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The Developmental Trajectory of Contour Integration in Autism Spectrum Disorders

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The developmental trajectory of contour integration in autism spectrum disorders

By

TED S. ALTSCHULER

A dissertation submitted to the Graduate Faculty in Psychology, sub program in Cognitive Neuroscience, in partial fulfillment of the requirements for the degree of Doctor of Philosophy,
The City University of New York

2014
The manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the Dissertation requirements for the degree of Doctor of Philosophy

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Abstract

The developmental trajectory of contour integration in autism spectrum disorders

by

TED S. ALTSCHULER

Adviser: John J. Foxe, PhD

Sensory input is inherently ambiguous and complex, so perception is believed to be achieved by combining incoming sensory information with prior knowledge. One model envisions the grouping of sensory features (the local dimensions of stimuli) to be the outcome of a predictive process relying on prior experience (the global dimension of stimuli) to disambiguate possible configurations those elements could take. Contour integration, the linking of aligned but separate visual elements, is one example of perceptual grouping. Kanizsa-type illusory contour (IC) stimuli have been widely used to explore contour integration processing. Consisting of two conditions which differ only in the alignment of their inducing elements, one induces the experience of a shape apparently defined by a contour and the second does not. This contour has no counterpart in actual visual space – it is the visual system that fills-in the gap between inducing elements. A well-tested electrophysiological index associated with this process (the IC-effect) provided us with a metric of the visual system’s contribution to contour integration. Using visually evoked potentials (VEP), we began by probing the limits of this metric to three manipulations of contour parameters previously shown to impact subjective experience of illusion strength. Next we detailed the developmental trajectory of contour integration processes over childhood and adolescence. Finally, because persons with autism spectrum disorders (ASDs) have demonstrated an altered balance of global and local processing, we hypothesized
that contour integration may be atypical. We compared typical development to development in persons with ASDs to reveal possible mechanisms underlying this processing difference. Our manipulations resulted in no differences in the strength of the IC-effect in adults or children in either group. However, timing of the IC-effect was delayed in two instances: 1) peak latency was delayed by increasing the extent of contour to be filled-in relative to overall IC size and 2) onset latency was delayed in participants with ASDs relative to their neurotypical counterparts.
Acknowledgments

This dissertation is the product of five years of study through which I have been guided with dedication, humor, and wisdom by my mentor, John Foxe, to whom I owe great thanks. In addition, his close collaborator Sophie Molholm, and a group of teachers not limited to, but including Jennifer Mangels, Nancy Foldi, Vivian Tartter, Jeffrey Halperin, David Masur, Ronda Facchini, Natalie Russo, and Hilary Gomes each gave generously of their time and knowledge and were challenging or nurturing, as the occasion demanded. I thank each of them and hope to continue our relationship long into the future. My colleagues at The Sheryl and Daniel R. Tishman Cognitive Neurophysiology Laboratory are a warmly collaborative bunch to whom I am truly grateful. Finally, Michael and mom have shown me extraordinary patience and support. I love them and would never have made it through a mid-career personal revolution without them. Some guys buy a little red sports car. I got a PhD in neuroscience… go figure.
Dedication

FOR MICHAEL
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Chapter One
1.1 Perceptual completion and Autism Spectrum Disorders – A way to understand global/local processing differences?

I have no trouble noticing the little details that no one else seems to see, and in fact I have no choice but to see every little detail. I’ll see the tiny plants in the concrete cracks, the placement of hair on the people around me, the light damage on cars beside me, the exact words and pictures of all the advertisements... I can’t block that out, I can’t just glance over it and move on, I have to stop and LOOK at every little thing before the whole scene makes sense. Every time there is a change in the scene, I have to look at everything all over again and re-draw the entire picture in my head before I can move on. If I don’t, there are blank spots in my "scene" – Ari “Visual Perception” from her blog Perception Ari 12/6/2010 (Akari, 2010)

In a typical environment human beings are confronted with a barrage of information. The air, your hand, the page you are reading now, their molecules are arrayed one after the other without the defined edges we perceive between them. We are typically unaware of how visual perception organizes the information surrounding us into discrete bundles, distinguishing what we experience as objects from each other as well as from everything else. The neat categorization we experience is something of an illusion resulting from a bias of the adult human brain to organize matter into distinct, coherent wholes early in visual processing at a level which is
beneath the level of consciousness (Koffka, K., 1935; Egly, R. et al., 1994; Blaser, E. et al., 2000; Schoenfeld, M.A. et al., 2003). Imagine if we were equally aware of each particle in the air, our skin, the page, if we wandered through an undifferentiated field of line-fragments, locations, and colors belonging to multiple objects. Imagine if we were obliged to figure out each time we encountered a new scene which fragment went together with which. An everyday scene would be so dizzying to put together that we could do little else. Instead, we acquire perceptive abilities that automatically bind together features, constructing objects that we know by their name and uses.

If our visual system imposes boundaries to make processing more efficient, we could also say that it imposes continuity. The branch of a tree in the foreground of our vision obstructs our view of a bird sitting a little further away. Gaps are present in the sheet of cells that make up the retina, including a 1-2 mm hole where the optic nerve exits (Quigley, H.A. et al., 1990), but the visual system allows us to experience a whole bird, even when blocked by the branch of a tree. This is thanks to perceptual completion or closure, whereby the visual system fills-in impoverished sensory signals (Foley, M.A. et al., 1997). Although common wisdom regards vision as a sense which translates the details of our world with exact fidelity, it could not quickly and automatically render the world as we see it without combining incoming sensory information with previous knowledge. Visual perception is in some significant part an inference. This is not a new notion. The psychologist William James had already observed more than 100 years ago:

*Whilst part of what we perceive comes through our senses from the object before us, another part (and it may be the larger part) always comes out of our own mind. (James, W., 1890)*
But if the ability to see as we do is not solely the result of external stimuli, if the brain is adding or changing signals in light of information experienced in the past, then one could imagine that a visual system that adds knowledge differently could create different perceptions.

Individuals with autism spectrum disorder (ASD) often describe their perceptual experiences very differently from neurotypical persons. When Kanner first described autism (Kanner, L., 1943; Kanner, L. & Eisenberg, L., 1956), he spoke of a balance of processing which lacks the typical bias for making coherent wholes. This aspect of the ASD phenotype (the outward manifestations of pathology) has been attributed to an inherent superiority in processing local details of a stimulus, information such as contrast or the orientation of a line segment (Mottron, L. et al., 2006) – or a weakness in processing its configuration – the global level of a stimulus (Scherf, K.S. et al., 2008). A more recent account describes a dysfunction in the application of previously acquired knowledge to the processing of local stimulus elements – the “hypo-priors” account (Pellicano, E. & Burr, D., 2012). This different integration of the global and local levels has been associated with some of the disorder’s core symptoms, such as focusing on small parts of objects rather than their use, or on the literal meaning of a phrase rather than its gist, both examples of ways persons with ASD may generalize less than their neurotypical counterparts.

It is unknown whether this difference exists at a conceptual level - whether it is a dysfunction of how information is used to accomplish higher cognitive processes, or whether the problem begins early in sensory processing. There is considerable evidence suggesting differences in early perceptual processing. It is the hypothesis of the central study of this dissertation that the development of perceptual completion, as an early integration of global and local information, may reveal something about mechanisms underlying ASD. A brief description of the stimulus
class and the metric we use follows. Comprehensive descriptions appear in the methods sections of Chapters 2, 3, and 4.

1.2 The Stimulus Class – Kanizsa Illusory Contours

The visual system accomplishes perceptual completion of regions, textures, and contours - for black and colored, stationary and moving stimuli. The studies that are the focus of this dissertation examine the completion of the contours of an illusory square (Fig 2.1), a process formally illustrated by Schumann (1904), although evidence going as far back as cave paintings from the Paleolithic era suggest that our ancestors may have been aware of this perceptual ability to fill-in or disambiguate incomplete contours (Hodgson, D., 2003). Optical illusions are legion in the study of visual processing because the information that exists at the stimulus level is not the same as the perception we experience. It is via this dissonance that we attempt to isolate the brain’s influence upon vision from the influence of the stimulus. Kanizsa-type illusory contour (IC) stimuli (Kanizsa, G., 1976) have been among the most widely used illusions to explore contour completion. They are used in the experiments covered in Chapters 2, 3, 4, and 5. Kanizsa IC’s are more graspable by reference to a picture than to any number of words. When the “mouths” of their Pacman-shaped inducers are aligned, depending on the number of inducers, viewers generally perceive the shape of a square, triangle, pentagon, etc. This shape is an inference since the contour viewed does not have a counterpart in veridical visual space. The information that would typically excite retinal cells and send a signal through visual cortex is absent, yet, the perception is that the contours of the mouths continue. The shape bound by this contour appears to be brighter than the background upon which it is superimposed (Jory, M.K. & Day, R.H., 1979; Mendola, J., 2003).
Kanizsa ICs have not only been of use in understanding contour completion, but also have served as a proxy of object processing in general since there is overlap in the brain regions involved in perceiving ICs and conventional objects. Recordings made from monkey neurons whose receptive fields (the area of space in which the presence of a stimulus will cause a neuron to respond) encode the space in the gap between IC inducers, have shown the same sort of activation they would for the presence of “real” contours (von der Heydt, R. et al., 1984).

Human fMRI work demonstrated activation of visual areas to ICs comparable to that which would be seen to similar shapes bounded by real contours (Mendola, J.D. et al., 1999).

When studied neurophysiologically, IC inducers are presented in two contrasting conditions which are highly similar. The conditions possess the same number of inducers, the same size inducers, the same array of inducers, and the same number of real contours. What is different about them is the orientation of the contours. Aligned contours induce the perception of an additional object above and beyond the inducers. Examining the difference between conditions attempts to remove the information associated with the inducers, which generate the incoming, low-level sensory signal. It focuses instead on the contribution of the visual system, which fills in the gap. This difference is indexed by a well-studied neurophysiological response with detailed temporal and spatial metrics, replicated in multiple studies in neurotypical adults (Murray, M.M. et al., 2002; Proverbio, A.M. & Zani, A., 2002; Foxe, J.J. et al., 2005; Shpaner, M. et al., 2009), making them ideal baseline measures against which to compare other groups.

You will find a more detailed overview of contour completion and experimental work with ICs in section 1.10.
1.3 The Metric – Visual Evoked Potentials

The experiments in chapters 2, 3, 4, and 5 were conducted using event-related potentials (ERPs). These are electroencephalographic (EEG) recordings, made from the scalp surface, of the electrical activity of large pyramidal cells of the brain’s outer layer – the cortex. These are associated with some event, in this case the presentation of IC inducers. This event is established as a baseline and both strength and timing of the activity are measured against it, making the metric a relative measure of electrical activity generated by large groups of neurons. Its units describe an amount of voltage (measured in µV), when it occurred (in ms), and the location of its generators in the brain can be estimated mathematically (Scherg, M. & Berg, P., 1991). If differences exist in the electrical activity, these can be measured with ERP whether or not the behavior of the person was different. When such brain processing differences also exist in close family members, this measure is taken to reveal characteristics that may reflect liability for disease, lying closer to underlying pathogenic mechanisms than outwardly manifest differences, such as the capacity to perform a task. Such underlying differences are called endophenotypes (Gottesman, II & Shields, J., 1973) and help bridge the gap in our knowledge between the symptoms we can see and the underlying causes at the level of cells or genes, which are largely unknown in the case of ASD. Once identified, these could function as biological markers of pathogenic mechanisms, some of which may possess the ability to facilitate earlier diagnosis or help lay the foundation for interventions that address pathogenesis rather than mitigate the symptoms.

The visually evoked potential (VEP) is the electrophysiological signal measured following presentation of a visual stimulus. Each presentation of a stimulus constitutes a trial. Multiple similar trials are averaged together which emphasizes the effects they have in common and
suppresses those effects which are different. The resulting average are plotted as a graph, with voltage amplitude on the vertical axis and time on the horizontal axis. This produces a wave-like form. The typical shape of the VEP has been replicated over thousands of studies. Separate positive or negative deflections of the wave occurring at defined times or latencies have been found to predict certain cognitive responses to stimuli. These isolated deflections are referred to as components. The more stable early components of the VEP, to which this dissertation makes reference, include:

C1 - measured most strongly over midline posterior scalp. The effect onsets around 50 ms, peaking around 90 ms. It is believed to be largely generated in the primary visual cortex (V1) (Foxe, J.J. & Simpson, G.V., 2002). In the human brain V1 is folded in half with the lower part of the visual field mapped onto one side of the fold and the upper part mapped onto the other. The resulting deflection is positive for stimuli in the lower visual field and negative for stimuli in the upper. Its activity can be modulated by basic stimulus parameters such as contrast (Jeffreys, D.A. & Axford, J.G., 1972; Di Russo, F. et al., 2002; Kelly, S.P. et al., 2008).

