

A Physiological Assessment of Lateral Interactions Within
the Early Visual Areas of Adults with ASD

Sabrina Censi, School/Applied Child Psychology

McGill University, Montreal

July 2014

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree
of Masters of Arts in Educational Psychology
© Sabrina Censi, 2014

Acknowledgements

Firstly, I would like to thank my supervisor, Dr. Armando Bertone, for all of the help and support in making this project possible; as well as all of his dedication in helping develop my skills as a competent researcher. I would also like to thank him for his financial support, as it has helped me greatly. Secondly, I would like to thank our collaborator, Dr. Dave Saint-Amour, for allowing me to use his laboratory to conduct the electrophysiological testing, and Mathieu Simard for analyzing the data collected; in addition to them taking the time to train me and answer all of my questions. I would also like my fellow lab members for the many discussions of research methodology and recruitment issues. Finally, I would like to thank all of the participants for their time and interest in the project.

Table of Contents

Acknowledgements	II
List of Figures	VI
Abstract	VII
Résumé	IX
Introduction	1
Background Rationale	1
Objectives	2
Chapter 1	3
Literature Review	3
Autism Spectrum Disorder	3
Perceptual Processing in ASD	4
Theoretical Frameworks Regarding Altered Perceptual Processing in ASD	5
Weak Central Coherence	5
Enhanced Perceptual Functioning	6
Altered Excitatory-Inhibitory Imbalance in ASD: possible Role in Perception	7
Using Steady State Visual Evoked Potentials to Assess the Integrity of Early Visual Processing in ASD	9
Windmill-Dartboard Paradigm	10
Lateral Masking Paradigm	12
Limitations to Previous Research	13
Current Study	13
Aim	14

Hypotheses	14
Chapter 2	14
Method	14
Participants	14
Study 1	15
Objective	15
Apparatus	16
Stimuli and Procedure	16
VEP Recording Procedures	16
Study 2	18
Objective	18
Procedure	18
Stimuli and Apparatus	18
VEP Recording Procedures	19
Chapter 3	20
Results	20
Data Analysis for the Windmill-Dartboard Paradigm	20
FI Differences between ASD and Comparison Groups	20
SI Differences between ASD and Comparison Groups	21
Data Analysis for the Lateral Masking Paradigm	22
Facilitatory and Suppression Responses at Target-Flanker Distance of 1.5 Lambda	23
Facilitatory and Suppression Responses at Target-Flanker Distance of 3 Lambda	25

Facilitatory and Suppression Responses at target-flanker distance of 3 lambda	27
Chapter 4	29
Discussion	29
Summary of Results	31
Lateral Interactions with the Windmill-Dartboard Stimuli	31
Lateral Interactions with the Lateral Masking Paradigm	32
Conclusions	33
General Discussion	33
Strengths	34
Limitations	35
Future Directions	36
Implications	36
Fundamental Research Level	36
Diagnostic and Intervention Level	37
References	38

List of Figures

Figure 1. Examples of Zemon & Ratliff's Windmill–Dartboard (W/D) stimuli	17
Figure 2. Examples of Polat, Sagi & Norcia's lateral masking paradigm	19
Figure 3. Graph showing the windmill-dartboard FI indices	21
Figure 4. Graph showing the windmill-dartboard SI indices	22
Figure 5. Graph showing the facilitatory responses at 1.5 lambda	24
Figure 6. Graph showing the suppression responses at 1.5 lambda	25
Figure 7. Graph showing the facilitatory responses at 3 lambda	26
Figure 8. Graph showing the suppression responses at 3 lambda	27
Figure 9. Graph showing the facilitatory responses at 6 lambda	28
Figure 10. Graph showing the suppression responses at 6 lambda	29

Abstract

Background

The importance of early perceptual alterations with regards to higher-level perceptual and cognitive functioning in Autism Spectrum Disorder (ASD) is increasing. This increase is due in part to several studies demonstrating altered autistic sensitivity to a variety of non-social visual, auditory and tactile stimuli whose perception is contingent on the functional integrity of early, *local* neural mechanisms. However, although atypical performance on non-social, visuo-spatial tasks is a defining characteristic of ASD, few biologically plausible hypotheses are available to explain them. Some have theorized that individuals with ASD may have atypical local connectivity resulting in altered response properties of early visual feature detectors, such as those processing simple visual patterns. The goal of these studies was to assess this hypothesis by measuring brain activity to simple visual information that is mediated by local, lateral interactions. To do so, steady-state visual evoked potentials (ssVEPs) to visual information mediated by lateral connectivity was measured in a group of adults diagnosed with ASD.

Methods

Nine participants with ASD and 11 typically developing participants, matched for full-scale IQ and age (18-35 years), were asked to passively view visual stimuli during Windmill-Dartboard (Ratliff & Zemon, 1982) and lateral masking paradigms (Polat, Sagi, & Norcia, 1997) while ssVEPs from four electrodes over the occipital cortex (Oz, POz, O1 and O2) were collected. For the Windmill-Dartboard paradigm, first- and second-harmonic components of the steady-state responses were used to calculate indices reflecting local facilitatory (FI) and inhibitory (SI) cortical interactions for all participants. For lateral masking paradigm, ssVEP data was collected while participants viewed low-contrast Gabor patches presented either in isolation (target), or

flanked by collinear/orthogonal Gabors at different contrasts (8, 16, 30%) and target-flanker distances (1.5λ , 3λ , 6λ).

Results

Group differences were not evidenced for either FI or SI cortical interaction indices obtained during the Windmill-Dartboard task. For the lateral masking paradigm, the results demonstrated between group differences in lateral interactions under specific experimental conditions. There were statistically significant facilitatory responses at a distance of 3λ , for both the ASD (at a contrast of 30%) and comparison group (at a contrast of 8%). However, only the comparison group demonstrated statistical significance of a suppression response at a contrast of 16%. In addition, only the comparison group demonstrated statistical significance of a suppression response at a contrast of 16% at a distance of 6λ .

Conclusion

The current studies attempted to directly examine lateral interactions by measuring steady-state visual evoked potentials (ssVEPs) elicited by Windmill-Dartboard and lateral masking paradigms. A lack of between group differences in ssVEP responses elicited by the Windmill-Dartboard task suggests unremarkable local facilitatory (FI) or inhibitory (SI) cortical interactions in ASD. However, ASD-specific demonstrations of increased suppression responses under certain experimental conditions during the lateral masking paradigm suggests that altered local lateral connectivity is at least in part responsible for early perceptual alterations manifested by individuals with ASD.

Résumé

But

Les altérations tôt de la perception en ce qui concerne le fonctionnement perceptif au niveau supérieur et le fonctionnement cognitif pour les individus avec trouble du spectre autistique (TSA) devient plus important. Cette hausse d'importance est en partie à cause de plusieurs études démontrant la sensibilité pour les individus autistes à une variété de stimuli visuels de base non-sociale dont la perception est subordonnée à l'intégrité fonctionnelle des mécanismes neuronaux tôt et locales. La performance atypique de la perception non-sociale est une caractéristique de l'autisme, mais il existe seulement quelques hypothèses plausibles pour les expliquer. Certains ont émis l'hypothèse que les personnes autistes peuvent avoir la connectivité locale atypique résultant dans des propriétés de réponse modifiés, tels que ceux du traitement des motifs visuels simples, tôt dans le système visuelle. L'objectif de ces études était d'évaluer cette hypothèse en mesurant l'activité du cerveau pour l'information visuelle simple, qui est médiée par des interactions latérales locales. Ceci est fait en usant des potentiels évoqués visuels (PEV) à l'information visuelle médiée par la connectivité latérale induite par des stimuli et des paradigmes visant l'intégrité de la connectivité latérale dans un groupe d'adultes diagnostiqués avec TSA.

Méthodes

Neuf participants avec TSA et 11 participants en développement typique, appariés pour QI et de l'âge (18-35 ans), ont été invités à regarder passivement des stimuli visuels comprenant de windmill-dartboard (Ratliff & Zemon, 1982) et lateral masking (Polat, Sagi, & Norcia, 1997). Entre temps, les PEV (steady state) de quatre électrodes sur le cortex occipital (oz, POZ, O1 et O2) ont été recueillies. Pour la tâche windmill-dartboard, les indices reflétant des interactions

corticales facilitatrices (FI) et inhibitrice (SI) pour tous les participants ont été calculer. Pour la tâche lateral masking, les données PEV ont été recueillies alors que les participants regardaient des Gabor patches présentés en isolement (cible), ou flanqués avec des Gabors colinéaires/orthogonales à différents contrastes (8, 16, 30%) et distances cible-flanker (1.5λ , 3λ , 6λ).

Résultats

Il n'y avait pas de différences entre les groupes pour les deux indices d'interaction corticaux FI ou SI obtenus avec la tâche windmill-dartboard. Pour la tâche lateral masking, les résultats ont montré qu'il y avait des différences dans les interactions latérales entre les deux groupes dans certaines conditions expérimentales. Il y avait des réponses statistiquement significatives de facilitation, à une distance de 3λ , pour le groupe autiste (à un contraste de 30%) et pour le groupe de comparaison (à un contraste de 8%). Cependant, seulement le groupe de comparaison a démontré une réponse statistiquement significative signification statistique de suppression à un contraste de 16%. De plus, seulement le groupe de comparaison a démontré une réponse statistiquement significative de suppression à un contraste de 16% à une distance de 6λ .

Conclusion

Les études actuelles ont tenté d'examiner directement les interactions latérales en mesurant des potentiels évoqués visuels steady-state provoquées par des tâches windmill-dartboard and lateral masking. Il n'y avait pas de différences entre les groupes pour la tâche windmil-dartboard, suggérant rien de surprenant pour les interactions corticales facilitatrices (FI) et inhibitrice (SI) dans l'autisme. Pourtant, il y avait des réponses de suppression dans lequel le groupe TSA a toujours eu une augmentation de suppression par rapport au groupe de comparaison pour la tâche de lateral masking. Étant donné que ce type de réponse ne se retrouve pas chez les participants en

développement typique, ces résultats suggèrent que la connectivité latérale locale atypique dans TSA est au moins en partie responsable pour la modification de la perception tôt pour les individus atteints de TSA.

Introduction

Background Rationale

Autism spectrum disorder (ASD) is one of the most prevalent and pervasive disorders of development, with an estimated prevalence between 2-3% (Blumberg et al., 2013; Kim et al., 2011). This neurodevelopmental condition is typically characterized by qualitative impairments in social and communication skills, as well as in the presence of restricted interests and behaviours (APA, 2013). Interestingly, a significant proportion of both non-social and social behaviours in autism are related to the visual domain, presented as either atypically absent behaviours, such as lack of interpersonal eye contact, or atypically present behaviours such as preoccupation with flickering or spinning objects. For the most part, the majority of vision-related research in autism has been concerned with assessing perceptual processes related to cognitive and/or social aspects of the autistic behavioral phenotype including peaks of performance on visuo-cognitive tasks (Bertone et al, 2003; Bertone et al, 2005), atypical face/gaze perception (Schultz, 2005), and visually-contingent joint attention behavior (Mundy et al., 2009). This focus on social and cognitive tasks is not surprising given the diagnostic relevance of such high-level impairments. However, it is this type of research that has been used to develop neurocognitive theories suggesting altered connectivity between functionally specialized networks comprising large-scale neural systems involved in social and executive functioning in autism (Brock et al., 2002; Castelli et al., 2002; Just et al., 2004; Rippon et al., 2007). As a consequence, early perceptual processing has been overlooked as an important contributing factor to cognitive and/or social impairments in autism (Belmonte et al., 2004). The importance of early perceptual alterations with regards to higher-level functioning has recently changed, due in part to various studies demonstrating a local feature bias to visual processing,

along with other studies that have shown altered autistic sensitivity to a variety of stimuli whose perception is contingent on the functional integrity of early, local neural mechanisms (Bertone et al., 2003; Behrmann, Thomas & Humphreys, 2006; Bertone et al., 2005; Dakin & Frith, 2005; Franklin et al., 2010; Simmons et al., 2009; Tommerdahl et al., 2008; Vandenbroucke et al., 2009).

