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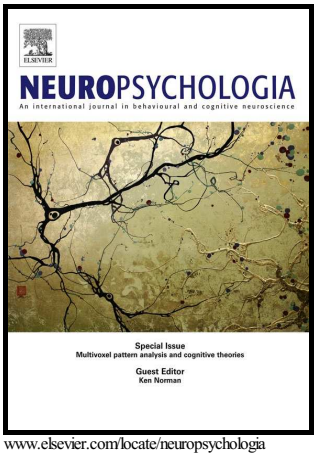

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Lateral inhibition in the autism spectrum: an SSVEP study of visual cortical lateral interactions

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Abstract

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Circuit level brain dysfunction has been suggested as a common mechanism through which diverse genetic risk factors and neurobiological sequelae lead to the core features of autism spectrum disorder (Geschwind 2009; Port et al. 2014). An important mediator of circuit level brain activity is lateral inhibition, and a number of authors have suggested that lateral inhibition may be atypical in ASD. However, evidence regarding putative atypical lateral connections in ASD is mixed. Here we employed a steady state visual evoked potential (SSVEP) paradigm to further investigate lateral connections within a group of high functioning adults with ASD. At a group level, we found no evidence of altered lateral interactions in ASD. Exploratory analyses reveal that greater ASD symptom severity (increased ADOS score) is associated with increased short range lateral inhibition. These results suggest that lateral interactions are not altered in ASD at a group-level, but that subtle alterations in such neurobiological processes may underlie the heterogeneity seen in the autism spectrum in terms of sensory perception and behavioural phenotype.

Key words: electroencephalography; autism; lateral inhibition; visual evoked potential; psychophysics

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1. Introduction

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Autism spectrum disorder (ASD) is a prevalent neurodevelopmental condition (Christensen et al. 2016) defined by impairments in social communication and restricted and repetitive behaviors (Association 2013). While the specific etiology of ASD remains unknown, differences in a number of interrelated neural mechanisms are proposed to underlie the condition. These include neural connectivity, the balance of neural excitation and inhibition (E/I balance), and lateral inhibition (Belmonte et al. 2004; Bertone et al. 2005; Courchesne 2004; Gustafsson 1997; Rubenstein and Merzenich 2003). Lateral inhibition refers to the ability of a neuron to inhibit the activity of its neighbors, and is an important low-level feature of neural systems. One major role of lateral inhibition is to refine the processing of information in sensory circuits. Given mounting evidence for sensory processing differences in ASD, lateral inhibition has come under recent scrutiny. By studying low-level aspects of sensory networks (such as lateral inhibition) in ASD, insight into the dynamics of larger scale network activity in ASD may be gained (Bertone et al. 2010).

Psychophysical tasks can be employed to assay lateral inhibition through its impact on perception. Using this approach, Bertone and colleagues describe evidence for enhanced lateral inhibition in individuals with ASD, based on evidence of enhanced contrast sensitivity for luminance-defined stimuli and impaired contrast sensitivity for texture-defined stimuli in ASD (Bertone et al. 2005). Findings from a lateral masking paradigm also suggest altered lateral interactions in ASD, however it is difficult to interpret whether this is due to enhanced or impaired inhibitory connections (Kéïta et al. 2011). Atypical event related potentials generated during object boundary detection have suggested that lateral inhibitory connections may be dysfunctional in ASD (Vandenbroucke et al. 2008). Orientation discrimination is also highly contingent on lateral inhibition, with enhanced orientation discrimination associated with increased neural inhibition (Edden et al. 2009; Katzner et al. 2011; Li et al. 2008). When measured in individuals with ASD, findings in this area have been mixed, with one report of enhanced orientation discrimination in adults with ASD (Dickinson, Bruyns-Haylett, et al. 2016), and other studies finding no group differences (Schwarzkopf et al. 2014; Shafai et al. 2015).

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From such mixed reports, it is difficult to interpret if, and how, atypical lateral interactions manifest across the autism spectrum. Furthermore, psychophysical tasks are susceptible to behavioral subjectivity, as they typically require the observer to make a decision, and to map this decision to a particular behavioral response. Differences in higher-level decision-making processes may confound psychophysical measurements in individuals with ASD (Pirrone et al. 2017).

Neuroimaging has been used extensively to investigate network properties over a larger spatial scale in ASD. Functional connectivity findings generally supporting long range under-connectivity and short range over-connectivity in ASD (for a review, see (Wass 2011a). While there is no agreed definition of

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short- and long-range connectivity (Vissers et al. 2012), the term short-range is often used to describe connectivity within a brain region, and the term long-range to describe connectivity between brain regions, lobes or hemispheres. Functional connectivity is typically inferred by comparing the time course of two measurements of neural activity taken concurrently using techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG) or magnetoencephalography (MEG). The proximity of measurements (and therefore scale of functional connectivity) that can be investigated using these techniques is limited by their spatial resolution. Consequently, the measurement of short-range connections by non-invasive brain imaging techniques is inherently difficult, and may contribute to the higher variability of findings regarding short-range, compared with long-range connectivity in ASD (Vissers et al. 2012; Wass 2011b).

Lateral inhibition is a highly-localized example of short-range connectivity. Measuring connectivity over such a precise spatial scale is traditionally limited to animal studies or histological techniques, rather than functional neuroimaging in human participants. However, by using EEG to study perceptual processes that are mediated by lateral inhibition, we can infer local functional connectivity on the spatial scale at which lateral inhibition occurs.