P1 - a positive deflection measured most prominently at lateral posterior sites. It onsets around 80 ms and peaks around 110 ms. It is highly sensitive to parameters of basic stimulus energy, e.g., size, contrast, and its generators are thought to include both dorsal and ventral extrastriate cortex (areas outside V1) (Di Russo, F. et al., 2002).

N1 - a negative deflection peaking at approximately 150 ms, whose generators lie in parietal and lateral occipital cortex. It is measured most strongly at lateral occipital scalp
sites and is larger when participants are engaged in discriminative as opposed to detection tasks (Ritter, W. et al., 1979; Di Russo, F. et al., 2002).

The earliest modulation of the VEP evoked by the difference between the two IC conditions has been measured during the N1 latency, with the illusion-inducing condition evoking a more negative response than the non-inducing condition (Fig 2.1). The difference has been termed the IC-effect. It peaks at approximately 150 ms (Hermann, C.S. & Bosch, V., 2001; Pegna, A.J. et al., 2002; Proverbio, A.M. et al., 2002; Yoshino, A. et al., 2006; Shpaner, M. et al., 2009), onsetting as early as 88 ms (Murray, M.M. et al., 2002). The lateral occipital complex (LOC), a cluster of visual regions associated with object processing, is most consistently implicated in its generation (Murray, M.M. et al., 2002; Pegna, A.J. et al., 2002; Foxe, J.J. et al., 2005; Shpaner, M. et al., 2009; Fiebelkorn, I.C. et al., 2010). Damage to the analogous regions in monkey visual cortex, led to deficits in discrimination tasks with ICs (Huxlin, K.R. et al., 2000), suggesting that it is obligatory for IC processing. The role of the LOC in visual object processing is more thoroughly detailed in section 1.9.

Activity associated with IC processing in lower-level visual areas V1 and V2 (e.g., Peterhans, E. & Von der Heydt, R., 1989; Ffytche, D.H. & Zeki, S., 1996), have encouraged many investigators to posit that these are the earliest IC-related responses. However, this work has not compared that activity with activity in the LOC, nor has it measured the timing of such effects. When low-level cortical effects are explicitly measured, they point to activity which follows, rather than precedes, that of the LOC (Lee, T.S. & Nguyen, M., 2001), suggesting that the earliest measured ERP effect following presentation of ICs – the IC-effect – occurs at approximately 150 ms and that subsequent lower-level effects are the consequence of feedback. EEG work in humans (Shpaner, M. et al., 2009) and intracranial recordings in monkey visual
cortex (Lamme, V.A. et al., 1999) have associated this effect specifically with the establishment of contours, an effect which precedes the filling-in of the shape bound by those contours. Work with human neglect patients, whose ability to pay attention to specific parts of visual space is damaged, suggests that this initial, boundary-completion phase of IC processing occurs without any need for awareness (Vuilleumier, P. et al., 2001).

Other VEP effects following IC presentation have been measured after 200 ms (Herrmann, C.S. et al., 1999; Proverbio, A.M. et al., 2002). VEP effects in the 250 to 400 ms range are often described as reflecting higher conceptual-level processes in object-processing. This is reflected in Doniger and colleagues (2000; 2001) perceptual completion work with fragmented images of everyday objects. No IC-effect is seen following presentation of these stimuli, but as the visual system completes these more complex images over a more extended period of time, a later effect is seen. Termed the negativity-for-closure (N_{cl}), its later onset and gradual modulation over time suggest completion processes that are more challenging to the visual system than the simple filling-in of the contours of a square. Intracranial work in humans has also implicated the LOC in generating the N_{cl}, but as part of a network of several brain regions (Sehatpour, P. et al., 2008).

Comparisons of IC processing in neurotypical and schizophrenic patients (Foxe, J.J. et al., 2005) and paradigms comparing task demands on participants (Murray, M.M. et al., 2006) suggest that the early and late effects underly different phases of IC processing. A comprehensive examination of contour completion and ICs is provided in section 1.10, detailing the IC-effect and N_{cl} as indices of an early, automatic boundary-completion phase implicating the LOC, and a later process seen in situations of increased burden, such as difficult to complete objects, tasks involving judgment, or processes compromised by pathology. This is a more detailed filling-in process facilitated by a network involving the LOC and other cortical regions.

1.4 The Questions Prompting These Investigations

An inquiry into the mechanisms underlying atypical sensory processing in autism motivated the studies detailed here, but a plunge into the problem space encouraged us to think backwards. If we were to draw conclusions based upon an understanding of atypical development of contour completion, we had to first understand its typical development. And if we hoped to understand its typical development using electrophysiology, we wished to better understand what the ERP effects in the literature suggested about how the brain completes ICs. ICs have been the subject of a century of inquiry, but all configurations of collinear inducers do not generate the experience of the illusion. Depending on parameters such as size or contrast, this illusion has been reported to be stronger, weaker, or not present at all (Dumais, S.T. & Bradley, D.R., 1976; Petry, H.S. et al., 1983; Shipley, T.F. & Kellman, P.J., 1992). Numerous studies interrogated the relationship between some parameter of IC inducers and what the viewer experienced, but a systematic manipulation had not been the subject of an electrophysiological investigation. If something about the global characteristics of these inducers cues the brain to process the local stimulus elements unrealistically – to make an inference that empty space “ought to be” filled in with a contour – what information contains these cues? The most common parameters influencing perception were inducer size, the distance of the inducers from each other, and the distance of the inducers relative to the overall size of the induced shape. This last variable is called “support ratio.” It could also be thought of as the portion of the contour that does not have to be completed (see Fig 2.2) (Shipley, T.F. et al., 1992).
So we began by asking, if adults report different experiences of illusion strength to manipulations of these parameters, is the brain’s activity also different? How far apart do the inducers have to be to no longer suggest that a contour “ought” to fill the gap? We investigated the systematic manipulation of the three variables of inducer size, contour extent, and support ratio upon the spatio-temporal dynamics of the classic IC-effect in neurotypical adults. This inquiry is the subject of Chapter 2. Challenging the limits of our dependent measure, we reasoned we might be more confident of how to use it to investigate development. We narrowed our developmental inquiries, focusing solely on the absolute extent parameter. Given how stereotypic the IC-effect is, we asked in Chapter 3: how do the spatio-temporal characteristics of IC completion develop in neurotypical persons from 6 years-of-age to adulthood? Are contours filled-in as efficiently? Are there multiple stages of maturity, suggesting an experience-dependent process? Finally, in the studies in Chapters 4 and 5, we asked whether the development of IC completion differs in individuals with ASD. Since an atypical integration of global and local information appears to be endemic to ASD, would that be reflected in the size, timing or generators of IC completion effects? Do the results suggest anything about ASD pathogenesis?

The remaining sections of this first chapter are devoted to an overview of each of our topics of inquiry. This begins with a description of ASD epidemiology, phenotype, and diagnostic criteria in section 1.5, and morphology and anatomy in 1.6. Section 1.7 details sensory processing differences documented in ASD. A description of global and local stimulus characteristics and neurotypical object processing follows in sections 1.8 and 1.9, completion in 1.10, and the neurotypical development of these processes in 1.11. In 1.12 we conclude with what is known about these processes relative to ASD. Following the detailing of the four studies
in Chapters 2, 3, 4, and 5 Chapter 6 explores possible interpretations of the results and implications they might have for understanding the pathogenic mechanisms of ASD.

1.5 Autism Spectrum Disorders – Phenotype, Epidemiology, Diagnosis

Medical and mainstream culture descriptions of autism are... very superficial descriptions of things autistic people do, with the implication that autistic people do these things simply because they like them, or for no reason at all. People with ASD have real problems. That some of us walk on our toes is not one of them. – Amanda Forest Vivian from her blog Somewhere Else (Vivian, A.F., 2010)

The term autistic was coined by Leo Kanner in 1943 in Baltimore to describe 11 patients who presented with similar characteristics of intense isolating aloneness. An autistic person, he wrote, “whenever possible, disregards, ignores, shuts out anything that comes to the child from the outside.” They are characterized by “an anxiously obsessive desire for the preservation of sameness” as well as an “inability to experience wholes without full attention to the constituent parts. . . . A situation, a performance, a sentence is not regarded as complete if it is not made up of exactly the same elements that were present at the time the child was first confronted with it. If the slightest ingredient is altered or removed, the total situation is no longer the same and therefore is not accepted as such.” (Kanner, L., 1943).

Nearly simultaneously, Hans Asperger in Vienna observed in a group of his patients a similar sense of isolation. “They do not make eye contact…[there is] a poverty of facial expressions and gestures… the use of language appears abnormal, unnatural…the children follow their own impulses, regardless of the demands of the environment.” (Asperger, H., 1991).

Originally, Kanner ascribed the atypical development as stemming from the parents. “Children with early infantile autism were the offspring of highly organized, professional
parents, cold and rational, who just happened to defrost long enough to produce a child” (Time July 25, 1960), an opinion echoed by renowned child psychiatrist Bruno Bettelheim, who famously regarded children with autism as the product of “refrigerator mothers” (Bettelheim, B., 1967). In the ensuing 50 years, twin studies have shown concordance rates of more 60 - 90% in monozygotic twins and less than 5% in dizygotic twins (Folstein, S. & Rutter, M., 1977; Bailey, A. et al., 1995), establishing the heritability of autism. Prevalence rates in siblings of diagnosed persons have been reported in the range of 2 – 6%, an approximately 25-fold higher risk than that found in the general population (Rutter, M. et al., 1999; Abrams, B.S. & Geschwind, D.H., 2008). Chromosomal anomalies have been shown to correlate with many aspects of the autism phenotype, which is highly variable. Autism is presently characterized as encompassing a spectrum of life-long neurodevelopmental disorders including Asperger Syndrome, childhood disintegrative disorder, pervasive developmental disorder not-otherwise-specified (PPD), and Rett syndrome, among many other rarer forms.

Autism is diagnosed on the basis of marked impairments in communication, but especially in social relatedness, and a markedly restricted repertoire of activity and interests. These classes of dysfunction manifest themselves in different individuals as impaired eye contact or use of gestures, failure to develop peer relationships, communicative speech delay, an inability to conceive of other people’s mental states or emotions, lack of spontaneous imaginative or symbolic play, inflexible adherence to routines which are disruptive to daily functioning, stereotyped motor mannerisms, and persistent preoccupation with parts of objects, symptoms which must be present prior to three years-of-age to be diagnostically relevant (American Psychiatric Association, 2000). Asperger Syndrome, presently included on the spectrum, differs from autism predominantly in the absence of language delay. However, this category will be
made obsolete when the Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorders*. As diagnostic criteria have evolved, what Kanner and Asperger originally described probably now sits at the more severe end of the spectrum.

A review of 43 epidemiological studies conducted since 1966 estimates an average prevalence of 10.6 cases per 10,000 for autistic disorder and 60 to 70 per 10,000 across the spectrum of developmental disorders (one child in 150) (Fombonne, E., 2009). A more recent review of 600 epidemiological studies estimates world-wide median prevalence at 62 cases per 10,000 (Elsabbagh, M. et al., 2012). The accuracy of these estimates is limited by variable diagnostic methods, availability of services, and awareness of ASDs among professionals and members of the general public. Diagnoses in males exceed those in females by a ratio of 4.3:1 (Newschaffer, C.J. et al., 2007). Further gradations of high- and low-functioning autism are made on the basis of intellectual functioning. An estimated 25-40% of individuals with ASD have an IQ under 70 (Baird, G. et al., 2000; Chakrabarti, S. & Fombonne, E., 2001).

The broader phenotype of ASDs includes characteristics occurring with a greater frequency in diagnosed individuals and their first-degree relatives than in the population at-large, which may correlate within families (Szatmari, P. et al., 1996). These include savant skills, that is, islands of outstanding talent in areas such as calculation or music, present in 10% or more of persons on the autism spectrum (Rimland, B. & Fein, D., 1988). Approximately 30% of individuals with ASDs have epilepsy, as compared with 1% of the general population (Kang, J.-Q. & Barnes, G., 2013). Other aspects of the broader ASD phenotype include tics, gastrointestinal disturbances, comorbid psychiatric diagnoses including mood and conduct disorders, aggression and attentional dysfunction, and motor irregularities including hypotonia, toe-walking and apraxia, and both hyper- and hypo-sensitivities to sensory stimuli (Gillberg, C.
The heterogeneity of phenotype across individuals with the more disabling symptoms overlapping with behavioral and learning disorders, and psychiatric illnesses, and the less disruptive end of the spectrum difficult to distinguish from variations within the typical population, speaks to the challenge of diagnosis.