Objective

There are few biologically plausible hypotheses that attempt to account for atypical lower-level perceptual processing in ASD (Vattikuti & Chow, 2009). One of which was proposed by Bertone and colleagues (2005), who suggest that the most biologically plausible type of atypical local connectivity congruent with their results is that of altered (i.e., strong or excessive) lateral inhibition (Gustafsson 1997a; Gustafsson 1997b; Gustafsson 2004), resulting in the inadequate formation of cortical feature detectors. More so, it is one of few data-driven and testable neural models that can account for both enhanced and diminished perceptual performance in autism that is contingent on the physical attributes defining the information being extracted. This theory has also been used to explain findings of impaired object boundary detection and altered effects of somatosensory stimulation in the tactile domain in autism (Tommasdall et al., 2008; Vandenbroucke et al., 2008). However, direct neurophysiological support for this hypothesis has yet to be demonstrated.

The proposed electrophysiological study has two parts. The first will assess whether atypical lateral interactions can be directly observed while the second will assess the effect of this expected increase in lateral inhibition on facilitatory and inhibitory responses on another type of visual paradigm. These studies represent the first direct assessment of whether lateral

connectivity is disordered in the brains of autistic individuals compared to typically developing individuals, consequently explaining the low-level processing differences seen in autism.

Chapter 1

Literature Review

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental condition that is typically characterized by qualitative impairments in social and communication skills, as well as in the presence of restricted interests and behaviours (APA, 2013). ASD is one of the most prevalent and pervasive disorders of development, with an estimated prevalence between 2-3% (Blumberg et al., 2013; Kim et al., 2011). Recently, there were changes in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) that now combines Autistic Disorder, Asperger Disorder and Pervasive developmental Disorder-Not Otherwise Specified PDD-NOS into a single Autism Spectrum Disorder diagnosis. This change is supposed to better reflect the dimensional nature of the disorder. In addition, the DSM-5 now collapses the domains of impairments in social and communication skills, as well as emphasising a hyper- or hyporeactivity to sensory inputs (APA, 2013). Sensory issues in ASD have always been a part of the disorder, as seen by Kanner's (1943) description of the children's reactions to loud noises and moving objects. ASD is a heterogeneous condition and no two individuals have the same profile. However, the difficulties all fall into the core domains and can be reliably measured, even with specific behaviours changing with development (Lord & Cook, 2013). Although there is a strong genetic component to ASD, diagnosis is solely based on behavioural measures including the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 2000) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter & Le Couteur, 1994). The most

common treatment approach for ASD includes educational and behavioural interventions, along with family support and an emphasis on functional communication (Lord & Cook, 2013).

Although sensory issues have always been part of ASD, the DSM 5 currently emphasizes hyper- or hyporeactivity to sensory inputs or unusual interests in sensory aspects of the environment which may better help explain perceptual processing in ASD.

Perceptual Processing in ASD

There are various explanations that try to elucidate perceptual processing for individuals with ASD and the atypicalities commonly found in this disorder. Over the years, there has been increasing evidence that demonstrates impairments in lower-levels of perception (i.e., non-social information) which affect performance on higher-level perceptual and cognitive tasks, and is independent of social functioning (Behrmann, Thomas & Humphreys, 2006; Bertone et al., 2003; Bertone et al., 2005; Mottron et al., 2006; Vandenbroucke et al., 2008). In general, individuals with ASD have a preference for local processing, argued to result in their often superior performance on the Block Design task of the Wechsler intelligence Scales, the Embedded Figures task and the Navon task (Behrmann, Thomas & Humphreys, 2006; Mottron et al., 2006). However, they have more difficulty than controls to group or integrate information into a coherent whole, a process that is necessary to complete higher-level perceptual tasks (i.e., face processing, global motion paradigms). Such tasks are referred to as more complex in nature, since they require additional neural processing to be resolved. It has been demonstrated that autistics process more complex visual stimuli less efficiently than neurotypicals (Bertone et al., 2003; Bertone et al., 2005; Mottron et al., 2006), and some of their observed atypicalities towards social information may be due to their attempt to limit excessive amount of information by self-stimulating or manipulating their perception of their perceptual environment (i.e.,

performing lateral glances). Furthermore, although they have typical levels of performance on tasks, they have an enhanced activation of visuo-perceptual regions in association with a diminished activation in regions that are devoted to higher order or socially relevant tasks (Mottron et al., 2006). These and other findings have led to the conclusion that perception plays a different and superior role in autistic cognition (Mottron et al., 2006). These results have also supported the general consensus that “perceptual features at low levels of processing are closer to autism’s core than previously believed” (Belmonte et al., 2004). In fact, several recently published review papers have outlined that autistic performance on perceptual tasks is both enhanced and diminished, often depending on the physical attribute of the visual information being extracted (Behrmann, et al. 2006; Bertone et al. 2010; Mottron, et al. 2006; Simmons et al. 2009). It is important to note that these visually-related performances are often specific to autism, having not been documented in other developmental conditions. Although it has been clearly established that local neural mechanisms underlying early perceptual processes are different in autism, there is little direct research done on the neurobiological explanation for this preference.

Theoretical Frameworks Regarding Altered Perceptual Processing in ASD

Weak Central Coherence

Central coherence is the idea that individuals process information in context allowing information to be pulled from higher-ordered processing. Simply put, it is the ability to attend to global information as opposed to more local and detailed information. On the other hand, a weak central coherence is the ability to better attend to local information as opposed to global information which reduces the ability to understand contextual meaning (Hill & Frith, 2003). The Weak Central Coherence (WCC) model, first described by Frith (1989), tries to explain the

detail-focused processing style thought to be common of individuals with ASD. At a neural level, the idea behind WCC hypothesis is that individuals with ASD may have poor connectivity throughout the brain, especially between areas responsible for low-level visual processing and higher-order cortical processing (Hill & Frith, 2003). Individuals with ASD perform better when local processing is needed such as the Block Design task of the Wechsler intelligence Scales or the Embedded Figures task as opposed to more global processing such as understanding a story being read to them (Hill & Frith, 2003). After some criticism, the WCC model has been modified to now suggest that individuals with ASD have a superior local processing style instead of a deficit in extracting global form and meaning. Also, the authors acknowledge that WCC does not explain deficits in social cognition (Happé & Frith, 2006).

Enhanced Perceptual Functioning

An alternative to the WCC theory is the Enhanced Perceptual Functioning (EPF) model, first proposed by Mottron and Burack (2001). This model proposed that individuals with ASD process visual information in a more locally oriented manner. As well, individuals with ASD perform better on visual tasks that use neurally simple visual stimuli (luminance-defined of first-order information) compared to more complex visual stimuli (texture-defined of second-order information). Furthermore, although individuals with ASD may demonstrate typical levels of performance on tasks, the findings from a recent meta-analysis suggests an enhanced activation of visuo-perceptual regions during cognitive task completion in ASD, in association with a diminished activation in regions that are devoted to higher order or socially relevant tasks (Samson et al., 2012). These and other findings suggest that perception plays a different, and possibly, a superior role in autistic cognition.

Although the WCC and EPF are valuable in terms of conceptual frameworks for understanding characteristic perceptual atypicalities in ASD, they do not elucidate on the neural underpinnings of such perceptual differences. However, as described in the subsequent section, there is a growing body of evidence suggesting that there is an imbalance in inhibitory-excitatory circuitry in ASD that may help explain the atypical perceptual functioning in this population (Bertone et al., 2005; Casanova et al., 2003; Gustafsson, 1997a ; Rippon et al, 2007; Rubenstein, 2010; Tommerdahl et al, 2007; Vandenbroucke et al, 2008).

Altered Excitatory-Inhibitory Imbalance in ASD: possible role in perception

A popular unifying theory for what causes ASD, as first described in 2003 by Rubenstein and Merzenich, is that the disorder reflects an imbalance between excitation and inhibition in the brain, in particular in circuits governing sensory processes, memory, and social and emotional behaviors. Various genetic and environmental factors may converge, in different combinations in different individuals, to produce a higher excitation/inhibition (E/I) ratio.

Recently, researchers have applied this hypothesis to sensory processing, describing the imbalance between GABA (the predominant inhibitory neurotransmitter) and glutamate (the predominate excitatory neurotransmitter) transmission as a possible origin for atypical perception in ASD. At the molecular level, researchers have found impairments with cellular minicolumns in individuals with ASD. Minicolumns are vertical columns that are involved in the organization of neurons and pathways in the neocortex, as well processing thalamic inputs through excitatory and inhibitory neurons. Lateral inhibition also plays an important role during the formation of minicolumns within the brain (Buxhoevedon & Casanova, 2002; Rubenstein & Merzenich, 2003; Silberberg et al. 2002). It has been hypothesized that minicolumns in ASD are more numerous and narrower compared to neurotypical individuals (Casanova et al., 2002; Gustafsson, 1997a;

Gustafsson, 1997b), possibly resulting from altered lateral inhibition in ASD. In addition, Gustafsson (1997a) posited a hypothesis that proper self-organization of feature maps does not take place in ASD, leading to excessive lateral inhibition narrowing the range of information for a column. On the other hand, Rubenstein and Merzenich (2003) postulated that at least some forms of autism are caused by a disproportionate high level of excitation (or disproportionately weak inhibition) in neural circuits that mediate language and social behaviors. Regardless of the direction of inhibitory-excitatory imbalance, an alteration may account for some aspect of autistic behavior (Casanova et al., 2002; Gustafsson, 1997a; Rubenstein & Merzenich, 2003). An imbalance biases the information-processing system toward more discrimination and may explain some of the features of ASD such as savant skills and hypersensitivities of all sensory modalities (Casanova et al., 2003).

As reviewed, influential cognitive hypotheses concerned with visual information processing in autism have reconciled atypical elementary and social perception in ASD by suggesting that autistic perception is locally-oriented, resulting often in enhanced performance on tasks where a local or detailed visual analysis is advantageous. Concurrently, such detailed analysis also results in inferior performance where an integrative or global approach is usually needed, particularly when such information is socially-laden, such as that conveyed by face perception (Behrmann, Thomas & Humphreys, 2006; Dankin & Frith, 2005; Mottron et al., 2006). This predominantly detailed analysis has been attributed to either a bottom-up processing style dominated by the altered activity of local visual mechanisms (Bertone et al., 2010; Mottron & Burack, 2001; Mottron et al., 2006), and/or a reduced influence, or dysfunction of *large-scale* neuro-integrative mechanisms resulting in a reduced global representation of non-social or social information (Frith & Happe, 1994; Happe & Frith, 2006).

The aim of the proposed studies is to assess whether local lateral interactions operating within early cortical areas in high-functioning autism differ from neurotypical observers. Although atypical local connectivity has been proposed in other sensory modalities in autism (Tommardal et al., 2008 – somatosensory), we are using the visual system – primary visual area or V1 - as an experimental model since its neuro-functional characteristics are relatively well-defined. In addition, neural network models suggest that both excitatory and inhibitory synaptic potentials contribute to lateral interactions in V1 (Zemon et al, 1980; Zemon & Ratliff, 1984), which are in turn intrinsically implicated in the response properties of early mechanisms mediating orientation and spatial frequency selectivity. The approaches used in the studies will be discussed in detail in the following sections.

