceiling effects in both groups, and thus lack the adequate sensitivity to detect group differences (see Dickinson et al., 2014 for a full discussion).**

We also report the novel finding that the peak frequency of visually-induced gamma activity is higher in ASC. **Peak gamma frequency was not found to decrease with age, as has been previously reported (Muthumumaraswarmy et al., 2009), although this may be due to age not being evenly distributed across the current sample. For example 75% of participants were aged between 18 and 34 and only 25% of participants were aged between 35 and 65.** As both enhanced orientation discrimination and higher peak gamma frequency are associated with higher levels of neural inhibition in the occipital cortex (Edden et al. 2009; Muthukumaraswamy et al. 2009), we suggest that our results may indicate an increase in occipital inhibition levels in ASC. This suggestion is in-line with a previous claim that atypical neural connectivity in ASC may lead to increased lateral inhibition (Bertone et al. 2005). However, as orientation discrimination threshold and peak gamma frequency have specifically been linked to GABAergic inhibition (Chen, Lemonnier, Lazartigues & Planche,

2014; Edden et al. 2009; Muthukumaraswamy et al. 2009) we suggest our data may indicate increased occipital GABA levels in ASC.

While evidence of superior orientation discrimination in ASC concurs with work in the auditory domain showing superior discrimination of pure-tone pitch in ASC, at first glance, this result appears to be inconsistent with existing studies 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 luminance discrimination and contrast sensitivity are unaltered (Franklin et al. 2010, Koh et al. 2010b). Taken together however, all of these findings are entirely consistent with the suggestion that GABAergic inhibition may be increased in ASC. For example contrast sensitivity is unrelated to GABA levels (Yoon et al. 2010), and medication which increases GABA levels, such as vigabatrin, leads to colour impairments in healthy individuals (Mecarelli, Rinalduzzi & Accornero, 2001). In other words, increased GABA levels have been associated with enhanced orientation discrimination and impaired colour discrimination, and have been shown to exert no effect on contrast sensitivity. These findings mirror existing psychophysical literature reporting perception in ASC. Further corroboration of our suggestion that GABA levels may be increased in the visual cortex in ASC comes from evidence that individuals with ASC show a slower rate of binocular rivalry than individuals without ASC (Robertson, Kravitz, Freyberg, Baron-Cohen & Baker, 2013). Together with evidence that higher GABA concentration in visual cortex and the administration of lorazepam are associated with slower rivalry dynamics in healthy volunteers, a reduced rate of binocular rivalry alterations may also suggest increased occipital GABA levels in ASC.

A more direct way to measure occipital GABA levels in ASC is to use MR-spectroscopy (MRS). To our knowledge, only one study has measured resting levels of occipital GABA using MRS in ASC (Gaetz et al. 2014), and no differences in occipital

GABA levels were found between individuals with and without ASC. However, close inspection of the data indicates that there was a small trend towards increased occipital GABA levels in ASC. As the sample size of this study was small – data were obtained from only eight individuals with ASC and ten controls - it is possible that this study was not sufficiently powerful to detect differences in occipital GABA levels between individuals with and without ASD. Nevertheless, the direction of the finding is in-line with our suggestion that enhanced orientation discrimination and higher peak gamma frequency indicate increased neural inhibition in the visual cortex of individuals with ASC

In their original article proposing increased E:I ratio in autism, Rubenstein & Merzenich (2003) suggested that E:I ratio may be increased in a number of key neural systems including sensory systems. Our finding suggests that this may not be the case for the visual cortex. Existing literature provides conflicting evidence with regards to other sensory modalities. As discussed above, at least some individuals with ASC show enhanced auditory discrimination, indicating increased inhibition in auditory cortex; however MRS studies have found lower GABA levels in auditory cortex in ASC (Gaetz et al. 2014; Rojas et al., 2014). These findings are from different research groups, and different individuals were recruited to the MRS and the auditory studies, therefore it is not possible to compare them directly. A more valuable approach would be to obtain MRS and psychophysical data from the same individuals, as was done by Puts and colleagues (Puts, Wodka, Tommerdahl, Mostofsky & Edden, 2014), who found reduced (worse) tactile discrimination thresholds and correspondingly lower GABA levels in somatosensory cortex in ASD.