A number of genetic disorders manifest a high prevalence of ASD and these account for an estimated 10-20% of diagnoses (Abrams, B.S. et al., 2008). For example, Smith-Lemli Opitz Syndrome (SLOS), an autosomal condition causing severely reduced synthesis of cholesterol, has an ASD prevalence of 71–86% (Sikora, D.M. et al., 2006). There is quite a bit of overlap in the phenotype of autism and Rett syndrome. 75–90% of Rett cases are linked to a mutation of the MECP2 gene (Samaco, R.C. & Neul, J.L., 2011). The DSM-IV subsumed Rett under the autism spectrum. Other genetic syndromes manifesting high frequencies of ASD include tuberous sclerosis, fragile X, neurofibromatosis, Angelman, and Prader-Willi (Zafeiriou, D.I. et al., 2013).

There are obvious challenges inherent in diagnosing a spectrum disorder with no single biological marker. Diagnosis requires that symptoms be present in early childhood, and intervention may ameliorate symptoms, and with them any state-dependent biomarkers, so often, identifying ASD can rely on retrospective report, whereas an endophenotype would not disappear. At present the diagnosis is, to a large degree, a judgment. Within the context of patient care, it is the job of the clinician not merely to identify symptoms, but to assess how disabling they are. In offering care it is more important that a diagnosis be useful than it be correct. However, researching the etiology of ASD remains a bit of a problem in that grouping individuals under a single category, albeit a spectrum, implies that averaging together many
individual measures of blood sample or neural activity will yield common mechanisms, when what underlies heterogeneous phenotype is likely heterogeneous. One genetic twin study reported high heritability for each of the three core classes of symptoms separately, but genetic heterogeneity among them (Ronald, A. et al., 2006).

It is important in a research context that diagnosis mean the same thing across individuals. To that end, many diagnostic tools have been developed. Among those mentioned below are the Child Autism Rating Scale (CARS) (Schopler, E. et al., 1994) - a behavioral observation scale meant to be completed by a trained observer. It has been highly criticized because it does not reflect *DSM-IV* criteria. The Autism Spectrum Quotient (AQ) (Baron-Cohen, S. et al., 2001) is a 50-question, adult self-report questionnaire which identifies autistic traits in the general population. The most comprehensive neuropsychological assessments providing diagnostically relevant information that are systematically collected are the *Autism Diagnostic Observation Schedule* (ADOS) (Lord, C. et al., 1999) and the *Autism Diagnostic Interview-Revised* (ADI) (Lord, C., Rutter, M., DiLavore, P.C., et al., 1994). These, together with judgment of an experienced clinician, currently serve as the gold-standard of diagnosis and are the means employed in the main studies of this dissertation to determine if a recruited participant met criteria.

The ADOS is a structured, standardized interactive assessment tool consisting of four modules customized for levels of language development. Its activities are designed to elicit a single aspect of the social-communication phenotype from a patient in a fashion appropriate to his or her developmental level but minimally impacted by spoken language ability. The outcome of the scoring algorithm offers evidence of the participant’s social and communicative deficits which are necessary, but not sufficient to diagnose an ASD, as well as producing a score
reflecting the subdomain of restricted interests and repetitive behaviors. More recently, the calibration of a standardized severity score (CSS) permits comparison of autism severity across subdomains for modules 1 – 3, normed for age and language development level (Gotham, K. et al., 2009), separate severity indices within social affect and restricted and repetitive behavior subdomains (Hus, V. et al., 2012).

The ADI is a comprehensive structured interview conducted with the patient’s primary caregiver. Its questions span the three areas of core ASD phenotype (Lord, C., Rutter, M., & Le Couteur, A., 1994). The advantage of the ADOS is that it permits the clinician to observe diagnostically relevant behavior first-hand, but the ADI has the added feature of discerning when symptoms were first observed developmentally. This is necessary given that age of onset is a diagnostic criterion for autism and a lack of speech delay is the deciding factor for differentiating between autism and Asperger’s Syndrome. The validity of the ADI is limited by the accuracy of the caregiver’s reporting, so clinical judgment is necessary in interpreting its indications.

1.6 Autism Spectrum Disorders – Evidence of Connective Pathology

high school... that's when my people-anxiety increased exponentially. Not only was I trying to puppet my body through each social interaction...but I was also increasingly aware that body language had meaning...and I was desperate to understand what the various gestures really signified... most of my insights about a conversation took place days or weeks later. I didn't socialize so much as forensically analyze the corpse of an interaction. – Mutineer, on his blog The Incipient Turvy (Mutineer, 2012)

The neuropathological correlates of ASD identified at the cellular and structural level are wide-ranging. None yet offers diagnostic sensitivity and specificity, but they point to ample evidence for ASDs as life-long neurodevelopmental disorders, and to an emerging picture of
disordered connectivity among regions as opposed to dysfunction of one focal region as an underlying mechanism of autism pathology.

**Cell Morphometry**

Differences at the cellular level have been associated with ASD including neuronal density in the fusiform gyrus (van Kooten, I.A.J. et al., 2008), anterior cingulate (Simms, M.L. et al., 2009), and the Purkinje cells of the cerebellum (Whitney, E.R. et al., 2008), dendritic spine density in cortical pyramidal cells (Hutsler, J.J. & Zhang, H., 2010), and increased microglial density in the dorsolateral prefrontal cortex (Morgan, J.T. et al., 2010). Subcortical, periventricular, hippocampal, and cerebellar differences in neuronal development have been observed (Wegiel, J. et al., 2010). Decreased mini-column width is an often-reported finding, especially in frontal cortex (Buxhoeveden, D.P. et al., 2006; Casanova, M.F., 2007; Casanova, M.F. et al., 2010). Minicolumns accomplish the uniform alignment and spacing of cellular elements – dendrites and axons - within a volume of cortex. As such they specify patterns of connections and their altered architecture offers morphometric support for hypotheses of altered connectivity in autism (Casanova, M. & Trippe, J., 2009). As morphometric data are derived from post-mortem tissue, interpretation of their results is limited by the adult age of most subjects, difficulties in controlling for co-morbidities, and a small mean number of participants (Mills Schumann, C. & Wu Nordahl, C., 2011). However they are valuable in pointing to differences in how neurons develop, which can impact connectivity between regions.

**Structural Anatomy**

Evidence of brain overgrowth prior to three years-of-age is a much replicated finding in autism (Hardan, A.Y. et al., 2000; Courchesne, E. et al., 2003; Hazlett, H.C. et al., 2005;
Anagnostou, E. & Taylor, M.J., 2011; Courchesne, E. et al., 2011). An approximately 10% increase in volume has been reported, peaking between two and four years of age and involving both grey matter (brain tissue comprised of cell bodies and dendrites which make up the regions commonly associated with brain functions) and white matter (the myelinated axonal fibers that facilitate connections between brain regions). Results implicating functionally associated brain regions include overgrowth in the amygdala, a sub-cortical structure associated with emotional processing (Sparks, B.F. et al., 2002), a finding subsequently correlated with the severity of social and communications symptoms (Schumann, C.M. et al., 2009). Overgrowth was reported in the striatum, where differences have been correlated with repetitive behaviors (Hollander, E. et al., 2005). Slowed growth and atrophy have also been measured. Reduced volume and neuron numbers were found in the amygdala (Schumann, C.M. & Amaral, D.G., 2006), the cerebellum (Stanfield, A.C. et al., 2008), and slowed growth rates and possible gray matter atrophy have been measured in the cortex (Hadjikhani, N. et al., 2006; Hardan, A.Y. et al., 2009), but these were found during adolescence and adulthood, so the point in development at which changes are measured is key to interpreting what neuroanatomy has to tell us about the pathogenesis of ASD. This is the rationale for the developmental approach taken in the studies in chapters three and four. Comparative investigations of early cortical overgrowth measured the largest differences in the temporal and frontal lobes, with smaller differences in the parietal lobes, and none in the occipital lobes (Carper, R.A. et al., 2002; Schumann, C.M. et al., 2010).

Another common anatomic finding is decreased corpus callosum volume, the large white matter tract that links the left and right cerebral hemispheres (Alexander, A.L. et al., 2007; Stanfield, A.C. et al., 2008; Frazier, T.W. & Hardan, A.Y., 2009; Keary, C.J. et al., 2009). These findings offer structural support for differences in interhemispheric connectivity (Quigley, M. et
which has been shown to correlate with behaviors in ASDs, such as the processing
speed of non-verbal tasks (Alexander, A.L. et al., 2007), cognitive planning and switching
(Keary, C.J. et al., 2009), and working memory for faces (Tallon-Baudry, C. et al., 2001).

Connectivity

Connectivity in the neurosciences can signify either the contiguity of neurons or groups of
neurons, referred to as structural connectivity, or it can refer to the inter-correlation of the
neuronal activity between non-adjacent brain regions, referred to as functional connectivity.
Generally, structural connectivity is visualized using diffusion tensor imaging (DTI), which
measures water diffusion to reveal the structure of larger white matter tracts. Functional
connectivity is indicated by co-activation of spatially distinct brain regions (Wass, S., 2011).

Oscillations, a common property in nature, are the regular fluctuation of some process between a
maximum and minimum value (think of the swing of a pendulum, or of the regular pattern of
sound waves). They are also characteristics of the electrical activity of neurons. This is the
mechanism proposed to coordinate firing rates among distant neural populations (Gray, C.M. et
al., 1989). The rate of such fluctuation is its frequency, measured in Hertz (that is, cycles per
second). Synchronous oscillatory activity in the beta bandwidth (13-15 hz) has been implicated
in long-range connectivity among neural populations working in concert (Gross, J. et al., 2004).
Oscillatory activity at specified frequencies can be measured using EEG (e.g., Mima, T. et al.,
Resonance Imaging (fMRI), which measures blood flow changes in soft tissue, can also be used
to measure temporal correlations of activity during tasks (Just, M.A. et al., 2004). It is used in
paradigms without tasks to measure so-called “resting-state” connectivity. This was introduced
to remove task confounds in an effort to find an MRI-based measure that correlated with structural connectivity (Greicius, M.D. et al., 2009).

Opinions are divided in the research community about whether ASDs would be better characterized as disorders of under- or over- connectivity. DTI has shown increased diffusion within white matter tracts in the frontal lobes of ASD individuals and their non-diagnosed siblings—taken as evidence for disordered structural connectivity (Greicius, M.D. et al., 2003; Barnea-Goraly, N. et al., 2010). Evidence for over-connectivity has been suggested by reduced mini-column width, in that this leads to more densely packed neurons in cortex. Evidence of over-connectivity is suggested by EEG coherence within the theta frequency band (3-6 hz) within frontal and temporal lobes (Murias, M. et al., 2007). Over-connectivity has been offered as an explanation for hyperfocus on visual details (Mottron, L. et al., 2006) or for a tendency toward forming representations of concepts that rely on finer and finer distinctions of individual instances rather than exploiting the overlapping they share with previously acquired knowledge to create generalizations (McClelland, J.L., 2000).

However, a picture of reduced long-range connections has emerged, suggesting over-connectivity within local areas with simultaneous under-connectivity between them as a candidate mechanism of ASD pathology (Belmonte, M.K. et al., 2004; Courchesne, E. & Pierce, K., 2005; Casanova, M.F. et al., 2006; Muller, R.A. et al., 2011; Wass, S., 2011), but see (Jones, T.B. et al., 2010). While it is apparent how under-connection or lack of synchronization between regions that synthesize information might manifest as disordered processing, one must exercise caution in interpreting over-connectivity as advantageous. Although patterns of connectivity have been correlated with performance advantages, more white matter within given focal areas has also been observed to be more diffuse, that is, less ordered (Muller, R.A. et al., 2011). Early
white matter overgrowth is likely to affect later development, impairing differentiation based on function. The point is that these patterns of connectivity exist within the context of each other. It is the connective profile in its entirety that will create a distinct pattern of performance which is likely to be less enriched by cross-talk from dispersed systems (Courchesne, E. et al., 2005).