Using Steady State Visual Evoked Potentials to Assess the Integrity of Early Visual Processing in ASD

The visual evoked potential (VEP) is the summed activity of a multiplicity of neuronal events. VEPs recorded from the surface of the head are commonly used in basic research on vision. One of the advantages of using VEPs is that it has clinical validity as a useful diagnostic tool in areas such as amblyopia, multiple sclerosis, and Parkinson's disease. More so, this diagnosis is achieved by the analysis of simple attributes of the VEP waveform, including amplitude and latency (Conte & Victor, 2009; Zemon & Ratliff, 1982).

Steady state visual evoked potentials (ssVEPs) have synchronous and high rates of repetition that prevents the sensory pathways from recovering before the presentation of the next stimulus. These elicited responses are considered to be continuous and are referred to as ssVEPs (Di Russo, Teder-Sälejärvi & Hillyard, 2002; Vialatte et al., 2010). The waveform for the ssVEP is sinusoidal in shape and is modulated at the fundamental stimulus frequency for unstructured

stimuli or at the second harmonic (double the stimulation frequency) for pattern-reversal stimuli. Measurement of the ssVEP is done by its amplitude (relative magnitude of a given harmonic of the response) and phase (stimulus frequency and the time delay between stimulus and brain response) (Di Russo, Teder-Sälejärvi & Hillyard, 2002; Vialatte et al., 2010).

Advantages to using ssVEPs include easily recordable and quantifiable signals as well as a signal that can be rapidly extracted from background noise. Furthermore, ssVEPs provides sensitive measure of spatial attention processes with emphasis on continuous measure of attentional focusing and switching processes. Also, the different temporal response characteristics of the magnocellular (the dorsal stream: where we are and how we guide movement) and parvocellular (the ventral stream: what we see) visual pathways allows for the study of the mechanisms of attentional modulation of these pathways in relative isolation from one another (Di Russo, Teder-Sälejärvi & Hillyard, 2002; Vialatte et al., 2010).

The current studies utilize two clinically validated paradigms that have previously been demonstrated to elicit lateral interactions and applying them to ssVEPs will allow for signals that can be easily recorded and extracted for analysis of atypical lateral interaction in ASD. These two stimuli are the Windmill-Dartboard and lateral masking paradigms.

Windmill-Dartboard Paradigm

The windmill-dartboard stimulus is a typical pattern-reversal stimulus with components that are driven by local luminance, local contrast and pattern information. All of these components are superimposed and are all activated at each reversal of the windmill-dartboard stimulus. It is possible to separate these components by comparing steady-state responses to spatially related stimuli in which local luminance changes have been equated but spatial contrast changes differ (Conte & Victor, 2009). For the current study, a similar strategy is applied to an

autism population to try to identify changes in neural interactions associated with this disorder by using the windmill-dartboard paradigm. Although the mechanisms of low level visual processing largely remain unexamined, it is hypothesized that there is atypical lateral interactions therefore explaining the use of VEPs to probe local lateral interactions.

The windmill-dartboard stimulus is designed so that some mechanisms respond to local luminance in an identical fashion, while others are more responsive to local contrast. This stimulus can also target separate kinds of lateral cortical interaction (Conte & Victor, 2009). This approach targets interactions that are highly local and that both excitatory and inhibitory synaptic potentials contribute to these lateral interactions (Conte & Victor, 2009).

Lateral interactions in the windmill-dartboard method are isolated by comparing responses to two stimuli. The first stimulus (W/D-OFF) consists of steady-state pattern-reversal of the center disk and annulus, while the second stimulus (W/D-ON) consists of the same modulated components as in the W/D-OFF stimulus, but two additional static annuli are present (Conte & Victor, 2009; Zemon & Ratliff, 1982). The first stimulus is a pattern-reversal modulation of a circular checkerboard and elicits a response whose waveform contains nearly identical responses at each phase of the reversal. The second stimulus is a reversal of the modulated regions that produces a transition between a *windmill*, with a small number of contours, and a *dartboard*, with a larger number of contours and edges (Conte & Victor, 2009; Zemon & Ratliff, 1982). It is this change in contrast across the borders of the contiguous static and dynamic regions that create a very different response waveform. Highly localized lateral interactions result from the varying contrast at common borders of contiguous static and dynamic segments (Zemon & Ratliff, 1982). The VEP changes are quantified by a facilitation index (FI) and a suppression index (SI). These indices reflect the different kinds of lateral interactions of

the VEP response (Conte & Victor, 2009). The second harmonic of the stimulus frequency is comprised of all even Fourier components and the second harmonic elicited by the W/D-OFF stimulus is larger than the second harmonic elicited by the W/D-ON stimulus. On the other hand, the fundamental stimulus frequency is comprised of all odd Fourier components and is elicited by the W/D-ON stimulus but not the W/D-OFF stimulus. The indices calculated from the Fourier components of the steady state are as follows: Facilitation Index (FI) = Fundamental (W/D-ON)/2nd Harmonic (W/D-ON) and Suppression Index (SI) = 2nd Harmonic (W/D-OFF)/2nd Harmonic (W/D-ON). The use of ratios helps to normalize for overall response size (Conte & Victor, 2009).

Recently, Weinger (2013) utilized electrophysiological methods to assess the visual pathways in children with ASD and demonstrated that the windmill-dartboard stimuli produces strong inhibitory lateral interactions in the ASD group, providing support for the theory of atypical lateral interactions for this population.

Lateral Masking Paradigm

The human visual system is comprised of neural channels that are selectively sensitive to different ranges of spatial frequencies and orientations. For the most part, the outputs from one channel do not affect the activity of channels responding to other ranges of spatial frequencies, orientations or spatial locations. However, there are still some inhibitory inputs that get received from channels from spatially overlapping receptive fields coding for neighboring spatial frequencies or orientations (Polat & Sagi, 1993). Researchers have demonstrated that there is evidence for lateral interactions between spatial filters, and go beyond that of a single receptive field. These lateral interactions between spatial filters are considered to be long range interactions between cells of similar orientation (Polat & Sagi, 1993).

The lateral masking paradigm consists of three Gabor signals arranged vertically, and utilizes the spatial interactions between channels that are sensitive to different spatial locations (Polat & Sagi, 1993). The central Gabor, which is viewed foveally, can be facilitated or suppressed by laterally placed Gabor patches. Facilitation occurs when laterally placed Gabor patches that are collinear, while suppression occurs when Gabor patches that are orthogonal to the central Gabor. As well, separation and contrast also affect these interactions (Polat & Sagi, 1993).

The lateral masking paradigm has been used behaviourally in an ASD population since contextual modulation effects have been evidenced at a behavioral level (Keita et al., 2011). Keita and colleagues (2011) have demonstrated that lateral interactions in ASD differ from a comparison group under certain experimental conditions. Specifically, the collinear facilitation was significantly greater for the ASD group as well as an increase in sensitivity to varying contrasts on facilitation compared to the comparison group. There is therefore evidence for atypical lateral interactions in ASD at the behavioural level.

Limitations to Previous Research

Regardless of the theoretical framework in ASD, there are still difficulties in combining research findings to create well-defined theories. Some of the challenges preventing well-defined theories include heterogeneous groups, wide-ranging age groups, and changes in symptomology over time (Fecteau et al., 2003; Tager-Flusberg, 2004). Also, there are few direct assessments of the theory of atypical lateral interaction proposed by Bertone and colleagues (2005) since a majority of the research in visual processing has focused on higher-order perceptual functioning instead of basic visual procession.

Current Study

Aim

The current study attempts to directly examine low-level visual processing using passive stimuli without requiring the completion of behavioral tasks. Lateral interactions are systematically assessed between neurons within early visual areas in autism using by measuring steady-state visual evoked potentials (ssVEPs) elicited by windmill-dartboard and lateral masking paradigms.

Hypotheses

If atypical lateral interactions are presented in the ASD group, amplitude of the first and second harmonic response components is expected to differ from that of the neurotypical participants (or comparison group) during the windmill-dartboard paradigm. Atypical lateral connectivity in the form of excessive lateral inhibition in the ASD group would result in an increased suppression index. Typically facilitation is expected when the orientation of the target and flankers are collinear and suppression is expected when the orientation of the target and flankers are orthogonal during the lateral masking paradigm. Atypical lateral interactions in the ASD group would result in a reduced VEP response to collinearity or a decrease in facilitation.

Chapter 2**Method****Participants**

The participants for the experiments were ten high-functioning adults (18-33 years) diagnosed with either Autistic Disorder or Asperger's Syndrome (based on DSM-IV criteria – referred to as the ASD group) who were recruited from the Specialized Autism Clinic at Rivière-des-Prairies Hospital, located in Montréal Canada. Ten typically developing adults, serving as the comparison group, were also recruited from the same database. The ASD and comparison

groups were matched individually on gender, chronological age (± 2 ys), and Wechsler Adult Intelligence Scale (WAIS) Full Scale IQ (FSIQ) (± 10). The inclusion criteria for the ASD participants were (i) a FSIQ of 80 or greater, and (ii) no medication and no comorbid disorders. Although it is difficult to recruit individuals with ASD that do not have a comorbid disorder, it is important to do so since any differences found with respect to lateral neural interactions are not due to factors such as the collateral effects of medication or other conditions. The advantage of recruiting from the database is that proper screening of participants was possible since diagnosis is done at the hospital, along with having access to all of the additional information needed in the selection process.

Study 1 - Physiological Assessment of Atypical Local Neural Lateral Interaction in ASD

Objective

Studies have demonstrated that VEPs can be used to measure neural activity originating from lateral interactions between neurons within early visual areas (Conte & Victor, 2009). In the current study, radial windmill-dartboard patterns were used to differentially select neuronal interactions across spatial frequencies. Windmill-dartboards solicit mechanisms mediating the lateral inter-modulation between the two neural areas that receive input signals at different frequencies of modulation. They have been successfully used in mediating early visual functioning in infant, schizophrenic and epileptic populations (Conte & Victor, 2009). This study represents one of the first attempts at directly assessing lateral interaction in ASD. The aim was to confirm that this phenomenon exists in ASD, and more specifically that there was an increase in lateral inhibition in this population. The study was conducted at the Neurovisual Electrophysiological Lab, directed by Dr. Saint-Amour, at Sainte-Justine Hospital, a pediatric hospital located in Montreal, Canada.

Apparatus

The stimuli presentation was generated by Presentation software on a Lenovo ThinkCenter PC computer, and presented on a gamma-corrected, 16-inch HP CRT G90fb monitor. Data was recorded with a Fz reference using the BrainVision Recorder™ program on a Lenovo ThinkCenter PC computer at a sampling rate of 1000 Hz. Electrophysiological data was collected using a AgCl-electrode located at Oz, O1, O2 et POz.

Stimuli and procedure

The participants were first asked to pass three simple visual tests before testing; far sighted acuity, near sighted acuity and a contrast sensitivity test. After the visual tests, the electrodes were placed on the scalp of the participant by using scalp abrasion at the placement areas and electrodes were attached using a conductive paste. The stimuli and procedure used were similar to that of Conte and Victor (2009). The stimuli were windmill-dartboard patterns that subtended 8.8 x 8.8 degrees and had a 1.0 degree of ring thickness (Figure 1). Steady-state stimuli were delivered at 100% contrast, and the stimulation rates were 4.22 Hz. The participants viewed the stimuli binocularly, and were instructed to fixate on a point presented in the center of the screen. Given the passive nature of the task, participants were asked to fixate the center of the screen at all times. In order to ensure fixation, participants were asked to respond to the color change of a centrally presented point, within the windmill-dartboard pattern. There were a total of four sessions that last 1 minute each. Breaks were taken between sessions to reduce fatigue. The total time for this part of the experiment was 10 minutes.