Rubenstein & Merzenich (2003) also stated that increased E:I ratio may be associated with some, but not all, forms of autism. The theory is based largely on the increased prevalence of epilepsy in ASC, which is estimated to occur in 5-46% of people with ASC (Bryson, Clark & Smith, 1988; Hughes and Melyn, 2005). None of the participants from

whom data are reported here had epilepsy or any seizure history, therefore, on the basis of the current data, our suggestion for increased visuo-cortical inhibition is restricted to the subgroup of individuals who have ASC but do not have epilepsy. **While the recruitment of a relatively homogeneous sample of participants, i.e. high-functioning adults with ASC with a relatively low incidence of co-morbid conditions, can be seen as a strength of this study, this sample is unlikely to be representative of the entire population of individuals with ASC. Indeed, although all of the participants had been given a clinical diagnosis of ASC by a trained clinician in the UK, not all of the participants reached the cut-off for ASC on the ADOS and / or the SRS. It will be important to establish whether the findings reported here are replicated in children with ASC, lower functioning individuals, those with increased symptom severity, and indeed individuals who have both ASC and epilepsy.**

The increased E:I ratio theory of autism has been linked by some to abnormal minicolumn structure in ASC (Casanova, Buxhoeveden, Switala and Roy, 2002a; 2002b). If the structure of columns of orientation selective cells is altered in ASC, it is likely that this would have some impact on orientation discrimination ability. Post-mortem studies have demonstrated that individuals with ASC show minicolumnar abnormalities in the frontal and temporal regions of the brain (Buxhoeveden et al., 2006; Casanova et al, 2002a; 2002b; Casanova et al., 2006), with minicolumns having reduced neuropil space (Buxhoeveden et al., 2006; Casanova et al., 2002b; Casanova, Buxhoeveden & Gomez, 2003), which has been postulated to lead to weakened inhibition (Casanova et al., 2003). However, computational modelling work has suggested that narrower minicolumns may actually lead to increased inhibition (Gustaffson, 1997). Adding to this mixed literature is recent evidence that minicolumns are in fact wider in sensory and higher order cognitive areas of cortex in ASC

(McCavanagh, Buckley & Chance, 2015). Therefore, it is difficult to interpret the current data in terms of minicolumnar abnormalities, as there is conflicting evidence as to how minicolumns are altered in ASC, and the consequences that this would have for E:I balance.

Considering our present finding in the light of existing data, it is clear that there is a need for larger studies that use different approaches to measure neural inhibition including measuring sensory discrimination across modalities, measuring GABA levels across different areas of the cortex, and measuring peak gamma frequency in the same individuals. Peak gamma frequency may represent a more reliable variable with which to investigate individual differences in cortical inhibition as it has been shown to be stable over time (Muthukumaraswamy et al. 2009), and also heritable (van Pelt, Boosma & Fries, 2012). Obtaining converging within-participant results using 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.

To our knowledge, this study is the first to report peak gamma frequency in ASC, although numerous studies have measured gamma power in ASC, yielding mixed results. Some studies find reduced evoked gamma power and increased induced gamma power in ASC (e.g. Rojas, Maharajh, Teale & Rogers, 2008) whereas other studies have found no difference in evoked (Gandal et al. 2010; Wright et al. 2012) or induced gamma power (Gandal et al. 2010). Here, we found no significant difference in either evoked or induced peak gamma power between the participants with and without ASC. Furthermore, there was no significant relationship between peak gamma frequency and peak gamma-power, a finding which concurs with existing data (Jia, Xing & Kohn, 2013).

In conclusion, here we report that in a group of high functioning adults with ASC both orientation discrimination thresholds and peak frequency of visually induced gamma activity were significantly altered compared to a well-matched control group. We suggest 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 - between different sub-types of ASD and / or between different brain areas 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).

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Table 1. 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 X^2)	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	1.38	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			

Figure 1. Schematic diagram of orientation discrimination task.