Consider, for example, human face processing in ASDs. Despite many anomalies reported in the recognition of and memory for faces, an fMRI comparison of strange and familiar face processing saw intact activity of the fusiform face area (FFA), temporal region correlated with face processing, however, a network of additional regions used by TD persons was not engaged in individuals with ASD (Pierce, K. et al., 2004). This altered connectivity between the FFA and the extended network correlated significantly with a clinical measure of autism severity (Kleinhans, N.M. et al., 2008). Another example can be seen in dysfunctional integration of information between the senses. ERP studies of children and adolescents revealed differences in the early integration of basic somatosensory and auditory stimuli (Russo, N. et al., 2010) and basic visual and auditory stimuli (Brandwein, A.B. et al., 2012) when TD individuals and those with ASDs were compared. A recent study showed marked deficits in the ability to integrate seen and heard speech, especially under noisy background conditions (Foxe, J.J. et al, in press).

The altered connectivity in ASDs is of particular interest vis-à-vis perceptual completion because of the location of the differences. Connectivity disruptions appear most abundant between frontal and posterior areas generally (Cherkassky, V.L. et al., 2006; Kana, R.K. et al., 2009) particularly the temporal lobes (Buxhoeveden, D.P. et al., 2006; Ben Bashat, D. et al., 2007; Just, M.A. et al., 2007; Murias, M. et al., 2007). A recent study not only measured reduced long-range and increased short-range oscillatory coherence within the delta band frequency (~ 0.5 – 4.0 Hz), it registered the largest deficit in frontal-occipital connections and
correlated this pattern of connectivity with ADOS severity scores, linking a potential neural mechanism of dysfunction with severity of ASD (Barttfeld, P. et al., 2011). A human intracranial study of perceptual completion has also revealed coherence between prefrontal cortex and LOC (Sehatpour, P. et al., 2008), suggesting that indices of completion could be candidate biomarkers for ASD.

Connectivity differences between the two cerebral hemispheres are also widely reported in ASD. In a functional connectivity study in males 12-42 years of age, those differences were found to be maintained into adulthood (Anderson, J.S. et al., 2011). Reduced delta and theta band resting-state interhemispheric coherence have been reported over frontal and temporal regions (Coben, R. et al., 2008). Just et al (2007) found that parietal and frontal activity during a task of executive function was less synchronized for ASD compared to TD participants and that this correlated with the reduced size of sub-regions of the corpus callosum – an association of functional under-connectivity, structural under-connectivity, and a cognitive task often impaired in ASD. Interhemispheric connectivity measured with fMRI in frontal and superior temporal gyri in ASD toddlers was strongly associated with expressive and receptive language, but negatively correlated with ADOS scores (Dinstein, I. et al., 2011). Frontal-parieto-occipital under-connectivity in ASD has been observed during a visuospatial task in the absence of performance differences, a difference which positively correlated with the volume of the corpus callosum (Damarla, S.R. et al., 2010). This brings together reduced connectivity of occipital and frontal regions with a measure of structural interhemispheric under-connectivity. Contour completion, as you will see in section 1.10, involves the integration of information from both hemispheres (Murray, M.M. et al., 2001; Murray, M.M. et al., 2002).
The correlation of connectivity abnormalities with the autism phenotype, both at rest and during visual spatial tasks, and the specific involvement of connections between occipital and frontal regions as well as between hemispheres, offers anatomical support for interrogating the electrophysiology of perceptual completion for markers of the neural mechanisms at work beneath autism pathology. Next we consider sensory processing in ASD.

1.7 Sensory Differences in ASDs

Atypical behavioral responses to sensory stimuli have been reported since Kanner’s initial characterization of autism (1943).

*For years as a child - 6–11 years or so... I had bad problems “seeing” big things, like furniture, rooms, etc. To see them, I would gallop by ~like a horse, not like a human runner, with my head cocked. The objects would not move so I did. When I am tired I always cock my head to try to recognize things and look through my fingers. -Michelle Dawson, personal communication (Mottron, L. et al., 2007)*

*My tactile sensitivities have led to dozens of little quirks, most of which started in childhood. I’ve never liked the feeling of water spraying on my face (oddly, I’m fine with having my face underwater). If I’m eating something messy with my fingers, I clean them on a napkin between every bite. When my skin gets too cold, it itches worse than a case of poison ivy. If someone kisses me, I immediately wipe the little wet spot from my face – “Tactile Defensiveness” from the blog Musings of An Aspie (Anon., 2012)*

*My hearing is like having a sound amplifier set on maximum loudness. My ears are like a microphone that picks up and amplifies sound. I have two choices: 1) turn my ears on and get deluged with sound or 2) shut my ears off... When I was a child, I feared the ferry boat that took us to our summer vacation home. When the boat's horn blew, I threw myself on the floor and screamed. - Temple Grandin “My Experiences With Visual Thinking” - (Grandin, T., 2000)*

First person accounts appear throughout this dissertation because they are eloquent expressions of subjective sensory experiences for persons with an ASD, but there are those who
argue that they skew toward high-functioning reporters, and can be swayed by a lack of awareness of what TD perception is like (Simmons, D.R. et al., 2009). That being said, 45-96% of children with ASDs report sensory issues of some kind. These can include hypersensitivity, which might be characterized by rapid onset, or an exaggerated or prolonged reaction. Or they can equally likely include hyposensitivity, which can include unawareness or slow responses. Diagnosed individuals report these in multiple sensory domains, and one individual can experience both hyper- and hypo-reactions (Leekam, S.R. et al., 2007; Marco, E.J. et al., 2011). Craving or prolonged engagement with sensory stimuli is also observed, generally referred to a sensory-seeking or ‘stimming.’ For example, many children like to rock, bounce, spin, flick their fingers in front of their eyes, or hum to themselves. A recent young visitor to our lab, for example, repeatedly put a plastic toy into a container, shaking it to produce an almost deafening noise, holding it to his ear for minutes at a time. It is unclear, however, whether such behavior is literally seeking stimulation, avoidant of some less desirable stimulus, or different in different individuals. Seeking behaviors were the most prominent symptom measured in 6-9 year-olds in a meta-analysis of 14 studies (Ben Bashat, D. et al., 2007).

Sensory differences are more prevalent in ASD than in other developmental disorders, they tend to lessen with age, and they are correlated with the severity of social symptoms in children (Baranek, G.T. et al., 2006; Ben Bashat, D. et al., 2007; Leekam, S.R. et al., 2007). A broad study of 104 individuals on the autism spectrum spanning early childhood to adulthood saw correlation of sensory dysfunction with ASD severity (Kern, J.K. et al., 2007). However, these results should be interpreted cautiously as the CARS, completed by a caregiver, was used to diagnose participants. Two recent studies found strong correlations between sensory processing
difficulties and the number of autistic traits, regardless of diagnosis (Robertson, A.E. & Simmons, D.R., 2012, 2013).

Both over- and under- arousal have historically been put forward as narrative explanations for the development of ASDs and their sensory manifestations. Over-arousal, it was proposed, led to withdrawal as a result of intrusive parenting (Tinbergen, E.A. & Tinbergen, U., 1972). Chronically high levels of stimulation from the brainstem reticular formation were believed to result in blocking of sensory pathways (Hutt, C. et al., 1964). Withdrawal from social aspects of the environment were prioritized because social stimuli were more complex and predictable and, therefore, more arousing (Dawson, G. & Lewy, A., 1989). An under-activated reticular system was considered responsible for an inability to connect past and present situations, preventing generalization and leading to under-reaction (Rimland, B., 1964), possibly due to the suppression of the limbic system (DesLauriers, A.M. & Carolson, C.F., 1969). Despite the many reports of sensory processing atypicalities, they do not differentiate those diagnosed with autism from those with, fragile X syndrome or blindness (Rogers, S.J. & Ozonoff, S., 2005). This leaves it unclear whether they contribute to the development of the phenotype or are secondary to it, but their ubiquity suggests a sharing of underlying causes. While our focus will be vision, a summary of atypicalities in audition and touch is offered first. Are dysfunctions in multiple modalities indicative of a common dysfunction in information processing, or do these unique problems represent subtypes of ASD that contribute to its heterogeneity?

_Audition_

_I am continuously puzzled by the amount of people that don’t flinch by large amounts of noise and vibration. Perhaps we should chuckle at them for under-reacting. – Anabelle Listic from her blog anabellistic.com (Listic, A., 2012)_
Given core deficits in social communication, auditory processing in ASD has been well studied. Auditory brainstem response studies, which measure the stimulation of brainstem and midbrain structures as the auditory signal arrives, have suggested that the timing of processing can be different from that of TD individuals, depending on the complexity of the stimulus (Rosenhall, U. et al., 2003; Russo, N.M. et al., 2008). Additionally, there is evidence of altered morphology in the neurons of the medial superior olivary nucleus, an auditory processing structure located in the brainstem (Kulesza, R.J.J. et al., 2011).

Enhanced pitch discrimination is estimated to be present in approximately one in five individuals with ASD and is more common in children than adolescents and adults. Adult pitch discrimination varies directly with the number of language deficits exhibited (Jones, C.R. et al., 2009; Bonnel, A. et al., 2010), but whether superior pitch perception is a result of less attention to language, or whether the preference which diagnosed individuals display for music and non-speech compared to speech interferes with language development is not clear (Dawson, G. et al., 1998; Kuhl, P.K. et al., 2005). Abnormal prosodic expression in speech is also a feature of the autism phenotype and prosody perception may also be impaired, but whether this is because it is melodic in nature or whether it is related to the affective content of the language remains unclear (McCann, J. & Peppe, S., 2003).

*I am unable to talk on the telephone in a noisy office or airport. Other people can use the telephones in a noisy airport, but I cannot. If I try to screen out the background noise, I also screen out the voice on the telephone.* - Temple Grandin

“My Experiences with Visual Thinking” (Grandin, T., 2000)

In addition, it appears that individuals with ASD have difficulty extracting auditory signal (the part of the signal containing the information of interest) from noise (all other content) (Plaisted, K. et al., 2003). Adults diagnosed with ASD have been measured as slower and less
accurate in localizing sounds in the context of noise (Teder-Salejarvi, W.A. et al., 2005). When participants were asked to detect speech in the context of noise in situations with and without cues embedded in the background, those with ASD required a higher signal-to-noise ratio to make use of the cues and perform at the same level as TD participants (Alcantara, J.I. et al., 2004), however, a more recent study of ASD children in our group suggests that such deficits are mild (Foxe, J.J. et al, 2013). This suggests that individuals with ASD may not integrate the cue with the signal as effectively. Neuropsychological measures of language comprehension and production in ASD have been observed to correlate with altered connectivity patterns measured with DTI. Both greater local connectivity and shorter connection length was measured. Strong local connectivity was also correlated with enhanced performance in neuropsychological evaluation, but only for participants with ASD (Li, H. et al., 2012).

In general, enhanced auditory processing of low-level stimuli is observed in persons with ASD. Impairments are seen in situations of increased complexity or task demand, however, they are present when processing speech and non-speech sounds. O’Connor’s review (2012) suggests that it is not the social content of speech per se that is leading to processing impairments as many suggest (Dawson, G. et al., 1998), but rather that speech may be exemplary of stimulus complexities which demand more integration. Differences in the way incoming sensory signals are integrated with and modified by existing knowledge is a common finding across modalities in individuals with ASD. Such integration is dependent upon more complex patterns of connectivity than simple extraction of signals. If ASD is typified by disordered connectivity, then processing that relies more on integration, may well be more disordered.
Tactile atypicalities are also reported in ASD (Tomcheck, S.D., 2007). Enhanced tactile sensitivity has been reported in individuals diagnosed with Asperger syndrome, but specifically in higher as compared to lower frequencies (Blakemore, S.J. et al., 2006). Autistic individuals appear to be more sensitive to vibration and thermal pain, but specifically when mediated by low-threshold unmyelinated nerve fibers (Cascio, C. et al., 2008). A study of cortical response to stimulation of the lip and fingers of the dominant hand measured with MEG suggested atypical representation of face and hand in somatosensory cortex in the ASD group (Coskun, M.A. et al., 2009).