VEP Recording Procedures

Scalp signals were obtained by using Grass AgCl electrodes positioned at Oz, POz, O1, O2 with a forehead ground. EEG activity was amplified 10 000 fold, filtered between 0.1-100

Hz and digitized at 1000 Hz. Electrode impedances were below 10 k Ω . Preliminary artifact rejection (via amplitude bounds) were automated and applied prior to signal averaging. Raw EEG was filtered between offline between 1-50 Hz. The EEG was analyzed using a Fast Fourier transform (FFT) and the amplitudes of the harmonics were looked at using BrainVision Analyzer™. Different waveforms were observed for the W/D-OFF and W/D-ON due to the differentially modulated regions of the stimuli. The VEP responses for each group to each stimulus condition were averaged and Fourier analyzed. Furthermore, the indices reflecting facilitatory (FI) and inhibitory (SI) cortical interactions were calculated using first- and second-harmonic response components. The equations for FI and SI were as follows: $FI = \text{Fundamental (W/D-ON)} / 2\text{nd Harmonic (W/D-ON)}$ whereas $SI = 2\text{nd Harmonic (W/D-OFF)} / 2\text{nd Harmonic (W/D-ON)}$.

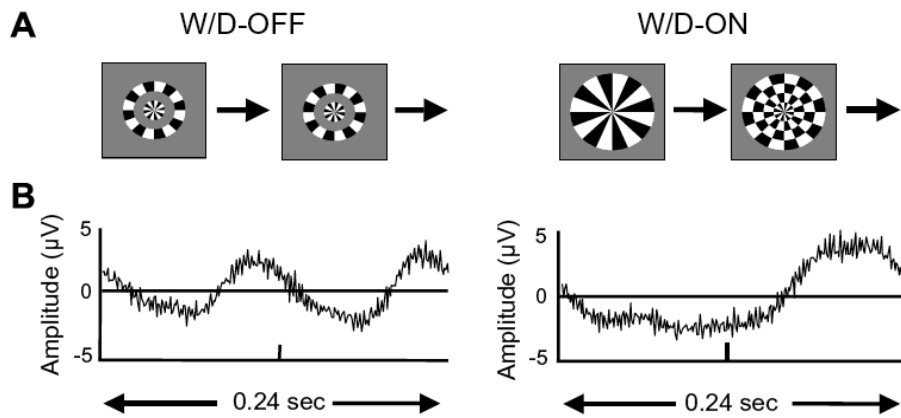


Figure 1. Examples of Zemon & Ratliff (1982, 1984) windmill–Dartboard (W/D) stimuli. Left: Windmill/Dartboard-OFF. Right: Windmill/Dartboard-ON. The modulated regions are identical in the W/D-ON and W/D-OFF configurations, but the static component of the pattern is present only in the W/D-ON configuration. Thus, interactions between the modulated and static regions result in differences between the VEP waveforms that the two stimuli elicit. (B) Averaged steady-state responses elicited by these stimuli from one normal control. Each waveform

represents the averaged response over one cycle of the stimulus.

Study 2 - Measuring Collinear Facilitation and Orthogonal Inhibition in ASD using Physiological Measures

Objective

Research has demonstrated that target detection can be facilitated or inhibited by the distance and orientation of flanking stimuli, which can be observed in lateral masking paradigms (Polat & Norcia, 1996). Facilitation occurs when flankers are collinear to the central Gabor (collinear facilitation) while inhibition occurs when flankers are orthogonal to the central Gabor (orthogonal inhibition). The second study used a lateral masking paradigm to assess lateral interactions in the same groups of ASD participants. As with the Windmill-Dartboard study, the idea is that atypical lateral interactions in the ASD group would be manifested by different facilitation and suppression responses compared to the comparison group. It was hypothesized that the increase in lateral inhibition in the ASD group would lead to a smaller collinear facilitation response observed in the lateral masking paradigm.

Procedure

The experiment started once the participant pushed a mouse key to start the trial. This was also a passive task only requiring the participants to maintain fixation and avoid eye movements. To keep the participant's attention, they were asked to respond to the color change of a centrally presented point on the Gabor patches. The participants would fixate on the central Gabor patch binocularly from a distance of 57 cm.

Stimuli and Apparatus

The stimuli used in this study are Gabor patches. These small, foveally viewed Gabor patches subtended 0.3 deg standard deviation, 3 c/deg carrier. These Gabor patches were presented in the center of a 13.8 x 10.4 degree field set to the mean luminance of the patches.

The Gabor patches were temporally modulated at 4.1 Hz in the on/off mode at contrasts of 8, 16 and 30 %. There was no change in the average luminance of 160 cd/m^2 . The Gabors were either presented alone (Figure 2, c) or in the presence of two flanking Gabors that were oriented either vertically (same as the foveal Gabor, Figure 2,b), or horizontally (Figure 2, c). The flank response alone were also measured separately (Figure 2 a, e). The two flanking Gabors were modulated at 4.1 Hz and were placed either 1.5λ , 3λ , 6λ from the foveal Gabor. They were of the same spatial frequency and of fixed foveal contrast of 50%. Each condition combination consisted of 10 trials each lasting 6 seconds. The different conditions were randomly presented and a small fixation point at the center of the screen was present to indicate the target location. The total time for the presentation of the Gabor patches was 45 minutes. However, participants could take breaks to reduce fatigue which extended the testing period.

VEP Recording Procedures

VEPs elicited by selected target-flanker combinations were measured. EEG was sampled at 1000 Hz over an amplifier passband of 0.1–100 Hz from an array of four electrodes centered at O_z , O_1 , O_2 and PO_z . In addition, test-alone and flank-alone VEPs were compared to the measured response to test-plus-flank together. The recording channel with the highest statistical reliability was selected for the group averages.

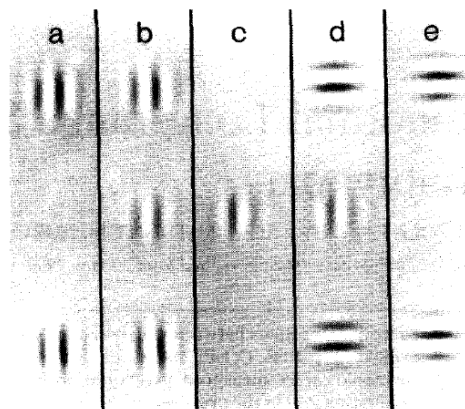


Figure 2. Examples of Polat, Sagi & Norcia's (1997) lateral masking paradigm. The series of foveal Gabors were either presented alone (c) or in presence of two flanking Gabor patches (b, d). The flanks were oriented either vertically (collinear, (a)) or horizontally (non-collinear, e)).

Chapter 3

Results

Data Analysis for the Windmill-Dartboard Paradigm

Facilitatory (FI) and inhibitory (SI) cortical interactions were calculated using first- and second-harmonic response components, using the following equations:

$$FI = \frac{\text{Fundamental (W/D-ON)}}{\text{2nd Harmonic (W/D-ON)}}$$

$$SI = \frac{\text{2nd Harmonic (W/D-OFF)}}{\text{2nd Harmonic (W/D-ON)}}$$

Student's *t*-tests were then conducted to assess if any significant group differences existed for either type of cortical interaction. The *t*-test is the appropriate analysis to use since it enables us to determine whether the means of two normally-distributed populations are equal. The assumptions for Student's *t*-tests, including data following a continuous scale, normal distribution, and equal variances, were met once the data was log transformed

FI Differences between ASD and Comparison Groups

The *p* value of Levene's Test for Equality of Variances was greater than an alpha level of .05 ($F(1, 19) = .961, p = .342$), therefore equal variances can be assumed. The result of the independent *t*-test conducted to compare mean FI indices for the ASD and comparison groups were not found to be statistically significant, $t(19) = .005, p = .996$ (Figure 3). These results indicate that individuals in the ASD group ($M = -.0311, SD = .40543$) had similar FI indices than did individuals in the comparison group ($M = -.0324, SD = .61115$). This result demonstrates that

the ASD and comparison groups had a similar facilitation response for the Windmill-Dartboard stimuli.

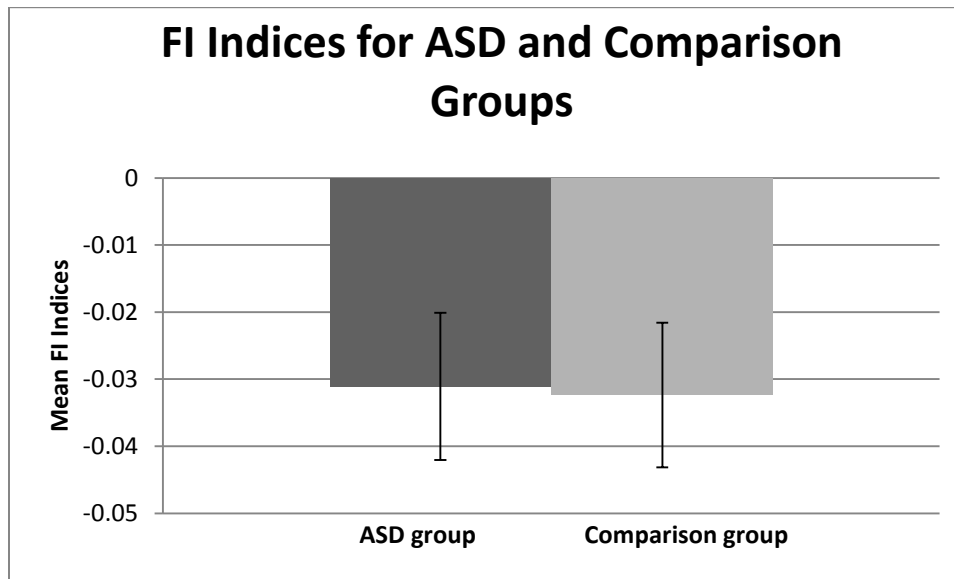


Figure 3. Graph showing the windmill-dartboard FI indices for both the ASD and comparison groups

SI Differences between ASD and Comparison Groups

The p value of Levene's Test for Equality of Variances was greater than an alpha level of .05 ($F(1, 19) = 2.89, p = .113$), therefore equal variances can be assumed. The result of the independent t -test conducted to compare SI indices for the ASD and comparison groups were also not found to be statistically significant, $t(19) = -.262, p = .797$ (Figure 4). These results indicate that individuals in the ASD group ($M = .4003, SD = .17421$) had similar SI indices than did individuals in the comparison group ($M = .4363, SD = .35043$). This result demonstrates that the ASD and comparison groups had a similar suppression response for the Windmill-Dartboard stimuli.

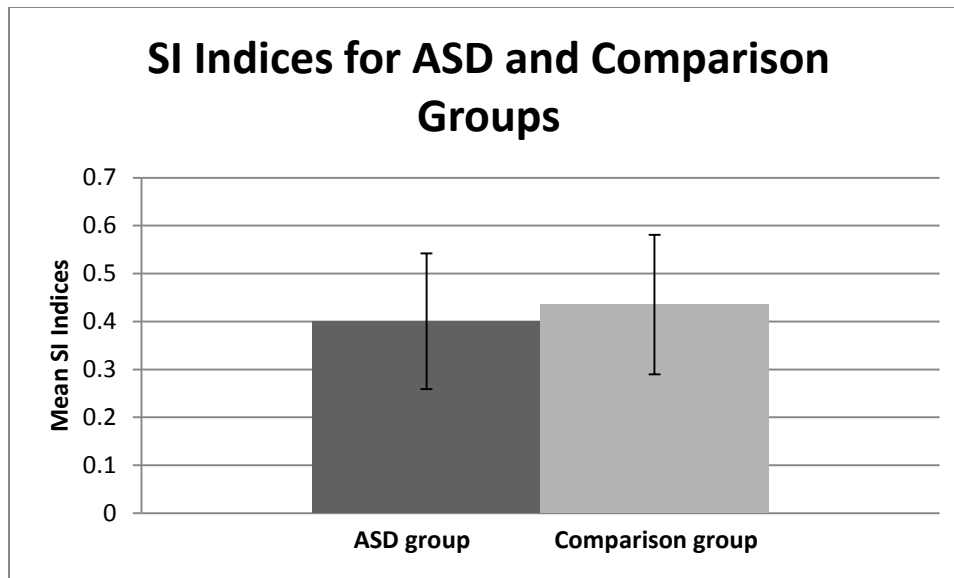


Figure 4. Graph showing the windmill-dartboard SI indices for both the ASD and comparison groups

In summary, there were no statistically significant differences between the ASD and comparison groups for either the FI or SI measures. These results suggest that Facilitatory (FI) and inhibitory (SI) cortical interactions, as measured with the Windmill-Dartboard stimuli, are unremarkable in ASD.