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1.1. SSVEP to assay lateral interactions

The neural response to low-level visual stimuli, measured through the visual evoked potential (VEP), is the net result of excitatory and inhibitory mechanisms governing many low-level visual features. The direct effect of inhibitory processes on the VEP has been demonstrated by applying a $GABA_A$ antagonist to visual and somatosensory cortices of animal models (Bruyns-Haylett et al. 2017; Daniels and Pettigrew 1975; V Zemon et al. 1980). These studies show that specific positive and negative aspects of the VEP time series are increased and decreased in magnitude following topical application of a GABA antagonist to the visual cortex of cats (V Zemon et al. 1980; Vance Zemon, Kaplan, et al. 1986).

Furthermore, manipulation of the VEP through the presentation of particular visual stimuli allows the integrity of both long- and short-range inhibitory lateral interactions to be inferred. As described above, ‘long-range’ is traditionally used in the literature to refer to connections between brain regions, lobes or hemispheres. Therefore it should be noted that whilst VEP measures reveal lateral interactions at different spatial scales, the ‘long-range’ connections investigated using VEP (and described throughout this paper) are occurring on a scale within primary visual cortex.

Temporally modulating the contrast of a visual stimulus evokes a steady-state VEP (SSVEP) at the frequency of contrast modulation (the fundamental frequency, given asymmetrical [e.g., appearance-

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disappearance] contrast modulation), and at integer multiples of the stimulus frequency (harmonic responses). This stimulus-evoked response can be extracted from EEG. Examples of stimuli that can be used to evoke a SSVEP through contrast modulation are carefully designed radial patterns: 'partial-windmill' (illustrated in Figure 1, panel B) and 'windmill-dartboard' (windmill-dartboard; illustrated in Figure 1, panel A; (V Zemon and Ratliff 1984; Vance Zemon, Victor, et al. 1986; Vance Zemon and Ratliff 1982). Long- and short-range lateral inhibitory connections play a critical role in determining SSVEP responses to partial-windmill and windmill-dartboard stimuli (Vance Zemon and Ratliff 1982), as the spatial arrangements of the two stimuli are designed such that responses from visual neurons are elicited over different spatial scales. Thus, by measuring and comparing the neural responses to these two stimuli, we can assess the integrity of both short- and long-distance lateral interactions in the visual system, and determine whether (and how) they are altered in ASD.

1.2. Windmill-dartboard and partial-windmill stimuli

Partial-windmill stimuli consist of contrast-reversing light and dark elements in circular and annular regions of the pattern, which are surrounded with uniform fields of light (equal in space-average luminance to the patterned regions). Partial-windmill stimuli elicit prominent SSVEPs at twice the stimulus frequency (second harmonic) in addition to higher even-order harmonic components. No significant fundamental frequency or other odd-order components are generated given the symmetric character of the contrast-reversing stimulus.

Windmill-dartboard stimuli are produced by replacing the uniform fields of light in the partial-windmill stimulus with static light and dark elements equal in contrast to the peak contrast in the dynamic regions. Windmill-dartboard stimuli generate a quite different SSVEP, even given the identical temporal modulation of contrast to that used with partial-windmill stimuli. The strongest response to windmill-dartboard stimuli is at the fundamental frequency. In addition, the prominent second harmonic response obtained with the partial-windmill stimulus is typically attenuated given the windmill-dartboard stimulus. The fundamental response elicited by the windmill-dartboard stimulus is considered to reflect the integrity of short-range lateral interactions, as the spatial extent of these interactions are on the order of the width of one cortical hypercolumn, a sub millimeter scale (Zemon and Ratliff, 1982; Conte and Victor, 2009). The effect of second harmonic attenuation acts over a greater spatial extent. These findings can be demonstrated by placing a small annular gap of uniform light between the modulating and fixed contrast regions of the pattern, which leads to attenuation or extinction of the fundamental response, and loss of second harmonic attenuation with greater gap widths (Vance Zemon and Ratliff 1982). The highly local connections can be quantified by studying the amplitude of the fundamental response. In order to eliminate the potential confound of using absolute EEG power can vary between participants due to non-neural factors, it is

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possible to compute the ratio between the fundamental response and the second harmonic response of the windmill-dartboard condition. This ratio is referred to as the facilitation index (FI) (Conte and Victor 2009). The short-range inhibition represented by the FI is said to be most likely mediated by GABAergic synapses (Vance Zemon, Kaplan, et al. 1986). This is supported by pharmacological manipulation using the drug gabapentin, a drug whose effects are mediated by increasing the action of GABAergic systems (Petroff et al. 2000; Treiman 2001), which leads to significant augmentation of the FI (Conte and Victor 2009). Therefore an increased windmill-dartboard fundamental response suggests stronger short range inhibitory interactions, whilst a decreased windmill-dartboard fundamental response suggests weaker short range inhibitory interactions.

Long-range interactions can be quantified by calculating a ratio referred to as the 'suppression index' (SI) (Conte and Victor 2009). This ratio compares the second harmonic response elicited by windmill-dartboard stimulation to the second harmonic response elicited by partial-windmill stimulation. A larger SI reveals stronger long-range lateral inhibition between neurons (Grose-Fifer et al. 1994; Vance Zemon and Ratliff 1982). Attenuation of the second harmonic response during windmill-dartboard stimulation relative to the second harmonic response during partial-windmill stimulation indicates the strength of long range interactions, with greater attenuation indicating stronger long-range interactions. However, whilst they are not indexing directly neighboring neurons, these stimuli are assaying connections on a millimeter scale. Therefore, whilst the term 'long-range' is used to describe these connections, it is important to note that these connections are still within primary visual cortex.