Tommerdahl et al (2007) compared TD and ASD adults on the benefit incurred in determining the spatial location of a vibrating stimulus on the hand as a result of adaptation. Adaptation is a reduction in sensitivity to a stimulus after prolonged exposure. So if a second stimulus is delivered at the same site, sensitivity to it will be decreased. In his study, Tommerdahl applied a third stimulus at a different location following adaptation. The distance between the locations varied. Successful detection with shorter distances indicated better spatial acuity. The length of the initial stimulus also varied. More adaptation resulted from the longer stimulus. In TD individuals, a long initial stimulus led to a dramatic improvement in spatial acuity, but no such improvement was seen in persons with ASD. With a shorter initial stimulus, ASD performance was superior to TD. The neural mechanism underlying the improved
localization in TD participants was presumed to be lateral inhibition (LaMotte, R.H. & Mountcastle, V.B., 1975). This is a process whereby sensory stimulation enhances the detectability of a competing stimulus by suppressing the response of adjacent locations, a process mediated by horizontal and feedback connections. Here is another example where it is not basic sensitivity to a stimulus per se, but modulatory sensory processing that appears to be different and can result in enhancement in some cases, and an impairment in others.

*Vision*

> My bed was surrounded and totally encased by tiny spots which I called stars, like some kind of mystical glass coffin. I have since learned that they are actually air particles yet my vision was so hypersensitive that they often became a hypnotic foreground with the rest of ‘the world’ fading away. -Donna Williams Nobody Nowhere (Williams, D., 1998).

> I asked J. to take me to the "other" grocery store (a type of natural/organic foods store I think). I wanted different kinds of flours, because it makes better breads and pancakes. But once we got there, I couldn’t see the flours I wanted. They were all in bins, which is great in some ways but makes it almost impossible for me to get what I need. I hadn’t expected bins. There were only letters, no distinguishing colors or pictures. And, all the letters were blurring together. Nothing wrong with my eyes, I’ve slowly begun to understand. It isn’t that my eyes can’t focus. It’s that I can’t decipher the words.... – Ari “A Different Grocery Store and Mixed up Sensory Input” from her blog Perceptions (Akari, 2011)

Hans Asperger’s initial descriptions of ASDs included anomalies of vision-related behaviors – “they do not make eye contact...they seem to take in things with short, peripheral glances..” (Asperger, H., 1991). Behavioral evidence for atypical visual experience in individuals with ASD is widespread and can present in individuals as a dislike of bright or flashing lights, focusing on tiny pieces of objects or little particles of dust, moving the fingers in the front of the eyes, fascination with reflecting or colorful objects, differences in gaze and eye contact, glancing
at objects out of the corner of one’s eye and many other manifestations. Anomalies in the visual modality are profusely documented, but that may be less a result of their greater frequency in autism than of how thoroughly studied vision is.

Optometry and Cortical Representation of Visual Space

At the most basic level, studies of children with ASD report higher than average incidence of refractive errors, reducing visual acuity, as well as higher incidence of strabismus (Scharre, J.E. & Creedon, M.P., 1992; Simmons, D.R. et al., 2009). Some of these studies pre-date modern diagnostic methods of ASD so they may reflect the more severe end of the spectrum. The mapping of visual space onto lower visual cortex differs for regions encoded by central and peripheral regions of the retina. MRI measures suggest that ASD and TD cortical representations of central and peripheral space were not different (Hadjikhani, N. et al., 2004).

Eye Movement

Atypicalities of eye movements have been studied in light of often observed eye gaze differences in this population. Eye movements fall into two main classes a) smooth pursuit: the steady coordinated tracking of an object, and b) saccades: rapid, intermittent, mostly involuntary movements of fixed speed which function to bring a target onto the fovea – the most central part of the retina where the receptors have the greatest resolution. Comparison of smooth pursuit movements has not revealed significant differences between groups of TD and children with pervasive developmental disorder (PDD) (Kemner, C. et al., 2004), but they did differentiate a subtype of PDD known as multiple complex developmental disorder (Lahuis, B.E. et al., 2009). Goldberg et al’s (2002) assessment of eye movements in high-functioning adolescents with autism measured deficits in saccade initiation in the absence of a visual target. Children with ASD were seen to make more saccades to frequent presentation of stimuli regardless of stimulus
type (Kemner, C. et al., 1998). Takarae et al found individuals on the autism spectrum to be less accurate in guiding saccades to their target, but only participants without a language delay undershot their target. The suggestion that basic eye movement differences could discriminate between those individuals with autism and those with Asperger Syndrome is intriguing (Takarae, Y. et al., 2004). However considerations of how eye movements impinge on autism must acknowledge differences in reactions to stimulus type and differences of attention, covered next.

**Visual Orienting & Attention**

The autism phenotype is characterized by numerous differences in orienting, that is, the focusing of attention. Acute perception for details over global form, a limited repertoire of interests, a failure to respond to one’s name, a disinclination to orient to “social stimuli” such as the movement of the human body or face, and an impairment in joint-attention – that is, a non-verbal engagement of two people’s attention to a third object – have been attributed to a dysfunction of visual attention in ASD (Elsabbagh, M. & Johnson, M.H., 2007), but it remains unclear whether the dysfunction stems from the object of attention or from the underlying mechanisms of attention. Wainright-Sharp and Bryson employed a classic cued-attention paradigm, in which a visual cue indicates the region of space where a stimulus may appear. Factors such as the validity of the cue or the presence of distractors were also manipulated. They showed that adolescents and adults with autism had difficulty in disengaging and shifting attention (Wainwright-Sharp, J.A. & Bryson, S., 1993). Several investigations have pointed to deficits in rapid and accurate attentional shifting (Courchesne, E. et al., 1994; Senju, A. et al., 2004), but Leekam and colleagues found no such impairment. They did, however, observe difficulties in the joint attention between children and adults to a third object (Leekam, S.R. et al., 2000). Iarocci and Burack (2004) examined covert orienting (the mental focus of attention
without moving the eyes) to a flash of light in the peripheral visual field while varying the validity of cues and the presence of a distractor. In 14 children with autism and their neurotypical counterparts they found no difference in covert orienting.

When TD persons see another person’s eyes move, they reflexively orient their attention in the direction to which those eyes indicated (Driver, J. et al., 1999). Senju et al (2004) found that TD children deploy such automatic attention in response to a cue of human eye movement more quickly than they do to arrow cues. However, children on the autism spectrum showed equal speed in response to both types of cues. This is one of many indications that individuals with ASD may orient differently to stimuli possessing biologically relevant information than do TD individuals. Comparing exogenous (attention one pays automatically, as to a loud noise) to endogenous attention (goal-driven attention) toward non-social stimuli, Renner and colleagues (2006) found less benefit of valid (cues determined by the nervous system to be reliably predictive) compared to invalid cues in exogenous orienting, but no differences in goal-driven attention. Furthermore, the degree of impairment in orienting correlated with impairment in motor function. Renner’s findings suggest an impairment in some mechanism of attention that is not related to stimulus type. An fMRI study of covert attention in persons with ASD demonstrated less frontal, parietal, and temporal activation than found in TD persons and greater activation of occipital and ventral occipital regions in the context of comparable task performance (Belmonte, M.K. & Yurgelun-Todd, D.A., 2003). These results suggest that different mechanisms underly visual attention in ASD. Recent evidence from a prospective study relates differences in visual attention to diagnostic outcomes at 36 months (Elsabbagh, M. et al., 2013). A sample of 104 infants, half of whom had an elder sibling with autism and were considered to be at increased risk for a diagnosis, were assessed for the speed at which they
disengaged from a centrally-presented stimulus to orient towards a peripheral one. The speed of attentional disengagement was not associated with diagnostic outcomes when measured at seven months but it was at fourteen months, but this difference also predicted infants who presented with other developmental outcomes at 36 months. So, while this may be a promising early warning sign for developmental issues, it does not have strong diagnostic utility specifically for ASD. Clearly the story of how vision, the orienting of attention, and the processing of social information interact is a complicated one and necessitates careful control in investigations of visual processing in the context of ASD. Furthermore, the Elsabbagh study suggests that visual attention changes across development, emphasizing the need to consider cognitive function developmentally.

\textit{Stimulus Detection}

Issues of optometry, eye movement, and attention can be expected to have an effect on vision, however, visual processing itself begins with the sensitivity to contrast differences in the environment. Sensitivity for static stimuli measured with standard contrast sensitivity charts (De Jonge, M.V. et al., 2007) or simple Gabor gratings of varying spatial frequencies (Milne, E. et al., 2009), do not appear different for viewers with and without ASD. However, poor detection of a bar-shaped stimulus embedded in visual noise has been measured (Sanchez-Marin, F.J. & Padilla-Medina, J.A., 2008). Unfortunately, this study’s use of the CARS calls their diagnostic criteria into question, but as we saw earlier, the extraction of signal from noise involves the integrative analysis of both context and signal prior to their segregation – an integrative process.

\textit{Visual Processing and Connectivity}

Bertone et al (2005) assessed visual detection of the orientation of grating stimuli (Fig 1.1) in persons with ASD, however, they separately manipulated luminance and texture of the stimuli.
They proposed that this differentiated processing mediated by lateral connections in V1 (luminance processing) from a process mediated by more complex feedback connections (texture processing). Individuals with ASD were stronger at detecting the orientation of gratings based on luminance than TD individuals, but weaker at detecting those defined by texture. Bertone took this to indicate that performance was enhanced for tasks mediated within focal regions of cortex and compromised for tasks requiring greater connection among regions. They attributed the enhanced luminance detection to excessive lateral inhibition. As a reminder, lateral inhibition suppresses activity in neurons that encode for unstimulated spatial locations which are near to stimulated locations. Cortical sensory neurons of individuals with ASD are grouped into narrower mini-columns, as mentioned earlier, and these columns are defined by inhibitory interneurons (Casanova, M. et al., 2003). So, if each column is responsive to a given range of orientation, then narrower columns could facilitate more sharply focused responses, hence, greater discriminatory function. Gustafsson (1997) proposed that increased inhibitory lateral feedback would delay sensory processing in ASD, destabilitizing its temporal dynamics, a hypothesis we explore in chapter 4. This offers a possible explanation for the enhanced low-level discrimination that has been so widely reported in ASD (e.g., O'Riordan, M. & Plaisted, K., 2001; Caron, M.-J. et al., 2006; Bonnel, A. et al., 2010). Bertone also suggested that increased lateral inhibition should adversely impact contour detection for more complex texture-defined stimuli.

Vandenbroucke and colleagues explicitly tested this last hypothesis using texture-defined stimuli (Vandenbroucke, M.W. et al., 2008). These are shapes defined by short black lines about the length of a hyphen (Fig 1.2). In their homogeneous condition, they are oriented in a single direction, defining a square that looks like static on a black-and-white television. When the
orientation of the lines is changed for an area inside the square, the place where the two orientations meet is perceived as a contour. Persons with ASD detected fewer texture-defined contours and this correlated with reduced ERP effects during the timeframe correlated with this process. This is an instance where multiple features (the short lines) have been combined into a coherent stimulus (the contour), a process involving lateral and, possibly, feedback connectivity (Zipser, K. et al., 1996).

What is emerging, then, is a picture of intact, if not enhanced, mechanisms of simple stimulus detection, but disordered early processing involving lateral or feedback connections. These often facilitate the modulation of incoming signals or their integration with other processing streams, and are seen when simple sensory features are combined to form objects.

### 1.8 Local and Global Processing

Since it is atypical integration of global and local stimulus levels in ASD that precipitated the present inquiry, it is incumbent upon us to define these terms from a phenomenological and a neuroscientific perspective. Local features are unique and indivisible elements of perceptual groupings. They include orientation, color, brightness, and spatial frequency and might be considered the units of perception, the parts that make the wholes. Local processing is an analysis which detects units which are combined into global forms. Global qualities concern those aspects of an object or grouping which refer uniquely to the interrelation of the parts. For example, a hand has five fingers, but it becomes a fist only when those parts are organized in a particular way (Feldman, J., 2003). According to the Gestalt psychologists who codified the grouping of perceptual features, this configuration is itself unique as a sensory unit, qualitatively different from the parts which prefigured it (Koffka, K., 1935). Studies of patients who have
deficits in identifying multiple, but not single, objects (simultagnosia), and who can identify objects based on global form, but are impaired when relying on internal details, have helped substantiate that global and local qualities of objects are not merely different in the abstract, but that their processing in the brain is dissociated (Riddoch, M.J. & Humphreys, G.W., 2004).

The Gestalt perceptual model emphasizes configural primacy, a quality which has often been investigated with the use of hierarchical stimuli (Fig 1.3). Neurotypical adults have faster reaction times to the global level (the larger letter) than the local (the smaller letter of which the larger is made). In presenting large H’s composed of small H’s versus large H’s composed of small S’s, conflicting information between local and global levels has been found to inhibit the speed of identifying the local letter, but not the global one – an effect referred to as interference. In an auditory discrimination task, responses were either facilitated or interfered with by the global level of the visually presented stimuli, but unswayed by the local level (Navon, D., 1977). Navon asserted that analysis of global properties precedes that of local properties in the context of serial processing or is faster in the context of parallel processing (Navon, D., 1981).