Data Analysis for the Lateral Masking Paradigm

Before analyzing the data, the peak responses from the EEG recordings were normalized by dividing the largest peak value from a participant to all other values for that participant, in order to reduce inter-participant variability. Central target alone and flanker alone ssVEPs, which will be referred to as the theoretical facilitation or suppression response, were summed and compared to the measured response to central plus flanker together, which will be referred to as the actual facilitation or suppression response. The facilitation response occurs when the flankers are collinear to the central target, while a suppression response occurs when the flankers are orthogonal to the central target. A facilitation response is said to occur when the actual response

is larger than the theoretical response. Conversely, a suppression response is evidenced when the actual suppression produces a smaller response than the theoretical suppression response.

Student t-tests were then conducted on normalized data. Within and between groups analyses were conducted for the ASD and comparison groups. Within group comparisons were conducted for the theoretical facilitation and suppression responses and for the actual facilitation and suppression responses for different target-flanker conditions. Then the actual facilitation and suppression responses were compared between the ASD and comparison groups.

The results described below are separated in terms of target-flanker distances (1.5, 3 and 6 lambda). Within each condition, the within and between facilitation and suppression responses will be discussed.

Facilitatory and Suppression Responses at Target-Flanker Distance of 1.5 Lambda

Figures 5 and 6 demonstrate the mean normalized “theoretical” and “actual” facilitatory (Figure 5) and suppression (Figure 6) responses for ASD and comparison groups conditions as a function of contrast (8, 16 & 30 %) for target-flanker distance of 1.5 λ . There were no statistically significant actual facilitatory responses at any contrast as the mean peak value for both groups did not statistically differ compared to the theoretical facilitatory responses for either the ASD group or the comparison group, all p values were greater than .05 (Figure 5). However, the ASD group did demonstrate a trend towards statistical significance of the actual suppression responses, compared to the theoretical suppression responses, at contrasts of 8% and 16% ($p = .07$, $p = .06$; respectively), and the comparison groups demonstrated a trend towards statistical significance of an actual suppression response, compared to the theoretical suppression response, at a contrast of 30% ($p = .08$) (Figure 6). There was also a trend towards statistical significance

in actual facilitatory responses for between groups at a distance of 1.5λ and a contrast of 30%, with the ASD group having a lower response than the comparison group ($p = .06$) (Figure 5).

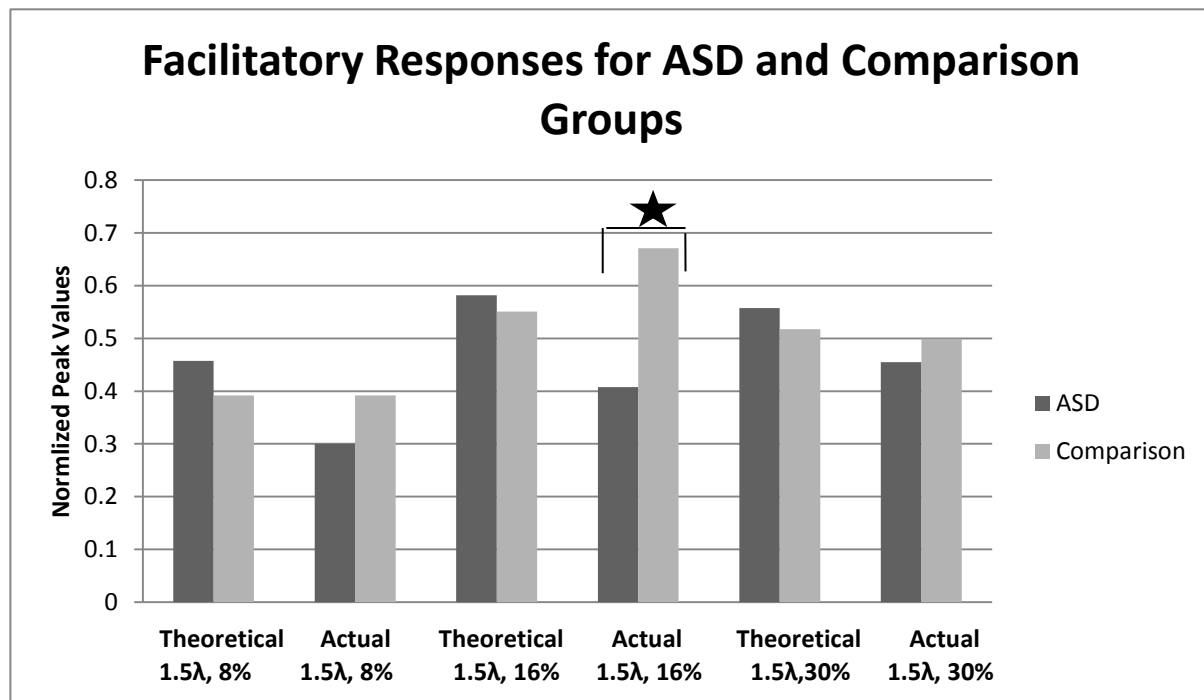


Figure 5. Graph showing the facilitatory responses for both the ASD and comparison groups. The theoretical facilitatory response corresponds to central alone + collinear flankers alone. The actual facilitatory response corresponds to the response from the central and collinear flanker presented together. ★ signifies trending toward statistical significance.

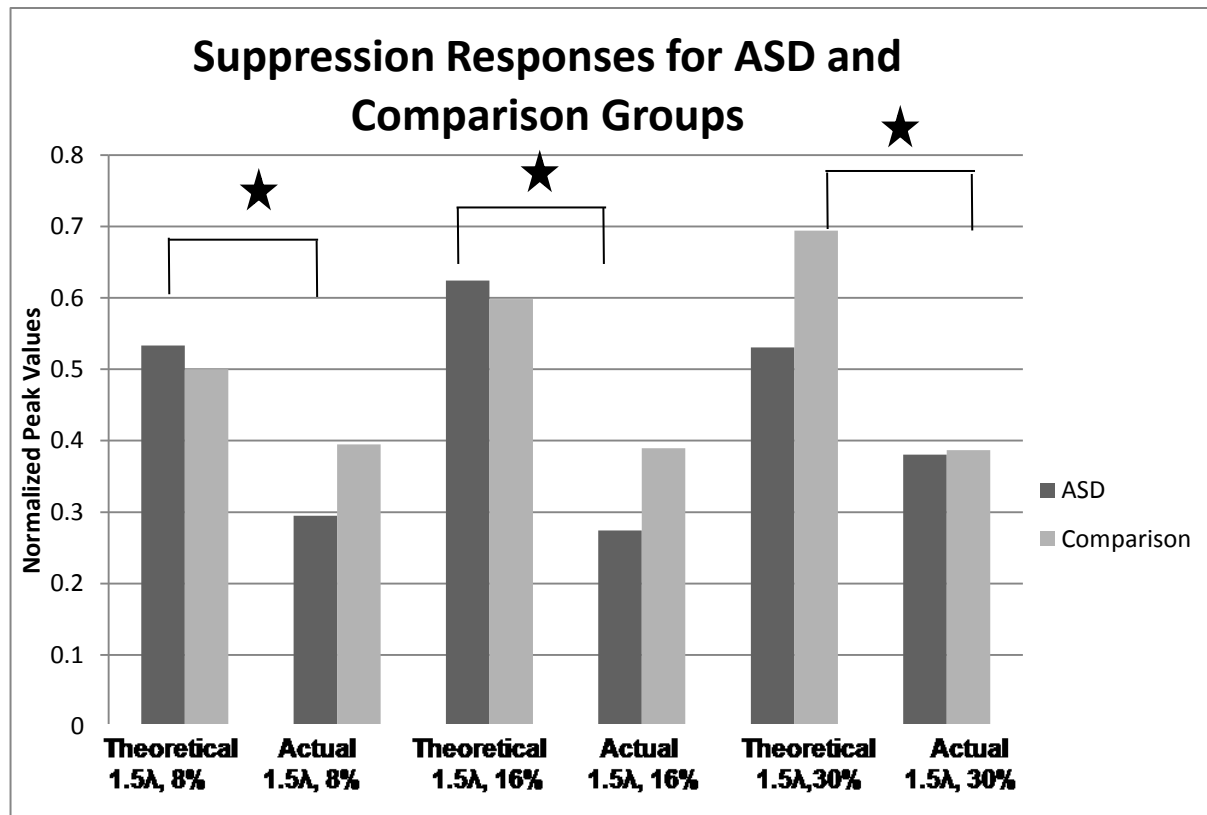


Figure 6. Graph showing the suppression responses for both the ASD and comparison groups. The theoretical suppression response corresponds to central alone + orthogonal flankers alone. The actual suppression response corresponds to the response from the central and orthogonal flanker presented together. ★ signifies trending toward statistical significance.

Facilitatory and Suppression Responses at Target-Flanker Distance of 3 Lambda

Figures 7 and 8 demonstrate the mean normalized “theoretical” and “actual” facilitatory (Figure 7) and suppression (Figure 8) responses for ASD and comparison groups for “theoretical” and “actual” conditions as a function of contrast (8, 16 & 30 %) for target-flanker distance of 3λ . Statistically significant actual facilitatory responses were found for both the ASD group at a contrast of 30% ($p = .05$), and the comparison group at a contrast of 8% ($p = .02$), compared to the theoretical facilitatory responses for both the ASD and comparison groups (Figure 7). In addition, the actual facilitation was lower than the theoretical facilitation for both groups. More so, the comparison group demonstrated statistical significance of an actual

suppression response, compared to theoretical suppression, at a contrast of 16% ($p = .05$) (Figure 8). There was also a trend towards statistical significance in actual facilitatory responses between the ASD and comparison groups at a distance of 3λ and a contrast of 30% ($p = .09$), with the ASD group having a lower response than the comparison group (Figure 7).