Recording SSVEPs to partial-windmill and windmill-dartboard stimuli has been used to index cortical lateral interactions in clinical populations such as schizophrenia, migraine headache, and epilepsy (Conte and Victor 2009; Coppola et al. 2013; Kim et al. 2005; Ratliff and Zemon 1984). Abnormal short-range inhibitory lateral connections have been found to be present in participants who experience migraine headaches using this method (Coppola et al. 2013). In addition, the GABAergic drug gabapentin has been shown to significantly increase the strength of short-range inhibitory lateral interactions in patients with epilepsy (Conte and Victor 2009).

The present study employs windmill-dartboard and partial-windmill stimuli in a SSVEP paradigm to investigate whether there are differences in either short- or long-range inhibitory lateral interactions in ASD. Previous literature would suggest that we may see increased inhibition in short range interactions in ASD (Bertone et al. 2005). However, both of the measures here could be considered short range in the context of previous functional connectivity studies. Therefore we can exploit the precise spatial resolution gained by using partial-windmill /windmill-dartboard stimuli to infer lateral inhibition and determine whether there are differences in lateral interactions between directly neighboring neurons, or longer range connections on a

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local scale in visual cortex. Increased short range inhibition in ASD would be supported here by increased amplitude of the fundamental response to windmill-dartboard stimulation in ASD compared to controls, which may also be present through an increased normalised FI response. Correspondingly, a decreased fundamental response or a decreased FI would indicate decreased short range inhibition. Increased long-range lateral inhibition in ASD would be supported by an increased SI response in adults with ASD compared to controls. By contrast, reduced long-range inhibition would be reflected in a reduced SI in ASD compared to controls.

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2. Method

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2.1. Participants

Sixty participants took part in the present study, 28 of whom had a diagnosis of ASD. Participants with ASD were recruited either from an existing participant database, or through a local NHS neurodevelopmental service that provides adult ASD diagnoses. Control participants, defined as individuals who have not received an ASD diagnosis, nor a first-degree relative with ASD, were recruited from an existing database of research volunteers. As described below, participants were required to have a minimum of 40 artifact-free trials in each condition to be included in the analyses. Five participants in the control group and four participants in the ASD group had excessive artifacts in their EEG recording and did not meet these requirements. Their data were therefore excluded from all analyses. All reported analyses therefore describe data from 25 participants with ASD and 27 control participants. Ten of the participants with ASD and eight control participants had taken part in a previous study conducted by our research group (Dickinson, Bruyns-Haylett, et al. 2016). Non-verbal intelligence was assessed in all participants using the matrix reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; (Weschler 1999). The two groups were closely matched on age, sex, and non-verbal intelligence. Demographic information is provided in Table 1.

Within the ASD sample, 22 participants had been diagnosed with Asperger's syndrome and three with autism. One participant with ASD had an additional diagnosis of ADHD; one had an additional diagnosis of OCD and one participant reported a history of seizures. Six participants with ASD and three control participants were taking medication at the time of the study. Removing the participants who were taking medication at the time of the study had no impact on the pattern of results and therefore results are reported with the data from these participants included.

Module four of the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2; (Gotham et al. 2007; Lord et al. 2000) was used to assess symptomology in the participants with ASD. The ADOS-2 is a standardised, semi-structured assessment tool used by both clinicians and researchers to assess communication and social interaction in ASD. 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 or absence of these behaviours. An algorithm score of 10 or above on the combined communication and social interaction subscales defines the cut-off for autism, and a score of 7 or above defines the cut-off for autism spectrum.

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The adult self-report version of the Social Responsiveness Scale 2nd Edition (SRS-2;(Constantino and Gruber 2012), a 65 item questionnaire, was used to assess social ability in both participants with ASD and control participants. A greater score on the SRS-2 indicates increased difficulties with reciprocal social communication . A T-score of 60 or above indicates the clinical cut-off for ASD. Neurotypical participants also completed the Autism Spectrum Quotient (AQ), a self-report questionnaire that measures autistic traits in the general population (Baron-Cohen et al. 2001). The AQ consists of 50 statements based around different social and communication preferences which participants indicate whether they agree or disagree with. The maximum score on the AQ is 50, with higher scores indicating a higher level of autistic traits. Autistic traits that do not reach clinical significance vary throughout the general population, and the AQ has been used by myriad studies to quantify autistic traits (e.g. Ruzich et al., 2015).

Due to time limitations, two participants with ASD did not complete the ADOS-2. Both of these participants scored above clinical cut-off on the SRS-2. Of the 23 participants who completed the ADOS-2, two did not meet the cut-off for autism spectrum. Out of these two participants, one scored above clinical cut-off on the SRS. Thus, one participant with ASD did not meet the criteria on the ADOS-2 or SRS-2, due to scoring below cut-off. As this participant had received an ASD diagnosis from a trained clinician, they were retained in our analyses (c.f. (Dickinson, Bruyns-Haylett, et al. 2016; Schwarzkopf et al. 2014). ADOS-2, SRS-2 and AQ scores are provided in Table 1.

The study received full ethical approval from the local research ethics committee. Participants provided informed written consent.

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Table 1. Demographic characteristics of participants included in analyses.