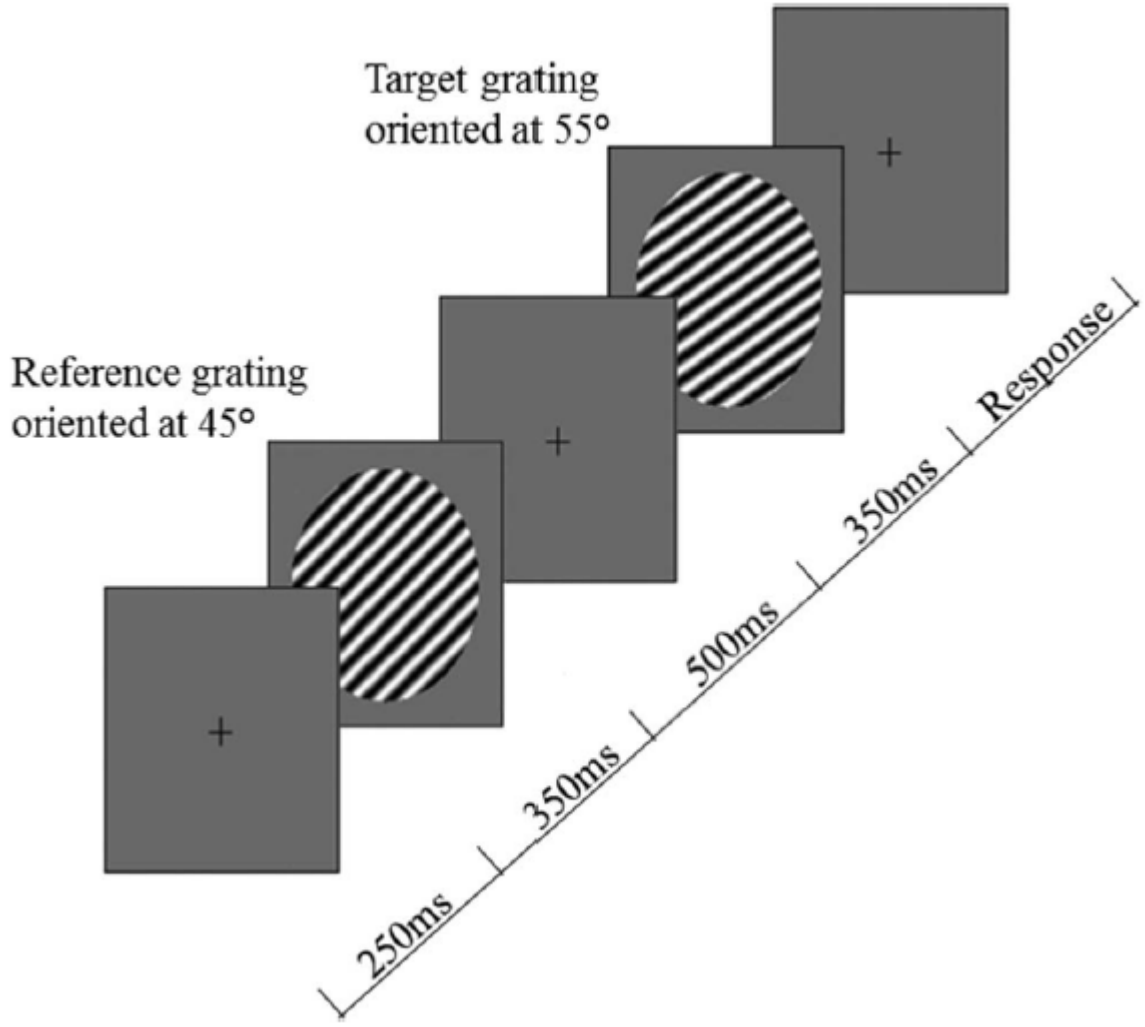

Figure 2. (A) Time frequency decomposition of all frequency bands (0-200Hz) for one participant. (B) Average scalp map of all selected independent component. (C) Time frequency decomposition of full gamma activity signal, including evoked and induced activity for one participant. (D) Time frequency decomposition of induced gamma band response for one participant. (E) The total power change at each frequency in the full gamma signal (figure 2C; plotted in blue) and in the induced gamma signal (figure 2D; plotted in green) for one participant.