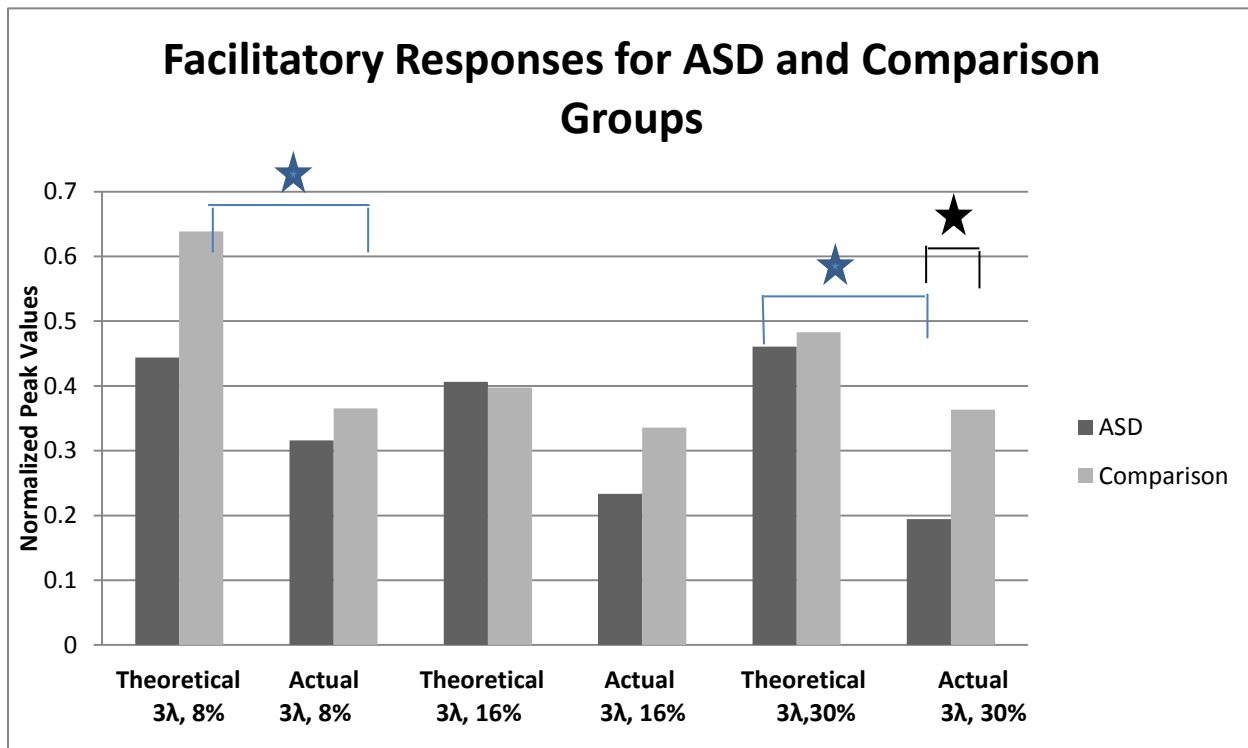


Figure 7. Graph showing the facilitatory responses for both the ASD and comparison groups. The theoretical facilitatory response corresponds to central alone + collinear flankers alone. The actual facilitatory response corresponds to the response from the central and collinear flanker presented together. ★ signifies trending toward statistical significance. ★ signifies statistical significance ($p \leq 0.05$).

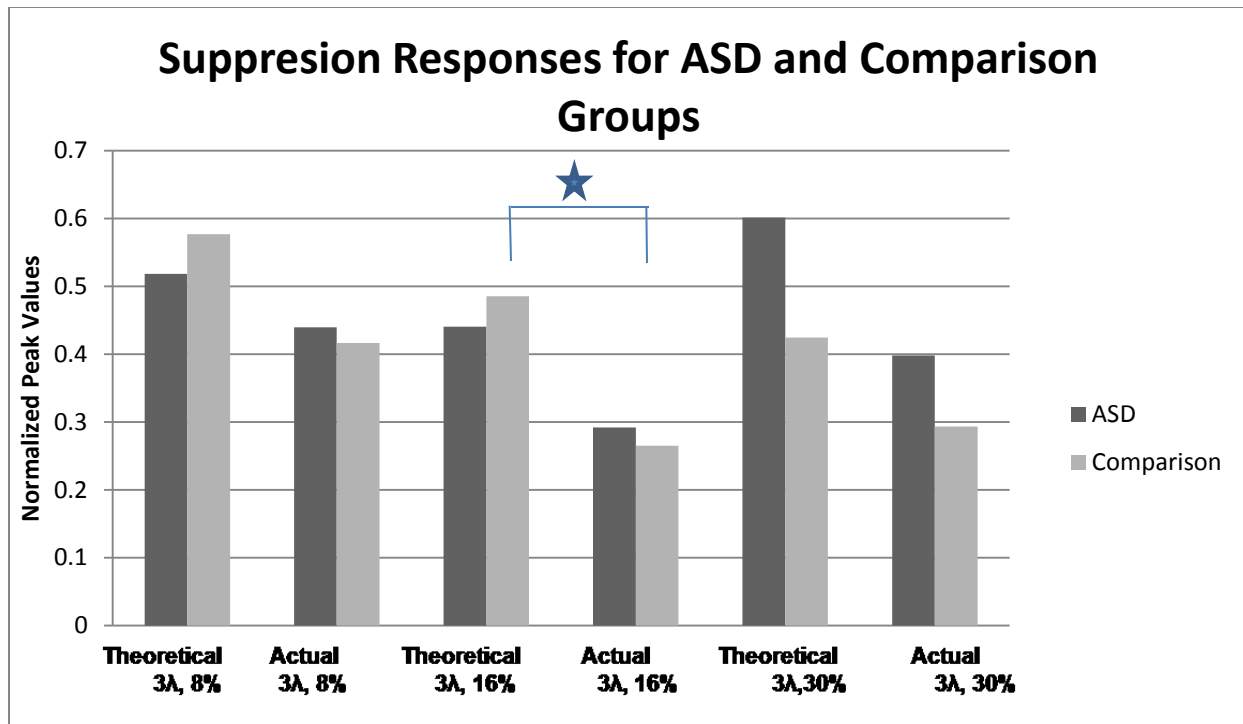


Figure 8. Graph showing the suppression responses for both the ASD and comparison groups. The theoretical suppression response corresponds to central alone + orthogonal flankers alone. The actual suppression response corresponds to the response from the central and orthogonal flanker presented together. ★ signifies trending toward statistical significance. ★ signifies statistical significance ($p \leq 0.05$).

Facilitatory and Suppression Responses at Target-Flanker Distance of 6 Lambda

Figures 9 and 10 demonstrate the mean normalized “theoretical” and “actual” facilitatory (Figure 9) and suppression (Figure 10) responses for ASD and comparison groups for “theoretical” and “actual” conditions as a function of contrast (8, 16 & 30 %) for target-flanker distance of 6λ . Statistically significant facilitatory responses were found for the ASD and comparison groups at a contrast of 8% ($p = .005$, $p = .03$; respectively), compared to the theoretical facilitatory responses for both the ASD and comparison groups (Figure 9). In both significant facilitatory responses, the actual facilitation was lower than the theoretical facilitation. More so, there was a statistical significance in actual facilitatory responses for between groups at a distance of 6λ and a contrast of 8% ($p = .025$), with the ASD group having

a lower response than the comparison group (Figure 9). Lastly, the comparison group demonstrated a statistically significant actual suppression response, compared to theoretical suppression, at a contrast of 16% and a trend to statistical significance of a suppression response at a contrast of 30% ($p = .05$, $p = .08$; respectively) (Figure 10).

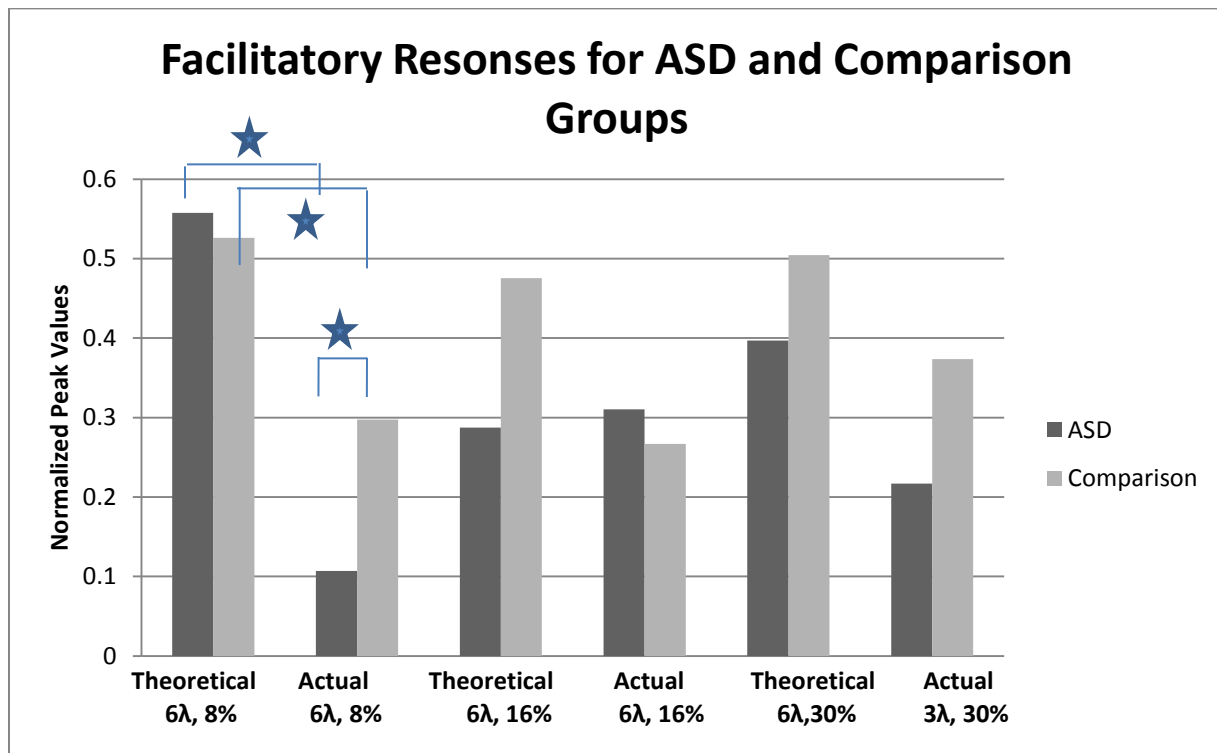


Figure 9. Graph showing the facilitatory responses for both the ASD and comparison groups. The theoretical facilitatory response corresponds to central alone + collinear flankers alone. The actual facilitatory response corresponds to the response from the central and collinear flanker presented together. ★ signifies trending toward statistical significance. ★ signifies statistical significance ($p \leq 0.05$).

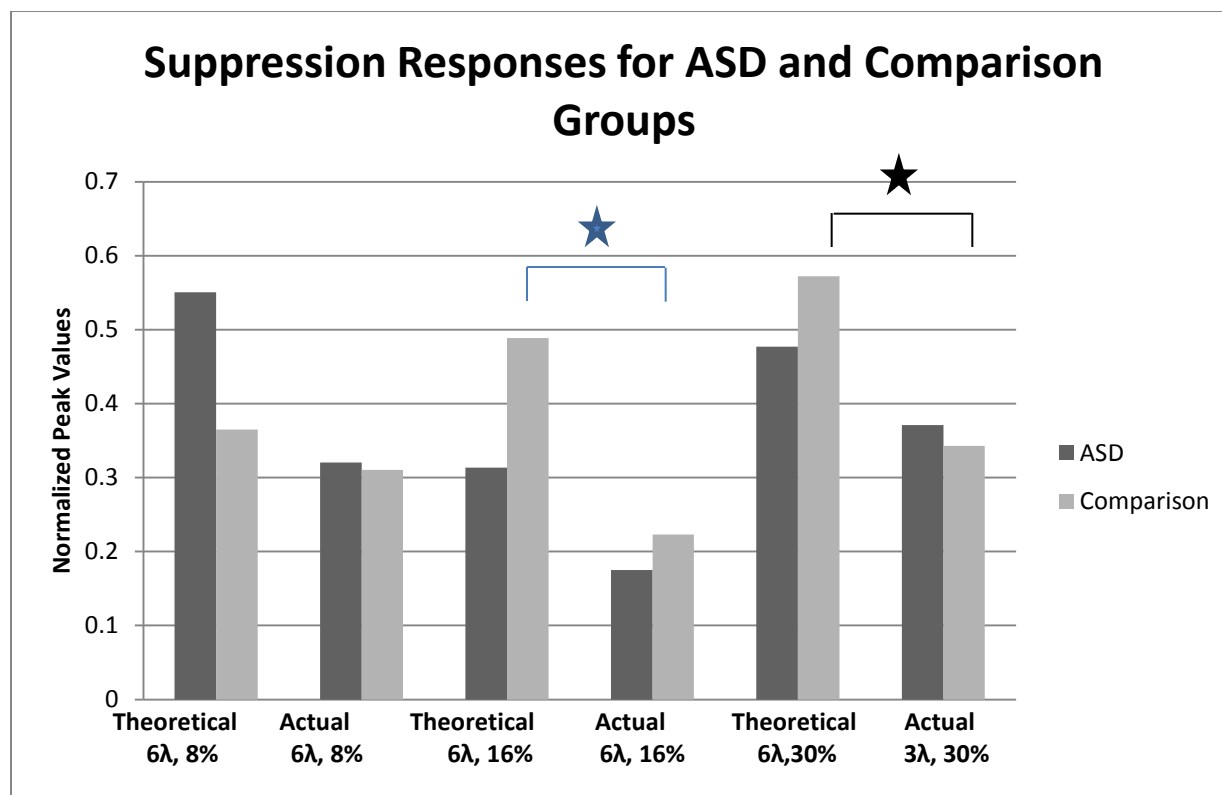


Figure 10. Graph showing the suppression responses for both the ASD and comparison groups. The theoretical suppression response corresponds to central alone + orthogonal flankers alone. The actual suppression response corresponds to the response from the central and orthogonal flanker presented together. ★ signifies trending toward statistical significance. ★ signifies statistical significance ($p \leq 0.05$).