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Measure	Autism Spectrum Disorder Group	Control Group	Group Comparison	
	Mean (SD), Range or number (%)	Mean (SD), Range or number (%)	Student's t (or X^2)	p
Age (years)	36.01(14.69), 16-68	34.58 (15.02), 18-71	.35	.73
Sex (N females)	8 (32%)	11 (40.7%)	.43	.51
Matrix reasoning raw score	28.33(4.29), 15-34	27.59 (4.29), 20-34	.62	.54
Matrix reasoning T-score	56.28 (14.88), 0-72	57.30 (8.14), 39-70	-.31	.76
ADOS-2 Communication and Social Interaction Total	10.73 (3.76), 3-16 (N=23)			
SRS T-Score	72.82 (10.02), 49-90 (N=22)	50.44 (8.79), 38-81 (N=25)	8.15	.000
AQ Score		16.44 (8.58), 5-37		

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2.2. EEG

EEG data were collected using the BioSemi ActiveTwo system (BioSemi, Amsterdam, The Netherlands). Recordings were taken from 128 electrodes at a rate of 2048 samples/s. Data were filtered online with a bandpass of 0.01 -140 Hz and digitised using BioSemi ActiView software. Direct-current offset voltages kept below +/- 25 mV. Recordings were carried out in an electrically-shielded room.

2.2.1. Stimuli

Stimuli were displayed on a linearised Viglen LCD monitor with a spatial resolution of 1024 x 1024 pixels and a frame rate of 60 Hz. Stimuli were presented using the PsychToolbox set of functions (Brainard 1997) in MATLAB (The MathWorks Inc., Natick, MA, 2000). Participants were seated 57 cm away from the monitor, asked to sit comfortably and keep movement to a minimum in order to reduce any electromyography (EMG) related artifacts.

Stimuli were based on windmill-dartboard and partial-windmill stimuli (Vance Zemon and Ratliff 1982). The windmill-dartboard pattern (illustrated in Figure 1, Panel A) is made up of a red central fixation point, at the center of a disk surrounded by three contiguous annuli. The four regions are radially divided

into 16 segments that are defined by two different luminance levels (+/- 32% depth of modulation). The light and dark elements in the central disk and second annulus contrast reverse, while the light and dark elements in the first and third annuli are fixed, creating the perception of a windmill pattern that switches to a dartboard pattern when contrast reversed.

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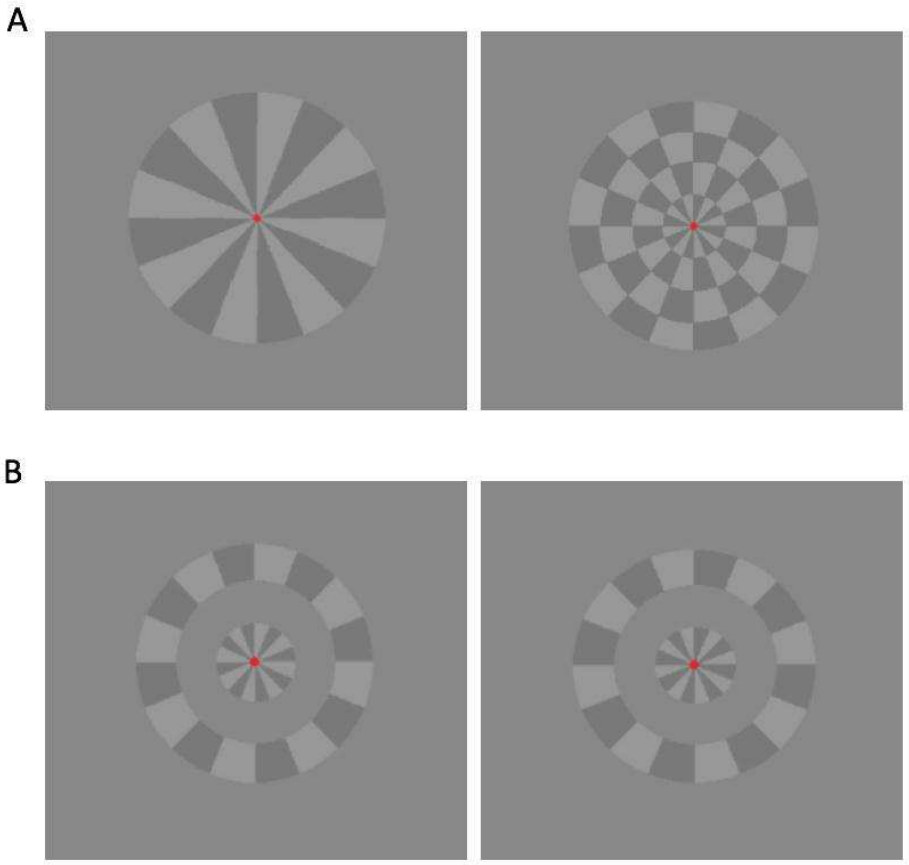

Figure 1. (A) Examples of the patterns used in the windmill-dartboard stimulus. (B) Examples of the patterns used in the partial-windmill stimulus.

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The partial-windmill pattern (illustrated in Figure 1, panel B) is identical to the windmill-dartboard, except for the first and third annuli. These annuli are not divided into segments and are instead set at a uniform (mean) luminance. The central disk and second annulus are radially divided, as in the windmill-dartboard condition, and these elements contrast reverse.

Therefore, in both stimuli there are dynamic regions (central disk and second annulus) in which the luminance-defined elements contrast reverse. In both stimuli, the first and third annuli are always static. In the windmill-dartboard pattern the alternate light and dark elements remain fixed. In both stimuli, the background is fixed at the mean luminance and the two levels of luminance in the patterned regions are set at a Michelson contrast of 32%.