As the size of the hierarchical figure increases, there is a transition from global to local advantage in reaction time (Kinchla, R.A. & Wolfe, J.M., 1979). (This is size measured in visual angle, or the area of the retina it activates. This metric is independent of the distance of the viewer from the object). When hierarchical figures measuring 3 to 12° of visual angle were shown to participants who were cued to focus their attention on the global or local level of the stimulus, experimenters saw no variation in interference to the manipulation of size, but did see a reaction time change (Lamb, M.R. & Robertson, L.C., 1989). The same group found that this effect was not dependent on absolute size but on size relative to the range of the stimulus set. Using two sets of stimuli, one ranging from 1.5° – 6° and other from 3° – 12°, the transition from
global to local advantage occurred at a larger visual angle for the larger set of stimuli, suggesting that context plays a role in determining the significance of size relative to global and local processing (Lamb, M.R. & Robertson, L.C., 1990). The effect of size manipulation on electrophysiological indices of IC processing will be investigated in chapters 2, 3, 4, and 5.

Numerous studies have suggested hemispheric asymmetry in processing global- and local-levels of stimuli. For example, right-hemisphere lesioned patients made more errors in remembering global relative to local properties of hierarchical stimuli, whereas those with left-hemisphere damage made more local-level memory errors (Delis, D.C. et al., 1986). Patients with left-superior temporal gyrus (STG) injury responded to global faster than to local targets, whereas uninjured controls responded faster to local targets. Right-STG injured patients responded faster to local than to global targets. In contrast, brain-injured patients without STG lesions performed typically, implicating hemisphere-specific mechanisms rather than generalized brain damage (Lamb, M.R., Robertson, L.C., et al., 1990), but it was the relative speed of response that was specifically impacted. Given sufficient time, patients are capable of responding accurately to both levels in the damaged hemisphere (Robertson, L.C. & Delis, D.C., 1986), suggesting that hemisphere-specific processing effects are better characterized as differences in efficiency or priority.

Lamb cites another patient who did not demonstrate interference – HJA. He is of particular interest to our inquiries because he suffered an integrative agnosia as the result of a stroke which damaged his inferior temporal-occipital cortices. This is the locus of the LOC, a cortical region implicated in the processing of ICs (Murray, M.M. et al., 2002; Foxe, J.J. et al., 2005; Sehatpour, P. et al., 2008; Shpaner, M. et al., 2009). HJA’s lesions were thought to have impaired the communication between the LOCs in his right and left hemispheres (Riddoch, M.J. &
Humphreys, G.W., 1987). The result was that HJA’s visual object identification was impaired but his tactile identification was intact and he could copy objects accurately. He could discriminate local elements and objects presented in silhouette, interpreted as access to global information; his deficit seemed to be specifically in integrating the two. Since the hemispheres differentiate global and local information but must integrate it in perception of an object, when processing hierarchical figures in which the global and local levels are incongruous, interference typically results (Lamb, M.R., Robertson, L.C., et al., 1990). However, in the case of HJA, a lack of interference was seen. This was attributed to the lack of cooperation between his two LOCs (Lamb, M.R., Robertson, L.C., et al., 1990; Robertson, L.C. & Lamb, M.R., 1991). The study of HJA’s unique lesions demonstrate that object processing likely relies on the integration of local and global stimulus levels which entails communication between the right and left LOCs. A recent investigation used transcranial magnetic stimulation (TMS) over left and right temporo-parietal junction of healthy individuals to suppress neural activity. They administered uni- and bilateral bursts, finding that only bilateral bursts altered behavioral measures of global perception, indicating that such processing involves the cooperation of both hemispheres. If ASD is characterized by disordered interhemispheric connectivity, then atypical integration of ICs could result.
1.9 Typical Visual Processing from Features to Objects

What Are Objects?¹

Different areas of visual cortex are responsive to features such as orientation (V1), color (V4), and movement (MT), but at some point these features are subsumed under the identity of a single coherent whole, that is, an object. If we think about how we use everyday perception, the detection and identification of objects might be regarded as the purpose of vision. But what exactly is an object? An object might be geometrically defined by the deformation of a line or plane or physically defined as differences in matter density which are perceived via changes in reflected light wavelength. However, some objects have internal contours or are made of multiple substances. To date, no set of psychophysical criteria has been agreed upon as encompassing all notions of objects. Cognitive psychology sees objects as units of recognition – they exist as a function of semantic knowledge. They are “bundles” of information idealized for efficient representation which can be stored in and extracted from memory. They facilitate the needs of conception as opposed to perception (Spelke, E., 1988). Objects describe volumetric units in a way that is both consistent and flexible. A door will always be a door regardless of size or the perspective from which we view it. So recognition must generalize across multiple views of the same object, which project different shapes on the retina, but also discriminate

¹ Literature devoted to the visual processing of faces as examples of configuration-dependent processing is abundant. The time course and anatomical regions implicated in face processing are similar, but not entirely the same, as for other objects. It remains a subject of debate whether facial processing is unique. Some claim that this must be the case because faces are uniquely relevant to our social species. Such investigations point to a dedicated sub-region for face processing (Kanwisher, N. et al., 1997). However, there are those who claim that cortex does not specialize for faces as classes of objects per se but rather as exemplars of configural grouping (Gauthier, I. & Nelson, C.A., 2001). In addition, many differences in the visual processing of faces in ASDs are reported (e.g., Pierce, K. et al., 2001). To avoid the confounds associated with this class of stimulus, that literature is not considered extensively here.
among highly similar objects in a single class, such as breeds of cattle or makes of car, which differ only in subtleties of configuration of their features.

In neuroscience, objects are often defined relative to attention. As creatures with limited cognitive processing resources, we have evolved means to prioritize the processing of some stimuli at the expense of others. Attention is a mechanism through which subsets of stimuli are given priority and irrelevant stimuli filtered out (Broadbent, D.E., 1958). Some evidence supports this selection occurring on the basis of location in the visual field (e.g., Posner, M.I. et al., 1980; Treisman, A.M. & Gelade, G., 1980; Desimone, R. & Duncan, J., 1995) other suggests it is based upon the features which comprise the object (e.g., Wolfe, J.M., 1994). Either basis is thought to facilitate enhanced processing for targets (Saalmann, Y.B. et al., 2007). Viewers show quicker reaction time to targets and greater accuracy in searches for them, but these advantages are conferred not only upon the location or feature selected, but to the entire area or all the features delimited by the boundaries, an effect termed the object-based spread of attention (Egly, R. et al., 1994; Martinez, A. et al., 2006; Fiebelkorn, I.C. et al., 2010). It is the area contained in these boundaries which we call an object. So an object might be described as the unit upon which attention acts.

Neuropsychological perspective

Just as people can be selectively impaired in the processing of separate features such as color or movement (e.g., Zeki, S. et al., 1991), deficits exist which uniquely impair the processing of groupings of elements, but not the elements themselves. Patient's with Balint Syndrome or simultagnosia, generally resulting from bilateral lesions of occipital-parietal cortex, have normal acuity, motion detection, and object recognition. They can identify single visual elements or one simple object if it appears before a plain background, but not against complex backgrounds and,
most unusually, they cannot perceive more than one object at a time. If a drawing is shown of two discs side-by-side, patients will see only one of them. However, if a line is added to join the discs, creating a picture of a dumbbell, both circles will suddenly become visible. Two overlapping triangles will be perceived as a single Star-of-David, however, if each triangle is a different color, patients will only see one of them (Luria, A.R., 1959). Balint Syndrome is an object-specific disorder selective for groupings of elements, but not the elements themselves (Scholl, B.J., 2001; Riddoch, M.J. et al., 2004).

Agnosias are modality-specific disorders of object recognition which spare sensory processing. In visual agnosia, patients can have trouble recognizing even the simplest of objects by sight, but may rapidly identify them by touch or when they are described verbally. Furthermore, they can often accurately draw parts of the object (Lissauer, H., 1890/1988). Such disorders make a strong case for the fact that objects are not merely tools of conception. The brain’s visual apparatus clearly dissociates perception of parts from the perception of wholes.

**Grouping and Binding**

One model of object processing suggests that the simplest solution would be to have a neuron for each object – a so-called grandmother cell (Barlow, H.B., 1972). But that would require a cell representing grandma in profile at ten feet, and another representing her from fifty feet. This solution would suggest that having seen grandma only from the right we could not recognize her from the left. The number of cells needed to encode the entire repertoire of feature combinations would be nearly infinite. A more flexible model suggests that objects are broken into units, that is, features – color, motion, brightness, orientation, etc. – which can combine in multiple ways. Each feature is processed in a dedicated anatomical module. For instance, V1 cells encode orientation but not movement. This speeds up object processing as these processes can occur in-
parallel. Grouping imposes structure on those elements. Binding is the neural mechanism by which they are integrated as an object.

The Gestalt psychologists were early codifiers of principles which they believed gave primacy to coherent groupings of stimuli over the individual elements of which they were composed. They considered configurations a unique sensory unit, qualitatively different from the parts which prefigured it. This has evolved into the old saw “the whole is greater than the sum of its parts” (Koffka, K., 1935). Gestaltists saw the processes as so influential that they described their principles as “laws” and so ubiquitous as to describe stimuli so organized as “good” grouping, in that this organization contains the most information in the fewest units. This reduced the complexity inherent to natural visual scenes, rendering the world orderly and pithy – a principle they called Prägnanz. The information present in a typical scene is bountiful and neural processing resources are not infinite, so such grouping functions to segregate a subset of the information in a scene for enhanced processing (Egly, R. et al., 1994; Martinez, A. et al., 2006; Saalmann, Y.B. et al., 2007).

The Gestaltists proposed that, all else being equal, the proximity or similarity of features such as size, color, or orientation, prompt grouping (Koffka, K., 1935; Wagemans, J. et al., 2012). For example, 6 rows of 6 black circles equally spaced and arrayed as a grid, will encourage the perception of a square but, if vertical pairs of circles are moved closer together, they group by proximity and columns are perceived, and if they alternate black and white, they are grouped by color and stripes are perceived (Fig 1.4). Simultaneous movement, texture, binocular disparity, and temporal coincidence also cue grouping (Gray, C.M., 1999).
But if features are each represented in anatomically distinct, albeit interconnected, regions, what brings the right features back together to create a single object representation? In a field of features comprising blue boxes and pink bunnies, what guarantees that the blue ends up with the boxes and the pink with the bunnies? This is the aptly named “binding problem.” Feature Integration Theory (FIT) posits that we can mediate the binding of individual features by virtue of their location in the visual field, by applying attention to each in turn, a laborious process, or we may use prior knowledge of feature combinations to predict which features should be joined, a faster process not requiring attention but sometimes resulting in errors (Treisman, A.M. et al., 1980; Treisman, A., 1996). Given that VEP differences have differentiated object categories at approximately 80 ms, peaking at 120 ms (VanRullen, R. & Thorpe, S.J., 2001) and human intracranial recordings have demonstrated occipito-temporal activation to various object categories at approximately 150 ms (Allison, T. et al., 1999), what mechanisms exist in the visual system that might facilitate such nearly instantaneous binding?