In summary, there were statistically significant differences within and between the ASD and comparison groups under certain experimental conditions. These significant results suggest that facilitatory and inhibitory responses were usually lower in the ASD group, as measured with the lateral masking paradigm, which are remarkable in this population.

Chapter 4

Discussion

For the most part, the majority of vision-related research in autism has been concerned with assessing perceptual processes related to cognitive and/or social aspects of the autistic behavioral phenotype (Courchesne et al., 2005; Mundy et al., 2009; Schultz, 2005). This focus

on social and cognitive tasks is not surprising given the diagnostic relevance of such high-level impairments. However, it is this type of research that has been used to develop neurocognitive theories suggesting altered connectivity between functionally specialized networks comprising large-scale neural systems involved in social and executive functioning in autism (Brock et al., 2002; Castelli et al., 2002; Just et al., 2004; Rippon et al., 2007). As a consequence, early perceptual processing has been overlooked as an important contributing factor to cognitive and/or social impairments in autism (Skottun et al., 2008). Although it has been established that local neural mechanisms underlying early perceptual processes are different in ASD, there is little direct research done on the neurobiological explanation for this preference (Vandenbroucke et al., 2008). One such biologically plausible hypothesis by Bertone and colleagues (2005) proposed that there is atypical local connectivity in ASD, specifically that of altered lateral connectivity.

The current studies tested this hypothesis by using visually evoked potentials (VEPs). VEPs are useful in assessing visual functioning, in that it is possible to examine the contributions of individual visual subsystems and are commonly used in basic vision research (Grose-Fifer, Zemon, & Gordon, 1994; Zemon & Ratliff, 1982). Lateral interactions are a particular type of neural process between neurons in the visual system, which can be elicited by windmill-dartboard stimuli and lateral masking paradigm (Polat, Sagi & Norcia, 1997; Zemon & Ratliff, 1982). Using an electrophysiological approach, the current studies directly assessed whether local lateral connectivity within early visual areas was different in ASD. To do so, ssVEPs for ASD and comparison groups were recorded while they were presented with arrays of visual stimuli (Studies 1 and 2) demonstrated to induce lateral interactions between neurons within

early visual areas. This study represents one of the first direct assessments of a neural hypothesis suggesting altered neural connectivity within primary visual areas in ASD.

Summary of Results

Lateral Interactions with the Windmill-Dartboard Stimuli

The windmill-dartboard stimuli were used to examine lateral inhibitory interactions within the primary visual cortex (V1). The results from Study 1 did not result in any group differences for either Facilitatory (FI) or Inhibitory (SI) indices, reflecting that cortical interactions were similar for ASD and comparison groups. Based on these results, the hypothesis that atypical perceptual functioning in ASD is at least in part mediated by atypical lateral interactions is not supported. However, these null results may be due to the stimulus parameters chosen. Specifically, the components (i.e., white and black pieces of the windmill-dartboard stimuli) used in the present study had a contrast of 100%. Typically, the contrast for such stimuli is usually at 30%, a lower level contrast. It is possible that the choice to use such a high contrast may have potentially been limited by response saturation to SI and FI conditions, and consequently, rendering the paradigm less sensitive to possible group-differences in responses. In order to assess this methodological, we are presently assessing other participants at a lower contrast of 30%.

In addition to interpreting data within the context of local lateral, interactions, further interpretation within the context of static and dynamic visual processing can be advanced based on the method and paradigm used. Specifically, researchers have demonstrated that the first harmonic is typically produced in the parvocellular pathway while the second harmonic is produced in the magnocellular (motion-sensitive) pathway (Grose-Fifer et al, 1994; Tootell et al., 1998). Since the ASD and comparison group had similar first and second harmonic responses to

the stimuli. From these results, there are no functional abnormalities with either of the pathways when assessed at a very early level of processing.

Lateral Interactions with the Lateral Masking Paradigm

In Study 2, lateral neural interactions were assessed by measuring ssVEP measures within the context of a lateral masking paradigm task. This paradigm was used to measure the influence of lateral stimulation (flankers) on a target while varying the target-flanker distance, target-flanker orientation, and contrast. The results demonstrated that there were differences in lateral interactions between the two groups under certain experimental conditions.

In the lateral masking task, participants were exposed to Gabor patches with varying distances, contrasts and flanker orientations. The collinear (facilitatory condition) or orthogonal flankers (suppression condition) were at three different distances (1.5, 3, and 6 lambda) and the Gabor patches were presented at contrasts of 8%, 16%, and 30%. There was no collinear facilitation in any of the conditions. This finding is not typical in either the neurotypical or ASD literature (Conte and Victor, 2009; Keita et al., 2011). For example, lateral masking paradigms have revealed a facilitation effect at 3 lambda, which implicates lateral connections in early visual areas and may be dependent on a receptive field size in V1 that is estimated to be about 2 to 3 lambda (Keita et al., 2011; Polat & Sagi, 1993; Polat & Tyler, 1999). In fact, the “facilitatory” responses in this current experiment were always lower for the ASD group than for the comparison group. However, suppression responses in ASD and comparison groups were differentially affected by the contrasts of the Gabors and varying distances. Specifically, a suppression response in ASD only occurred at a distance of 1.5 lambda (at contrasts of 8% and 16%) while a suppression response in the comparison group occurred across all distances (at

contrasts of 16% and 30%). Although further analysis of the results is still required, the findings seem to provide partial evidence for atypical lateral interactions in the ASD group.

Conclusions

The current studies attempted to directly examine lateral interactions by measuring steady-state visual evoked potentials (ssVEPs) elicited by windmill-dartboard and lateral masking paradigms. The hypothesis for the windmill-dartboard paradigm was that the amplitude of the first and second harmonic response components would differ from that of the comparison group. This hypothesis was not supported as no between-group differences in lateral inhibitory interactions were found.

The hypothesis for the lateral masking paradigm was that atypical lateral interactions in the ASD group would result in a decrease in facilitation, which was expected when the orientation of the target and flankers were collinear; suppression was expected when the orientation of the target and flankers were orthogonal. The results did not demonstrate any facilitatory responses for either the ASD or comparison group. Instead, there were significant decreases in facilitatory responses at distances of 1.5λ and 16%, 3λ and 30%, and 6λ and 8%. In every condition, the ASD group always had lower facilitation response compared to the comparison group. Although these results are not what is typically found with the lateral masking paradigm in non-clinical populations (Polat, Sagi & Norcia, 1997), these between-group difference do suggest atypical lateral connectivity within early areas of participants with ASD.

General Discussion

Research in the area of lateral interactions in ASD is sparse; however the results from the study, both with the windmill-dartboard and lateral masking paradigms, do not correspond with other studies conducted with these paradigms. Weigner (Published thesis, 2013) demonstrated

that the windmill-dartboard stimuli demonstrated an increase in lateral inhibition for children with ASD. These interactions are proposed to be GABA-mediated, which is said to provide additional evidence for increased cortical inhibition in individuals with ASD. The results from Weigner (2013) provide support for the superior skills in the areas of local perceptual processing and enhanced lateral inhibition in individuals with ASD by biasing the response properties of early perceptual mechanism towards being able to processes increasingly detailed information (Bertone et al., 2005, Mottron et al., 2006). A psychophysics experiment conducted by Keita and colleagues (2011) found differential facilitation effects observed in the ASD group (with greater facilitation) compared to the comparison group. This differential influence of surrounding spatial stimuli on the detection of a visual local target in ASD may reflect a very early atypicality in visual processing, as early as the primary visual cortex. In addition to behavioral and functional findings, it has been proposed that ASD is characterized by an atypical minicolumnar phenotype. More specifically, it is hypothesized that minicolumns have reduced width across brain areas and reduced peripheral neuropil space, in which most inhibitory elements typically reside, and alter the balance between excitatory and inhibitory lateral connectivity (Buxhoevedon & Casanova, 2002; Casanova et al., 2002; Gustafsson, 1997a; Gustafsson, 1997b; Silberberg et al. 2002; Rubenstein & Merzenich, 2003).

Strengths

These studies are one of the first that aimed at directly assessing lateral interactions in ASD to determine whether there is evidence to support the hypothesis of atypical lateral interactions, or of an increased lateral inhibition (Bertone et al., 2005). Research in ASD is most often focused on higher-order visual processing, while the current study focuses on low-level visual processing. Both the windmill-dartboard and lateral masking stimuli have been validated

with various clinical populations and have been demonstrated to elicit lateral interactions. More so, the procedure from Victor and Conte (2009) and Polat and colleagues (1997) have been used in the current studies. Another strength is that the recruitment of the participants aimed at reducing the heterogeneity of the adult sample with respect to ranges in age, level of functioning, and screening for comorbid disorders and medications. More so, all participants used in the present studies have strict ASD diagnoses that were done by trained clinicians at Rivière-des-Prairies Hospital. Full IQ scores were also obtained by completing cognitive testing on the comparison group in order to match participants on IQ. Lastly, both experiments used passive stimuli which allows for a wider range of ASD recruitment including non-verbal individuals, individuals with lower IQs, and allows for testing at a younger age since individuals with ASD can complete this task, irrespective of their verbal ability level.

Limitations

The generalizability of the findings is limited to adult males with ASD, since there were no females in the sample. In addition, small sample sizes, as with most of the research in ASD, are a limitation to this study. Finally, more testing is needed to conclude that windmill-dartboard and lateral masking paradigms are effective methods of assessing visual processing in ASD since these visual stimuli are only now being applied to ASD research. It has been theorized that individuals with ASD might have greater difficulty synchronizing the activity of stimulus-related cell assemblies resulting in an increase in neural noise for these individuals (Milne, 2011; Rubenstein & Merzenich, 2003). This increase in neural noise can interfere with input recordings and not reveal group differences.