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Stimuli in both conditions contrast-reversed at a frequency of ~3.72 Hz. Participants were instructed to fixate on a central red dot whilst viewing the stimuli. There were two blocks of each type of stimulus, which were presented randomly. Within each block, the contrast reversing stimuli were displayed for 100 seconds. Between each block of stimuli, participants had a self-timed break.

2.2.2. Offline EEG Analysis

Offline data analysis was performed using EEGLAB (Delorme and Makeig 2004), and in-house MATLAB scripts. Data were referenced to the vertex electrode. Data were high-pass filtered to remove frequencies below 0.1 Hz, and low-pass filtered to remove frequencies above 100Hz, using a finite impulse response filter, as implemented in EEGLAB.

Data analysis was restricted to one channel (which corresponds to Oz in the International 10-20 system), in line with previous studies that have employed this method (Kim et al., 2005; Conte and Victor, 2009; Coppola et al., 2013). Data were separated into 4-second epochs, based on stimulus onset markers. Any epochs with artifacts were removed. Only participants with at least 40 epochs in each condition were included in the final analysis. Participants with ASD had an average of 49.64 (SD=.81) epochs in the windmill-dartboard condition and 49.52 (SD=1.76) epochs in the partial-windmill condition. Control participants had an average of 49.59 (SD=.80) epochs in the windmill-dartboard condition and 49.63 (SD=.88) epochs in the partial-windmill condition. The number of epochs did not vary between the two groups for either the windmill-dartboard ($t(50)=.213$, $p=.83$) or partial-windmill condition ($t(50)=-.29$, $p=.78$).

2.2.3. Frequency Analysis

Epoched data from both the partial-windmill and windmill-dartboard conditions were averaged to one 4-second epoch for each participant for each condition. Using a fast Fourier transform (FFT), it was confirmed that all participants showed a clear spectral peak at 3.72 Hz (fundamental response) and 7.45 Hz (second harmonic response). Following this initial check of data integrity, a discrete Fourier transform was performed to extract the frequency components at 3.72 and 7.45 Hz for each condition. The first 538 ms of data were excluded from analysis in order to eliminate onset artifacts. The final 234 ms was also excluded from analyses. This period was chosen so as to not truncate a cycle of response. Thus, the data analysed for both the windmill-dartboard and partial-windmill conditions consisted of 3.23 seconds and represented 12 full cycles at the stimulus frequency of 3.72 Hz. Two variables were derived for each condition: the amplitude of the fundamental and second harmonic frequency components.

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In addition to obtaining the amplitude of fundamental and second harmonic components for each condition, normalised responses were obtained by calculating ratio scores, as described in the introduction, the facilitation index (FI) and the suppression index (SI):

FI = fundamental amplitude (windmill-dartboard condition)/second harmonic amplitude (windmill-dartboard condition)

SI = second harmonic amplitude (partial-windmill condition)/second harmonic amplitude (windmill-dartboard condition)

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3. Results

Independent sample t-tests were employed to assess whether there were any between-group differences between participants with and without ASD in any of the SSVEP metrics. All analyses indicated no significant group differences. In both the partial-windmill and windmill-dartboard conditions, there were no significant differences between groups in amplitude of the fundamental or second harmonic components (see Figure 2 & Table 2). There were no significant differences in the amplitude of either the fundamental ($t(50)=.75$, $p=.46$, $d=.23$) or second harmonic components ($t(50)=-.39$, $p=.70$, $d=.11$) in the partial windmill condition (see Table 2, and Figure 2A). There were also no significant differences in the amplitude of either the fundamental ($t(50)= -.65$, $p=.52$, $d=.18$) or second harmonic components ($t(50)= -.35$, $p=.73$, $d=.10$) in the windmill dartboard condition (see Table 2, and Figure 2B).

Table 2. Amplitude *(μV)* of components in partial-windmill and windmill-dartboard conditions, and normalised ratio scores, for both groups.

	ASD	TD	Group Comparison
Measure	M(SD)	M(SD)	Student's t (p value)
Partial-windmill Fundamental	.22 (.14)	.19(.12)	.75 (.46)
Partial-windmill 2nd Harmonic	2.22 (1.24)	2.35(1.21)	-.39(.70)
Windmill-dartboard Fundamental	1.68 (1.17)	1.92(1.48)	-.65(.52)
Windmill-dartboard 2nd Harmonic	2.09 (1.23)	2.22(1.30)	-.35(.73)
FI	.99 (1.00)	.94(.50)	.26(.80)
SI	1.14(.51)	1.15(.35)	.03(.98)