**Visual System Anatomy**

Hubel and Wiesel introduced the idea that the visual system was a hierarchical anatomical structure from their work in cats and non-human primates (Hubel, D.H. & Wiesel, T.N., 1965, 1968). Their model progressed from receptive fields which were sensitive to small areas of space and simple features, to those of increasingly greater complexity and size. It was accepted that information proceeded in a feedforward manner, that is, the output of simpler receptive fields provided the input for the next most complex level, a notion which persisted for some time. Felleman and Van Essen (1991) consolidated the work of numerous colleagues who had identified functionally distinct regions of visual cortex and the connections between them (e.g., Jones, E.G. & Burton, H., 1976; Rockland, K.S. & Pandya, D.N., 1979; Ungerleider, L.G. &
Mishkin, M., 1982; Maunsell, J.H.R. & Van Essen, D., 1983) to map primate visual cortex. They identified 32 visual and visually-associated regions on 10 cortical levels, with over 300 ascending, descending and lateral connections, providing anatomical evidence for feedback and cross-level communication in addition to feedforward. The hierarchy originates at the light-sensitive cells of the retina, proceeds to the lateral geniculate nuclei of the thalamus, projecting then to primary visual cortex (V1). Ungerleider and Mishkin (1982) were among those instrumental in segregating the hierarchy into two parallel streams. A faster, dorsal or “where” stream has cells which are not color-sensitive but encode contrast. They quickly carry gross information regarding motion and spatial location to posterior parietal cortex via V1 layer 4Ca to layer 4B, and the middle temporal area (MT). The cells of the slower ventral or “what” stream are more sensitive to detail and color. They are implicated in the recognition of objects. This stream proceeds through visual areas V1 layers 4Cβ, 4A, 3B, and 2/3a, then to V2, and V4, progressively encoding greater visual complexity and larger areas of space (Kobatake, E. & Tanaka, K., 1994; Lamme, V.A. et al., 1998; Riesenhuber, M. & Poggio, T., 2000) until reaching the lateral occipital complex (LOC) which can encompass the scale of typical objects (Grill-Spector, K. et al., 2001; Malach, R. et al., 2002). The LOC falls partly inside of the inferior temporal (IT) cortex, the sub-areas of which encode for various object types. The IT in non-humans appears the nearest functional equivalent of the LOC in humans. The LOC is of particular interest here because of its involvement in IC processing. Early visual cortex is retinotopically organized so that each area of external space corresponds to a location on that cortical region, as though a map of that area were projected right onto the surface of the cortex (DeYoe, E.A. et al., 1996). These maps are generally arranged so that half the visual field is
represented in each hemisphere. However, the LOC is largely non-retinotopic (Grill-Spector, K. et al., 2001).

**The Lateral Occipital Complex**

Even if there are not distinct cells for every object, at some level of the visual cortex neurons likely are sensitive to coherent assemblies of features and yet insensitive to the features themselves, a property called cue-invariance. In non-human primates, single-cell recordings from IT cortex have compared the viewing of real, familiar objects from four viewpoints. 49% of IT neurons assayed were responsive to only some views of objects, but the others were invariant to viewpoint and in some cases to color – even when different views projected a different shape on the retina (Booth, M.C. & Rolls, E.T., 1998). So primate IT neurons are capable of encoding information about multiple dimensions of objects simultaneously, without regard to individual features. In humans, the LOC, has demonstrated invariant responses to luminance, texture, motion, and contrast changes (Grill-Spector, K. et al., 2001), and format (grayscale photographs versus line-drawings) (Kourtzi, Z. & Kanwisher, N., 2000).

Located on the lateral bank of the fusiform gyrus at the occipitotemporal junction, the LOC is a system of extrastriate regions that extends ventrally and dorsally. It has been subdivided into two divisions: posterior-dorsal – sometime referred to as LO – and anterior-ventral – the posterior fusiform gyrus. Sub-regions have been identified as selective for specific categories of objects. For example, lateral and ventral subdivisions are preferentially activated by faces and animals (Puce, A. et al., 1996; Chao, L.L. et al., 1999). Houses and scenes activate both dorsal and ventral subdivisions, although different ventral areas are activated than those by faces and animals (Epstein, R. et al., 1999). Still other areas may be selective to categories such as tools and strings of letters (Allison, T. et al., 1994; Chao, L.L. et al., 1999). The entire region
encompassed by the LOC extends from occipital to posterior temporal cortices and responds
more strongly as measured with fMRI to intact objects with clear shape interpretations than to
stimuli which cannot be interpreted as having clear shapes (Grill-Spector, K. et al., 1998;
Kourtzi, Z. et al., 2000). This can be seen whether or not the viewer performs a task, it does not
differ for familiar versus unfamiliar objects, or when images are filtered to only access high
spatial frequency information (detail) or low spatial frequency information (gross form) (Malach,
R. et al., 1995). ERP recordings have measured the earliest binding effects of ICs over lateral
occipital sites and source localized them to the LOC, onsetting at about 88 ms and peaking at
about 150 ms (Murray, M.M. et al., 2002). Effects over lateral occipital scalp sites have been
measured to a variety of classes of object compared to scrambled images (Allison, T. et al.,
1999).

Adaptation, whereby repeated presentations of the same stimulus result in reduced activation
of neurons sensitive to it, has been used to measure invariance. If that region is invariant to size,
it is reasoned that repeated presentation of a given object should result in adaptation, regardless
of whether size is varied. With this approach, an invariant response of LOC was measured to the
same objects, even when manipulation of size varied, but different effects were seen for different
objects, even those which shared the same outline (Grill-Spector, K. et al., 2001).

In masking paradigms, the presentation of a second stimulus just before or after a briefly
presented target can impede a person from awareness of seeing that target, however, information
from it appears to be encoded by the visual system below the level of awareness. In one such
paradigm, if the duration of presentation increased from 20 to 500 ms, recognition of the target
improved (Grill-Spector, K. et al., 2000). This improvement correlated with fMRI activation of
the LOC, but not with activation of V1, suggesting that the improvement occurred at the object
rather than the feature level of the stimulus. When the same participants were trained to improve their performance of difficult-to-recognize images presented for 40 ms, their performance improvement correlated with an increase in LOC activation, suggesting that the role which the LOC plays in object processing can be tuned over time.

There is disagreement about whether the LOC is invariant to viewpoint. Using adaptation, an invariant response of LOC to object size and location was measured, but not to various viewpoints of the object rotated around its vertical axis (Grill-Spector, K. et al., 1999). However, Vuilleumier and colleagues (2002) saw view-dependent right-hemisphere effects and view invariant left-hemisphere effects, and James and colleagues (2002) found bilateral effects, a difference they attributed to experimental task differences. It would hardly be surprising if the LOC, as is true of monkey IT (Booth, M.C. et al., 1998), had both view-specific and view-invariant neurons. There is evidence that cue-invariance may exist on a gradient across the LOC.

A human fMRI study compared LOC response to images of faces and cars which were broken into smaller and smaller square parcels. These parcels were re-arranged to achieve various levels of fragmentation – a process called scrambling (Fig 1.5). The larger the number of parcels which stayed together, the more global structure of the image was retained. The most posterior areas of visual cortex - areas V1 and V2 - actually showed enhanced MRI activation to scrambled as compared to intact faces, as they are more responsive to features than to configurations, whereas activation reduces in response to scrambling as one moves anteriorly toward the LOC. Areas most sensitive to objects demonstrate the largest reductions of MRI activation to fragmenting. The LOC’s activation is decreased when images are fragmented into only 4 pieces. Within the LOC, sensitivity to scrambling increases as one moves anteriorly (Lerner, Y. et al., 2001).
The visual hierarchy proceeds from areas with smaller receptive fields, sensitive to simple features – areas we have called lower or early – to areas with larger receptive fields that encode for more complexity – areas we have called higher or late. Historically, assembling objects was described as a process of moving up the hierarchy from lower to higher, from basic to more complex, perhaps because this is the way human beings assemble multi-part projects – from baking a cake to producing a work of art. We build from the ground up. Bit by bit, as the Sondheim quote on page 10 would have it. But really, we don’t bake our cake, nor did Georges Seurat, the subject of Sondheim’s song, paint *A Sunday Afternoon on the Island of La Grande Jatte*, blind to the end product. An appreciation of the goal precedes the assembly of the pieces. In fact, I would argue that it is considering how we want the cake to taste or in Seurat’s case, taking in the sun bathers and strolling couples from every conceivable angle to encompass the experience of that Sunday afternoon that facilitates a skilled assembly of the pieces. Similarly, Feature Integration Theory suggests that while features are extracted, either selective attention – mediated by parietal cortex – or knowledge - involving the LOC and hippocampus (Sehatpour, P. et al., 2008)– may be applied. To facilitate this, our visual system must be equipped to move between parts and wholes from the top-down as well as from the bottom-up.

**Connectivity and Visual Processing**

In the context of the interplay between sensory inputs and internal representations, thought to be conveyed by feedforward and feedback mechanisms respectively, it is worth revisiting the issue of anatomical connectivity. Ample feedback, as well as feedforward connections exist nearly every level of the visual hierarchy (Felleman, D.J. et al., 1991; Payne, B.R. et al., 1996). Horizontal connections link neurons across local regions (Gilbert, C.D., 1993). The flow of information is also seen to move forward and back over multiple iterations, as though regions of
cortex were having a conversation, so-called recurrent models (Grossberg, S., 1994; Pollen, D.A., 1999; Sehatpour, P. et al., 2006). In addition, network models describe simultaneous processing among areas of cortex, activity thought to be synchronized via oscillations (Gross, J. et al., 2004) –which could be the glue for uniting dispersed features into a single object (von der Malsburg, C., 1981/1994; Treisman, A., 1996; Mercier, M.R. et al., 2013).

Feedforward and feedback connections in rodents are similar in number and provide mostly excitatory input via synapses onto large pyramidal neurons of cortex, though approximately 10% - 20% have inhibitory effects (Gonchar, Y. & Burkhalter, A., 1999), and they demonstrate similar conduction velocities in monkeys (Girard, P. et al., 2001). However, there are differences aside from the direction in which they convey information. Feedforward projections originate in superficial cortical layers and terminate in layer IV, whereas feedback originate in both superficial and deep layers but terminate anywhere but layer IV (Rockland, K.S. et al., 1979). Human feedforward connections appear adult-like by four months of age, whereas feedback projections’ maturation is comparatively prolonged (Burkhalter, A., 1993). This temporal dissociation as a function of development is a crucial point as it may make feedforward and feedback connective fibers differentially vulnerable to certain kinds of environmental and genetic injuries (Berezovskii, V.K. et al., 2011). Indeed, schizophrenia patients who present similar difficulties to persons with ASDs in integrating features into global configurations, show delayed VEP effects associated with another early automatic visual perception task which likely depends heavily on feedback, but appears to be dissociated from feedforward processes (Kemner, C. et al., 2009). Interestingly, the growth path of feedback connections involves growing past the point where they will eventually terminate, and then growing between existing structures. It is theorized that they might reach their mature targets because cell density is
pruned back (Burkhalter, A., 1993). Accounts of increased brain volume in ASD (Hazlett, H.C. et al., 2011) point to greater cell density early in childhood, suggesting a potential anatomic basis for selective deficits in feedback projections.

Intracranial recordings demonstrate that feedforward projections from V1 can transmit information to V2 in less than 10 ms, and temporal cortex by 80 ms (Nowak, L.G. et al., 1997; Schroeder, C.E. et al., 1998). Feedback from higher areas to primate V1 occur within just 30 ms after the initial forward-moving volley of information (Zipser, K. et al., 1996). Foxe and Simpson’s ERP work in humans demonstrates that information may move from V1 to prefrontal cortex, following the presentation of simple visual stimuli, in as little as 30 ms. This suggests a remarkably early timeframe during which higher information could influence visual processing (Foxe, J.J. et al., 2002). Work in macaques suggests that, given the timing of the earliest measurable activation of areas V4 and IT in the ventral visual stream, this already includes the influence of dorsal stream feedback (Schroeder, C.E. et al., 1998).

Feedforward processing facilitates the extraction of featural information, but exclusively bottom-up models of processing envision low-level detection occurring prior to any configurational organization without the benefits of feedback and horizontal connections. Convergent models, linking low level cortices with parallel processing and/or prior knowledge, allow for input to one receptive field to be influenced by information contained outside that receptive field, or to allow the processing of disconnected features to be processed in the context of previously experienced configurations.

The responses of neurons encoding for a receptive field can adapt their response properties to varying orientation or size. Such abilities were conceived of as being mediated by horizontal connections within V1 (Das, A. & Gilbert, C.D., 1995, 1999), but contour-related responses of
V1 neurons have been modulated by learning or attention, which is likely to be the influence of feedback from higher areas (Gilbert, C. et al., 2000; Li, W. et al., 2008). Explicit testing of lower visual cortical responses under conditions of reduced feedback from area V5/MT caused by cooling, has led to suppression of V1, V2, and V3 activity (Bullier, J. et al., 2001), providing physiological support for modulation of lower cortical responses by feedback from higher cortical areas. V1 receptive fields have a center-surround architecture facilitating the accentuation of perceived contrast by combining a responsive center served predominantly by feedforward inputs, with a surrounding ring whose action is suppressive. Using the same cooling technique to reduce feedback from V2 and V3, reduced suppression in the receptive field surround, suggesting that feedback directly impacts the sensitivity of V1 receptive fields (Hupe, J.M. et al., 2001). Such interactions function to analyzed features in the context of broader knowledge by modifying lower cortical area activity. Moreover, the effect of MT inactivation upon V1, V2 and V3 responses can be seen in just 10 ms.