Future Directions

The current study only included adult participants; therefore future plans consist of testing the windmill-dartboard and lateral masking paradigms with children and adolescents. Information from three different developmental periods (children, adolescents, and adults) will provide a complete developmental perspective and enhance our understanding of atypical lateral connectivity, if present, in ASD. Furthermore, this will allow us to determine whether perceptual influence changes across developmental periods. Studies like the ones presented here are important since they will allow for the understanding of how abnormalities in basic low-level stimuli translate into higher-order perceptual differences across different periods of development. This is especially important since early perceptual atypicalities mediated by local neural alterations have for the most part been explained as a collateral consequence of larger-scale dysfunction; their underlying neural substrate has never been defined (Just et al., 2004; Rippon et al., 2007). Although sometimes used to explain higher-level perceptual deficits in ASD (i.e., face perception), local neural alterations may constitute a neural origin for visually-related cognitive and behavioral phenotypes manifested in ASD.

Implications

Fundamental Research Level

Defining local network alterations in ASD may lead to working hypotheses regarding its causal genotype. Future studies will be needed to assess the functional integrity of GABAergic-related transmission in the visual cortex, an important neurotransmitter mediating intra-cortical inhibition that is crucial for several brain functions and has been linked to ASD's etiology (Persico & Bourgeron, 2006). Potentially, such neural endophenotypes (i.e., atypical GABAergic-related synaptogenesis) can be incorporated into causal models and be used to infer target

candidate gene or gene clusters implicated in the pathogenesis of ASD. A better understanding of GABAergic transmission in ASD may have important implications regarding remediation via pharmacological intervention, whether at perceptual, cognitive and/or behavioural levels.

Diagnostic and Intervention Level

The electrophysiological signature derived from the proposed studies may be used as a diagnostic measure, if found to be specific to ASD. Electrophysiological signatures as a diagnostic measure have been proposed in other patient populations (Conte & Victor, 2009; Kim et al., 2005). This measure is of particular interest for non-verbal ASD patients, given the passive nature of data acquisition.

Understanding the development of lateral interactions and how it is manifested during different age periods is important when devising intervention plans. Individuals with ASD are among the most difficult and costly to treat, and the impact their families in terms of quality of life are enormous and sometimes devastating. This is because many current intervention approaches assume that perceptual abilities and strategies in ASD are intact. If effective intervention strategies are to be improved and/or developed, an accurate and objective characterization of sensory and perceptual processing in ASD is clearly needed. As well, there is a plausible early origin for atypical visual perception in ASD. Understanding the nature of perceptual deficit and strengths in ASD, at the different stages in development, is therefore crucial for the improvement of such approaches.

References

- American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders DSM-5. Washington, D.C.: American Psychiatric Association.
- Banich, M.T. (2nd edition). (2004). *Cognitive Neuroscience and Neuropsychology*. Boston, MA: Houghton Mifflin Company.
- Behrmann, M., Thomas, C. & Humphreys, K. (2006). Seeing it differently: visual processing in autism. *Trends Cogn Sci*, 10, 258-264.
- Belmonte, M. K., Cook, E. H., Anderson, G. M., Rubenstein, J. L., Greenough, W. T., Beckel-Mitchener, A., ... & Tierney, E. (2004). Autism as a disorder of neural information processing: directions for research and targets for therapy*. *Molecular psychiatry*, 9(7), 646-663.
- Bertone, A., Mottron, L., Jelenic, P. & Faubert, J. (2003). Motion perception in autism: a "complex" issue. *J Cogn Neurosci*, 15, 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, 2430-2441.
- Bertone A, Hanck J, Kogan CS, Chaudhuri A, Cornish KM (2010). Using perceptual signatures to define and dissociate condition-specific neural etiology : Autism spectrum disorder and fragile X syndrome as model conditions. *Journal of Autism and Developmental Disorders*, 40, 1531-1540.
- Blumberg, S. J., Bramlett, M. D., Kogan, M. D., Schieve, L. A., Jones, J. R., & Lu, M. C. (2013). Changes in prevalence of parent-reported autism spectrum disorder in school-aged US children: 2007 to 2011–2012. *National health statistics reports*, 65(20), 1-7.
- Brock, J., Brown, C. C., Boucher, J. & Rippon, G. (2002). The temporal binding deficit

- hypothesis of autism. *Dev Psychopathol* 14, 209-224.
- Buxhoeveden, D. P., & Casanova, M. F. (2002). The minicolumn hypothesis in neuroscience. *Brain*, 125(5), 935-951.
- Casanova, M.F., Buxhoeveden, D.P., Switala, A.E. & Roy, E. (2002). Minicolumnar pathology in autism. *Neurology*, 428—432.
- Casanova, M. F., Buxhoeveden, D., & Gomez, J. (2003). Disruption in the inhibitory architecture of the cell minicolumn: implications for autism. *The Neuroscientist*, 9(6), 496-507.
- Castelli, F., Frith, C., Happe, F. & Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain*, 125, 1839-1849.
- Conte, M. M., & Victor, J. D. (2009). VEP indices of cortical lateral interactions in epilepsy treatment. *Vision research*, 49(9), 898-906.
- Courchesne, E. & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr Opin Neurobiol* 15, 225-230.
- Dakin, S. & Frith, U. (2005). Vagaries of visual perception in autism. *Neuron*, 48, 497-507.
- Di Russo, F., Teder-Sälejärvi, W. A., & Hillyard, S. A. (2002). Steady-state VEP and attentional visual processing. *The cognitive electrophysiology of mind and brain (Zani A, Proverbio AM, eds)*, 259-274.
- Fecteau, S., Mottron, L., Berthiaume, C., & Burack, J. A. (2003). Developmental changes of autistic symptoms. *Autism*, 7(3), 255-268.
- Fombonne, E. (2003). Epidemiology of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord*, 33, 365-381.
- Fombonne, E. (2009). Epidemiology of pervasive developmental disorders. *Pediatric*

- research*, 65(6), 591-598.
- Franklin, A., Sowden, P., Notman, L., Gonzalez-Dixon, M., West, D., Alexander, I., Loveday, S., & White, A. (2010). Reduced chromatic discrimination in children with autism spectrum disorders. *Dev Sci*, 13, 188-200.
- Frith U & Happe F (1994). Autism: beyond "theory of mind". *Cognition*, 50, 115-132.
- Goldstein, E.B. (7th edition). (2007). *Sensation & Perception*. Belmont, CA: Thomson Higher Education.
- Grose-Fifer, J., Zemon, V., & Gordon, J. (1994). Temporal tuning and the development of lateral interactions in the human visual system. *Investigative ophthalmology & visual science*, 35(7), 2999-3010.
- Gustafsson, L. (1997a). Inadequate cortical feature maps: a neural circuit theory of autism. *Biol Psychiatry*, 42, 1138-1147.
- Gustafsson, L. (1997b). Excessive lateral feedback synaptic inhibition may cause autistic characteristics. *J Autism Dev Disord*, 27, 219-220.
- Gustafsson L. (2004). Comment on "Disruption in the inhibitory architecture of the cell minicolumn: implications for autism". *Neuroscientist*, 10, 189-191.
- 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.
- Hill, E. L., & Frith, U. (2003). Understanding autism: insights from mind and brain. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 358(1430), 281-289.
- Just, M. A., Cherkassky, V. L., Keller, T. A. & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of

- underconnectivity. *Brain*, 127, 1811-1821.
- Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous child*, 2(3), 217-250.
- Kim, D., Zemon, V., Saperstein, A., Bulter, P. D., & Javitt, D. C. Dysfunction of early-stage processing in schizophrenia: harmonic analysis. *Schizophrenia Research*, 76, 55-65.
- Kim, Y. S., Leventhal, B. L., Koh, Y. J., Fombonne, E., Laska, E., Lim, E. C., ... & Grinker, R. R. (2011). Prevalence of autism spectrum disorders in a total population sample. *American Journal of Psychiatry*, 168(9), 904-912.
- 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.
- Lord, C., & Cook, E. H. (2013). Autism spectrum disorders. *Autism: The Science of Mental Health*, 28, 217.
- 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.
- 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.
- Mottron, L., & Burack, J. A. (2001). Enhanced perceptual functioning in the development of autism.
- Mottron, L., Dawson, M., Soulieres, I., Hubert, B. & Burack, J. (2006). Enhanced perceptual

- functioning in autism: an update, and eight principles of autistic perception. *J Autism Dev Disord*, 36, 27-43.
- Mundy, P., Sullivan, L. & Mastergeorge, A. M. (2009). A parallel and distributed-processing model of joint attention, social cognition and autism. *Autism Res*, 2, 2-21.
- Persico, A. M. & Bourgeron, T. Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends Neurosci* 29, 349-358 (2006).
- Plaisted, K., O'Riordan, M., & Baron-Cohen, S. (1998). Enhanced visual search for a conjunctive target in autism: A research note. *Journal of Child Psychology and Psychiatry*, 39(5), 777-783.
- Polat, U & Norcia, A. M. (1996). Neurophysiological evidence for contrast dependent long-range facilitation and suppression in the human visual cortex. *Vision Res*, 36, 2099-2109.
- Polat, U., & Sagi, D. (1993). Lateral interactions between spatial channels: suppression and facilitation revealed by lateral masking experiments. *Vision research*, 33(7), 993-999.
- Polat, U., Sagi, D., & Norcia, A. M. (1997). Abnormal long-range spatial interactions in amblyopia. *Vision research*, 37(6), 737-744.
- Polat, U., & Tyler, C. W. (1999). What pattern the eye sees best. *Vision Research*, 39(5), 887-895.
- Rippon, G., Brock, J., Brown, C. & Boucher, J. (2007). Disordered connectivity in the autistic brain: challenges for the "new psychophysiology". *Int J Psychophysiol*, 63, 164-172.
- Rubenstein, J. L. (2010). Three hypotheses for developmental defects that may underlie some forms of autism spectrum disorder. *Current opinion in neurology*, 23(2), 118-123.
- 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.

- Samson, F., Mottron, L., Soulières, I., & Zeffiro, T. A. (2012). Enhanced visual functioning in autism: An ALE meta-analysis. *Human brain mapping*, 33(7), 1553-1581.
- Schultz, R. T. (2005). Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *Int J Dev Neurosci*, 23, 125-141.
- Silberberg, G., Gupta, A., & Markram, H. (2002). Stereotypy in neocortical microcircuits. *Trends in neurosciences*, 25(5), 227-230.
- Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision Res*, 49, 2705-2739.
- Skottun, B. C. & Skoyles, J. R. (2008). Coherent motion, magnocellular sensitivity and the causation of dyslexia. *Int J Neurosci* 118, 185-190.
- Tager-Flusberg, H. (2004). Strategies for conducting research on language in autism. *Journal of Autism and Developmental Disorders*, 34(1), 75-80.
- Tommerdahl, M., Tannan, V., Holden, J. K. & Baranek, G. T. (2008). Absence of stimulus-driven synchronization effects on sensory perception in autism: Evidence for local underconnectivity? *Behav Brain Funct*, 4, 4-19.
- Tootell, R. B., Hadjikhani, N., Hall, E. K., Marrett, S., Vanduffel, W., Vaughan, J. T., & Dale, A. M. (1998). The retinotopy of visual spatial attention. *Neuron*, 21(6), 1409-1422.
- 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, 1013-1024.
- Vialatte, F. B., Maurice, M., Dauwels, J., & Cichocki, A. (2010). Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. *Progress in neurobiology*, 90(4), 418-438.

Weinger, P. M. (2013). *Electrophysiological Assessment of Visual Pathways in Children with and without Autism Spectrum Disorder* (Doctoral dissertation, YESHIVA UNIVERSITY).

Zemon, V., & Ratliff, F. (1982). Visual evoked potentials: evidence for lateral interactions. *Proceedings of the National Academy of Sciences*, 79(18), 5723-5726.

Zemon, V., & Ratliff, F. (1984). Intermodulation components of the visual evoked potential: responses to lateral and superimposed stimuli. *Biological cybernetics*, 50(6), 401-408.