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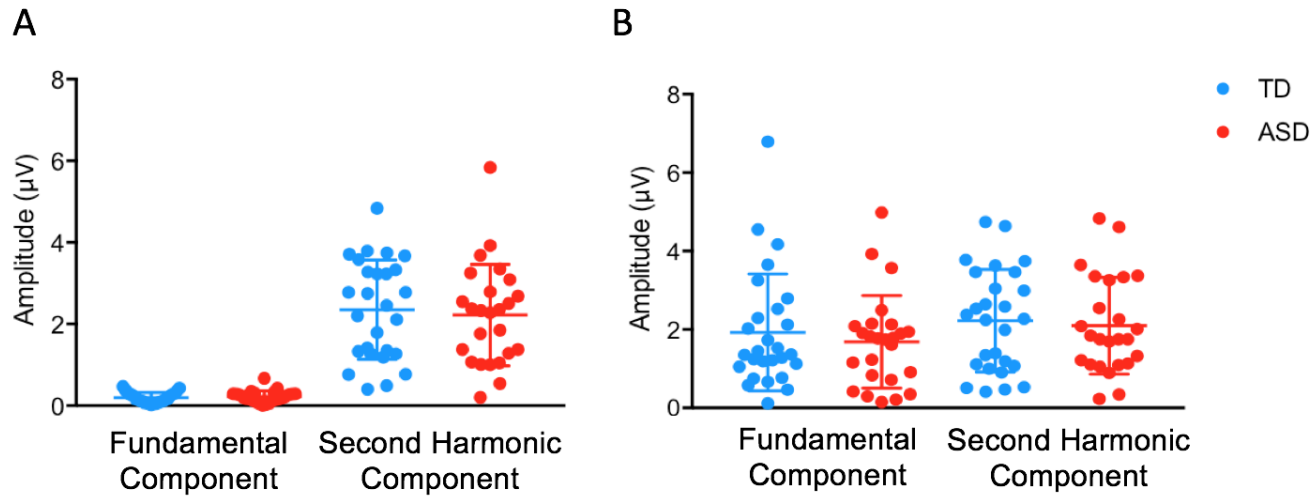

Figure 2. Dot plots demonstrating the amplitude of fundamental and second harmonic components (with group mean and error bars representing SD) for both ASD and control participants in (A) the partial windmill condition, and, (B) the windmill dartboard condition.

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There was also no significant difference in either the FI or the SI between the two groups (see Table 2, and Figure 3). The FI was not significantly altered between individuals with ASD and controls (t(50)=.26, p=.80, d=.06), with both groups, on average, showing no second harmonic suppression in the windmill-dartboard condition (compared to the fundamental component in the windmill-dartboard condition). The SI was not significantly altered between individuals with ASD and controls (t(50)=.03, p=.98, d=.02), with both groups, on average, showing weak suppression of the second harmonic response in the windmill-dartboard condition (compared to the second harmonic response in the partial-windmill condition).

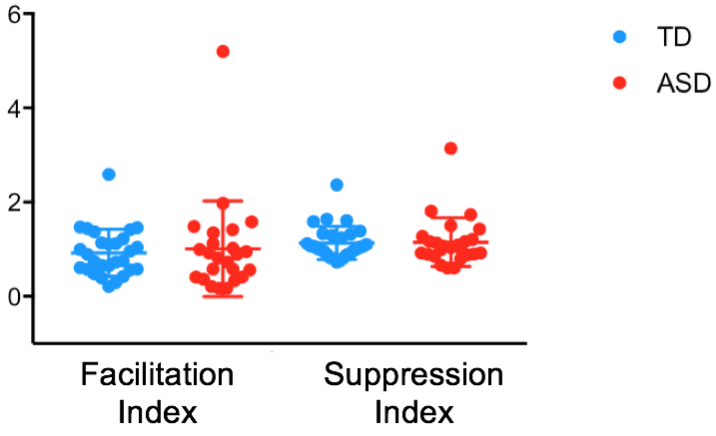

Figure 3. Dot plots demonstrating the facilitation index and the suppression index (with group mean and error bars representing SD) for ASD and control participants.

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Behavioral Correlation

Considering the heterogeneity of ASD, exploratory analyses were conducted to identify whether there was any association between ASD symptomatology and SSVEP metrics.

The amplitude of the fundamental component in the windmill-dartboard condition was significantly correlated with ADOS-2 score (r = .43, p =.04, 95% confidence interval (CI), [.02, .72], see Figure 4A). This relationship remained consistent after controlling for both age and matrix reasoning (r= 0.47, p= 0.03). No other amplitude measure was related to ADOS-2 score (Partial windmill fundamental r=0.18, p=0.42; Partial windmill harmonic: r=0.09, P=0.68; Windmill-dartboard harmonic: r=0.10, p=0.65; FI: r= 0.20, P=0.35; SI: r= -0.09, p=0.67). The relationships between ASD symptomology, as measured through self-report SRS-2 scores, and SSVEP metrics were also assessed. No EEG amplitude measure was associated with SRS-2 score in the ASD group (Partial windmill fundamental r=0.22, p=0.32; Partial windmill harmonic: r=0.12, P=0.60; Windmill-dartboard fundamental: r=0.12, P=0.60; Windmill-dartboard harmonic: r=-0.01, p=0.98; FI: r= 0.10, P=0.66; SI: r= 0.13, p=0.58, see Figure 4C).

The relationship between autistic symptomatology and amplitude measures was explored in the control group by studying measures of subclinical autistic traits. Similarly to ASD symptoms assessed through ADOS scores, increased scores on the SRS-2 were associated with the amplitude of the fundamental component in the windmill-dartboard condition (r=.47, P=.02, 95% CI, [.09, .73], see Figure 4C). This relationship remained consistent after controlling for both age and matrix reasoning (r=0.45, p=0.03). However, on closer inspection of the data it was clear that this relationship was driven by an outlier. No other amplitude measure was related to SRS-2 score (Partial windmill fundamental r=0.25, p=0.23; Partial windmill harmonic: r=0.21, p=0.31; Windmill-dartboard harmonic: r=0.27, p=0.19; FI: r= 0.20, p=0.34; SI: r= 0.03, p=0.90).