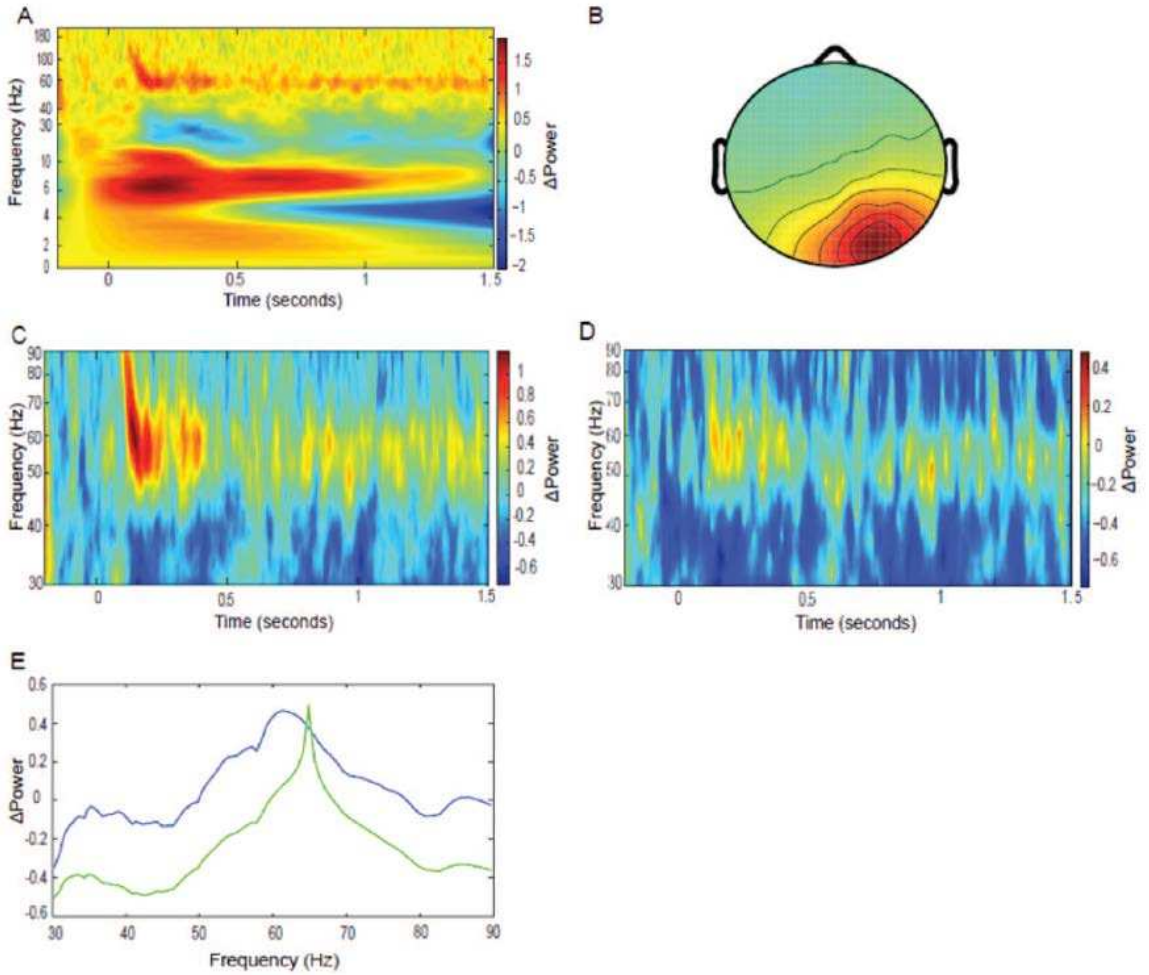

Figure 3. (A) Box plots demonstrating oblique orientation discrimination thresholds for both ASC and control participants. (B) Box plots demonstrating vertical orientation discrimination thresholds for both ASC and control participants. (C) Box plots demonstrating peak gamma frequency for both ASC and control participants.