Increased AQ scores were associated with both amplitude of the fundamental component in the windmill-dartboard condition (r=.40, p=.04, 95% CI, [.02, .68]), and also the FI (r=.40, p=.04, 95% CI, [.02, .67], see Figure 4B). These relationships were not driven by an outlier, but do not remain significant after controlling for age and matrix reasoning (r=.0.37, p=0.07; r=.38, p=.06). No other amplitude measure was related to AQ score (Partial windmill fundamental r=0.05, p=0.80; Partial windmill harmonic: r=0.09, p=0.67; Windmill-dartboard harmonic: r=0.09, p=0.65; SI: r= 0.14, p=0.48).

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It should be noted that due to the large number of exploratory results presented here, no correlations would remain significant with a Bonferroni adjusted alpha level (.002).

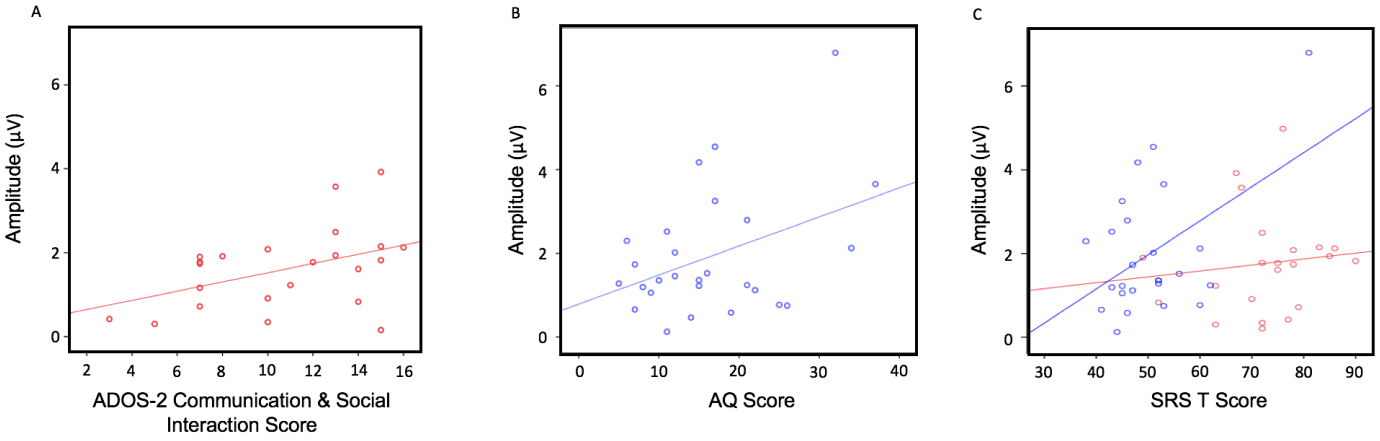

Figure 4. Scatter plots demonstrating the relationship between the amplitude of the fundamental component in the windmill dartboard condition and (A) ADOS scores in participants with ASD, (B) total AQ score in the control participants, and (C) SRS T scores in both participants with ASD (red), and control (blue) participants.

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4. Discussion

Here we investigated lateral inhibitory interactions in ASD using a SSVEP paradigm. No group-level differences were found between a high-functioning group of adults with ASD compared to age-matched control observers in the partial-windmill fundamental or second harmonic components. No group

differences were found in the normalised SI response, which compares the partial-windmill second harmonic to the windmill-dartboard second harmonic response. These results suggest that there are no differences in long-range lateral interactions in the sample of ASD adults studied here. In addition, no group differences were found in the fundamental or harmonic windmill-dartboard response, or in the normalised FI response, which compares the windmill-dartboard fundamental to the windmill-dartboard second harmonic response. These results suggest that short-range inhibitory lateral interactions are not significantly different in the sample of ASD adults studied here.

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The results presented here therefore suggest there are no group-level differences in lateral interactions in ASD. These results are inconsistent with previous reports of altered lateral interactions (Bertone et al. 2005; Dickinson, Bruyns-Haylett, et al. 2016; Kéïta et al. 2011; Vandenbroucke et al. 2008), and disrupted connectivity in ASD (Wass, 2011). There are many potential reasons for differences between the present results and those of previous studies investigating lateral interactions in ASD. The nature of the technique used to measure circuit level brain function could be one major source of variability. For instance, in the context of the pervasive difference that have been found in long range functional connectivity (Wass, 2011), as noted in the introduction, both the 'short-range' and 'long-range' interactions assayed here would be classed as short-range in studies inferring functional connectivity from fMRI or EEG data. Therefore we may see different results as we have examined interactions on a much smaller spatial scale than 'functional connectivity' in the conventional sense (i.e., between distributed brain regions).

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Discrepancies regarding if, and how, lateral interactions are altered in ASD are representative of the wider literature exploring E/I balance (of which lateral inhibition is an important aspect), in ASD. One hypothesis regarding the pathophysiology of ASD centers on differences in the balance of neural excitation and inhibition, which is mediated by the effective magnitude and timing of excitatory and inhibitory synaptic inputs to a cortical neuron or network. However, a diverse range of techniques have been used to investigate E/I balance and results vary across the literature, with finding of increased excitation relative to inhibition, increased inhibition relative to excitation, and no E/I imbalance (Dickinson, Jones, et al. 2016).

This inconsistent literature may reflect that E/I balance manifests across the autism spectrum differentially, and may be associated with key clinical features of the condition. One approach that may be more sensitive than studying group level differences is the investigation of individual differences in relation to E/I balance in ASD. This approach was taken by a recent study which found that measurements of the primary inhibitory neurotransmitter, GABA, did not differ between groups, suggesting no E/I imbalance in ASD (Brix et al. 2015). However, GABA levels were found to be associated with autistic symptomatology. Lower levels of GABA were associated with increased autism severity. This suggests that E/I balance may be altered differentially across the ASD spectrum.

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Therefore, in addition to comparing lateral interactions at a group level, we conducted additional exploratory analyses to assess whether variability in cortical lateral interactions was associated with a major source of individual differences across the autism spectrum: clinical severity of ASD symptoms. We found that the fundamental response to windmill-dartboard stimulation was associated with clinical severity, in that increased ASD severity (as measured by ADOS-2 algorithm scores) was associated with a higher amplitude of fundamental response. Given that this response reflects short-range lateral interactions, this finding indicates that increased ADOS scores may be associated with increased strength of lateral interactions. No other EEG variables were associated with clinical severity. It is important to note that the fundamental response was correlated with clinical severity, yet the normalised response was not. It is helpful to have a normalised response to account for absolute differences in EEG amplitude among participants. However, an association between the fundamental response in the windmill-dartboard condition in the absence of significant correlations with other EEG variables, would suggest that this relationship is likely to be specific to short-range lateral interactions, and is not driven by overall higher amplitude responses in participants with increased clinical severity. It should also be noted that whilst a higher amplitude fundamental response in the windmill dartboard condition was associated with ASD symptomatology based on ADOS scores in the ASD group, it was not related with self-report SRS-2 scores. The discrepancy between these two measure of ASD symptomatology may be due to the nature of the assessment (observer vs. self-report). Previous research has demonstrated divergence between ASD adults self-report of their own symptoms, compared to observer report (Bishop and Seltzer 2012). It is also a possibility that the association between clinical severity (ADOS) and EEG is a type I error.

The exploratory findings presented here suggest that variability in the strength of inhibitory lateral interactions may be associated with the heterogeneity of ASD, and speaks to the importance of appreciating that cortical interactions may not be altered consistently across the autism spectrum. However, it needs to be noted that the behavioral associations presented here are exploratory, and do not remain significant after correction for multiple comparisons. Future research will attempt to further investigate variability in lateral interactions specifically.

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4.1. Limitations & Future directions

The adults with ASD who took part in the current study are representative of only part of the autism spectrum. For instance, our results do not represent around half of the ASD population who show some degree of intellectual impairment (Charman et al. 2011; Rivard et al. 2015; Yeargin-Allsopp et al. 2003). In the future we will employ the SSVEP technique described here with a sample of participants who are more

diverse in terms of clinical presentation. This technique is particularly well suited to study a wide range of populations, as it requires no overt behavioural response, and it can also be collected during a relatively brief period of time, due to the robust SSVEP response. Exploratory data presented here suggest that the windmill-dartboard /partial-windmill SSVEP technique may provide useful insight into variability in lateral inhibitory connections associated with clinical heterogeneity in ASD. By employing a large and diverse sample of individuals with ASD in future studies, we ascertain whether this is the case, and shed light on E/I balance over the entirety of the autism spectrum.

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Future studies that explicitly investigate individual differences in lateral inhibition will also elucidate the relationship between individual differences in low level neurophysiological function and clinical features in ASD. For instance, atypical sensory processing is commonly reported in ASD (Baranek et al. 2006; Ben-Sasson et al. 2009; Cesaroni and Garber 1991; Jones et al. 2003; Smith and Sharp 2013; Tomchek and Dunn 2007). Sensory symptoms can affect a variety of modalities including vision (see (Simmons et al. 2009)for a review), audition (see (Haesen et al. 2011), and touch (Cascio et al. 2008). Sensory symptoms also manifest in a variety of ways, including both hyper- and hypo-responsiveness to sensory stimuli (Crane et al. 2009). Lateral inhibition plays a major role in low-level sensory processing. Therefore, studying individual differences in lateral inhibition may improve our understanding of the neurophysiological differences that underlie variability in sensory symptoms.

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4.2. Conclusion

Here we employ a windmill-dartboard/partial-windmill SSVEP technique to sensitively assay short-range cortical lateral interactions that are difficult to measure using conventional functional neuroimaging techniques, or psychophysical measures alone. These data clearly show that there is no difference in lateral interaction between a group of adults with ASD and a well-matched neurotypical control group. However, we cannot rule out the possibility that a different sample of participants with ASD (for example children, or a more diverse range of cognitive function), may show atypical lateral interactions. The fact that we did find a correlation between ADOS scores and the integrity of cortical lateral interactions may suggest that individuals with more severe ASD symptoms have atypical lateral interactions. However, a future investigation, with a different group of participants is required to confirm or refute this suggestion. The suggestion that the integrity of cortical lateral interactions is associated with clinical heterogeneity of ASD is important, as it highlights that the neurobiological underpinnings of ASD may not manifest in a ubiquitous way across the condition. Future research will address the specific nature of individual differences in lateral interactions in order to improve our understanding of how variability in cortical circuits and their dynamics contribute to the etiology of ASD.

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Highlights

Cortical lateral interactions are said to be atypical in autism spectrum disorder (ASD).

The specific nature of these differences are unknown.

The SSVEP response to carefully designed visual stimuli can assay lateral interactions.

Lateral interactions within visual cortex are intact in ASD at a group level.

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