Kapadia and colleagues (2000) measured effects of visual grouping processes recording from monkey V1 and measuring behavior in humans. The neurons selected encoded for the receptive field of a visual target. Participants viewed the target – a vertical line – in the context of a pair of additional lines flanking it in a vertical or a horizontal array. When the target was presented alone, it elicited a strong response. When the flankers aligned with the target at 6 and 12 o’clock, their response was more than triple the size as when they were presented alone. This is just the sort of neural enhancement predicted to result from grouping, and is a perfect example of the Gestalt adage: the whole is other than the sum of its parts. When the flankers’ positions were changed to either side of the target (at 3 and 9 o’clock), the neural response fell below
baseline, even though those same flankers elicited a strong response when presented without the target. This is an example of a contextual effect described earlier – lateral inhibition.

Texture-defined stimuli have been used to study the grouping of features in the creation of an object. As mentioned earlier, this occurs in two phases, an earlier boundary detection and a later filling-in process. An ERP investigation measured a correlation between boundary detection and activity over occipital scalp at 92 ms and later activity over temporal and parietal scalp from 104 to 120 ms, suggesting that boundary detection may involve more feedforward processing (Scholte, H.S. et al., 2008). The earliest activity correlated with filling-in activity occurred over temporal regions at 112 ms, with later parietal and occipital scalp activations at 172 ms, suggesting involvement of feedback.

If prior knowledge about objects contributes to the processing of the features that comprise them, then not only might we expect activation of the LOC, but lower sensory areas should be affected as well. MRI responses in LOC and V1 were compared for participants viewing moving dots (Murray, S.O. et al., 2004). In one condition, the dots formed a coherent object and in the other, the velocity of each dot’s movement was randomly scrambled, producing a stimulus with the same quantity and velocity of dots, but without coherence. As coherence increased, LOC activity increased but V1 activity decreased. The same investigators presented four non-continuous line segments looking like a diamond occluded by three black bars. When the diamond moved horizontally behind the bars, participants reported their perception alternating between a diamond and separate line segments. They indicated each time their perception shifted. Substantial reduction in V1 and increase in LOC activity resulted during the time that the diamond was perceived, and V1 activity accurately predicted the shift.
Feedback facilitates prediction of how sensory inputs will group relative to past experience and the LOC may function to disambiguate activity represented at lower levels and, via feedback, reduce irrelevant encoding at the feature-level (Lee, T.S. & Mumford, D., 2003). This is reminiscent of the Gestaltist’s idea of Prägnantz. The reduction in activity is the outcome of predictions generated in higher areas. These feed back to lower sensory cortex and inhibit the feeding forward of anything matching the prediction, thus the updated signal contains only unexpected input and is, therefore, more sparse (Rao, R.P. & Ballard, D.H., 1999).

Alternatively, feedback may function to intensify only those aspects of the input which conform to the model, sharpening the subsequent signal (Vinje, W.E. & Gallant, J.L., 2002). In either case, neuronal activity is refined. This suggests that vision gradually resolves the ambiguity of incoming signals and the LOC may represent hypotheses regarding object properties which, as ambiguities resolve, suppress earlier representations (Pollen, D.A., 1999; Kersten, D. et al., 2004).

Bar and his colleagues have used masking to convincingly suggest that object processing involves the activation of higher areas prior to lower-level ones (Bar, M. et al., 2006). They compared trials in which adults identified masked pictures of objects. Using MEG, they differentiated successfully from unsuccessfully identified pictures based on left orbitofrontal activity onsetting at approximately 130 ms. This was 50 ms prior to temporal lobe activation. They then used fMRI to compare objects filtered for their low spatial frequency (gross form) and high-spatial frequency (fine detail), finding that low spatial frequency elicited a greater signal in the orbitofrontal cortex. Given the role of the orbital frontal cortex in the generation of expectations in emotional processing and decision making, they proposed that low spatial frequency inputs processed within the faster dorsal stream, project to the orbitofrontal cortex.
This information then feeds back to temporal object-sensitive areas, narrowing the subset of likely object representations that could be activated, increasing the efficiency of visual processing via a rapid prediction mechanism (Bar, M. et al., 2006), suggesting that inference is a regular aspect of object processing, not a special case reserved for ICs.

It may not be apparent that context changes sensory information, but if you are like most viewers, when you look at the tilt illusion (Fig 1.6), you will perceive perfectly vertical lines to slant when they are embedded in the diagonal grating patterns. All sorts of behaviors show that context derived from prior knowledge benefits object recognition. For example, a fork is more quickly recognized in a kitchen than a violin (Palmer, S.E., 1975). In processing multi-object configurations, accuracy and speed of recognizing an ambiguous object are improved when a previous object strongly associated with the same context was correctly recognized first (Bar, M. & Ullman, S., 1996). Improved response time and accuracy has also been measured in recognizing an object in a typical versus atypical spatial configuration. Context facilitates grouping when information is incomplete. If your printer ran out of ink while printing a picture of a chair and the image was missing several fragments, you likely could still group those fragments as a chair. You would not suddenly perceive only unorganized line fragments. Rather, your visual system can fill-in the missing pieces (Doniger, G.M. et al., 2000).

1.10 Contour Completion or Filling-in

If IC completion is a type of grouping, then colinearity and proximity cue the grouping of inducers as an object, and filling-in the contours is the outcome of that grouping. As this process onsets at approximately 90 ms, this argues for contour completion as one of the earliest steps in delimiting objects from the rest of space. Such processes can explain why we don’t see a hole in our field of vision where our retina has a 2 mm space without photoreceptors (Quigley, H. A. et
al., 1990). Now, one might reasonably argue that perhaps higher cognitive processes facilitate ignoring the gap. However, following presentation of color-spreading illusory stimuli (Fig 1.7) viewers see an afterimage. This response is believed to result from adaptation of neurons to a visual stimulus, arguing for filling-in as an active perceptual process (Shimojo, S. et al., 2001).

Furthermore, the same spread of attention which facilitates enhanced processing to all features inside of object boundaries regardless of whether they are the target, an effect discussed on page 52, can be measured as well within ICs (Martinez, A. et al., 2007). This suggests that, although these representations are not the result of sensory information in our environment, they are, for the purposes of the visual system, objects nonetheless.

As mentioned earlier, there is overlap in the cortical regions involved in perceiving ICs and those that process “real” contours. Recordings made from monkeys viewing ICs via electrodes implanted in V2 neurons encoding the gap between inducers show the same sort of activation they would for the presence of “real” contours (von der Heydt, R. et al., 1984). An fMRI study in neurotypical human participants demonstrated lateral occipital activation in response to ICs and relatively weaker signals in V1, V2 and V3 with comparable activation to similar shapes bounded by “real” contours (Mendola, J.D. et al., 1999).

While collinearity is one cue to fill-in contours between inducers, it seems sensible that this will not occur across gaps of infinite width – otherwise any and all aligned contour fragments might be bound. Stimulus parameters such as inducer size, luminance, contrast, and the distance between inducers have been assayed behaviorally, measuring their effect on the subjective experience of illusion strength. The metrics used have varied - perceived brightness and depth, contour salience, and contour sharpness have all been assayed, although these may not have measured the same attributes (Banton, T. & Levi, D.M., 1992). For example, the salience of ICs
increased as illumination and size decreased (Dumais, S.T. et al., 1976). As contour extent increased, perceived IC strength declined (Petry, H.S. et al., 1983; Watanabe, T. & Oyama, T., 1988; Banton, T. et al., 1992). Shipley and Kellman (1992) asked participants to rate the “clarity” of ICs on a scale of 1 to 10 while they varied inducer size or spacing, holding the other variable constant. Clarity increased with increased inducer size and decreased with extent, but the effects were not independent. It is impossible to hold one of these factors constant without also varying the proportion of IC extent to overall contour length - a variable called support ratio (see Fig 2.2). These three variables have been exhaustively manipulated in intracranial work in primates and behavioral paradigms in humans, but not in electrophysiological human investigations. That manipulation is the focus of the EEG study detailed in Chapter 2.

There has been considerable controversy surrounding when and where in the hierarchy of visual processing IC processing occurs. Suggestions that ICs were cognitive interpretations of features posed top-down models for boundary completion (Gregory, R.L., 1965), but this was countered by influential work by Von der Heydt showing V2 responses for various types of IC stimuli in single neuron recordings from monkeys. These responses mimicked responses seen to “real” contours, despite the fact the there was no sensory information to stimulate the neuron within its receptive field. But these responses only occurred when two inducers were visible. If one of the inducers was covered, the neuron no longer responded (von der Heydt, R. et al., 1984). Furthermore, as they widened the gap between inducers, the neural response weakened, as was observed in the behavioral response in humans described above. While they measured responses in approximately 30% of V2 cells, none of the IC stimuli evoked responses in V1, not even when the gap was narrowed so that the inducer fell partly inside the receptive field. The investigators contended that a purely cognitive account is refuted by such neuronal responses in
lower level visual cortex in the absence of a physical stimulus. Given that presentation of half
the stimulus produced negligible response but that two inducers evoked a strong response, these
properties exemplify the Gestaltist notion that configurations impact perception non-additively
(Peterhans, E. et al., 1989). However, using different stimuli defined by line gratings or
contextually cued groupings of line fragments, some response has been measured in V1 neurons
of monkeys (Grosos, D.H. et al., 1993; Sugita, Y., 1999).

In humans, V2 sensitivity to ICs has been widely reported, and in V1 more sporadically using
functional imaging (e.g., Hirsch, J. et al., 1995; Ffytche, D.H. et al., 1996; Larsson, J. et al.,
1999; Mendola, J.D. et al., 1999), leading many to posit bottom-up models of contour
completion, but such activity does not necessarily indicate that this is either the only or the
earliest effect. While the spatial resolution of MRI is excellent (on the order of 1mm²) its
temporal resolution Monkey recordings demonstrate that detecting contours assembled from
collinear fragments is both dependent on learning and subject to top-down influences (Li, W. et
al., 2008).

Activity in extrastriate regions, especially the LOC, has been implicated in the processing of
ICs, sometimes in addition to and sometimes in the absence of lower visual cortex activation
(e.g., Goebel, R. et al., 1998; Larsson, J. et al., 1999; Mendola, J.D. et al., 1999; Seghier, M. et
al., 2000; Murray, M.M. et al., 2002; Pegna, A.J. et al., 2002; Ritzl, A. et al., 2003). Lesioning
of IT cortex in monkeys led to deficits in discrimination tasks with ICs (Huxlin, K.R. et al.,
2000), implying that IT, the putative equivalent of the LOC in humans, (VanRullen, R. et al.,
2001) is necessary, if not sufficient for IC processing.

EEG and MEG studies demonstrate that the earliest IC modulation occurs during the visual
N1 latency, peaking around 150 ms in neurotypical adults (Hermann, C.S. et al., 2001; Pegna,
A.J. et al., 2002; Proverbio, A.M. et al., 2002; Yoshino, A. et al., 2006; Shpaner, M. et al., 2009), and onsetting as early as 88 ms (Murray, M.M. et al., 2002). The earliest effects of the difference between IC presence and IC absence most consistently source localized to the LOC (Murray, M.M. et al., 2002; Pegna, A.J. et al., 2002; Foxe, J.J. et al., 2005; Shpaner, M. et al., 2009; Fiebelkorn, I.C. et al., 2010) or with MEG to the anterior lateral occipital region (Halgren, E. et al., 2003). As mentioned in section 1.3, this has been called the IC-effect. Despite the evidence of feedback processes in vision, the assumption in so many accounts was that V1 and V2 activity must represent feedforward processing. However, Shpaner et al (2013), using Gabor path stimuli (Fig 1.10) and employing recording methods to evoke the largest early activations possible, saw no contour-completion related VEP modulation during the C1 timeframe (60-95 ms), a component believed to index feedforward V1 activity (Di Russo, F. et al., 2002; Kelly, S.P. et al., 2008). Lee and Nguyen’s recordings from monkey visual cortex neurons did measure activation at 65 to 95 ms in V2 and 100 to 120 ms in V1, but, these are late enough to incorporate feedback from higher areas (Foxe, J.J. et al., 2002). Most evidence for V1 and V2 involvement has been estimated to occur after 170ms until as late as 300 ms (Seghier, M.L. et al., 2006; Shpaner, M. et al., 2013), effects which, together with evidence of earlier LOC involvement, are indicative of feedback and recurrent processes between higher and lower visual areas. An MEG study demonstrated that, after weak activation at right occipital and temporal poles peaking at 110 ms after onset, IC processing elicited the most prominent activation in the LOC at 155 ms which then appeared to spread to lower visual cortex, that is, in a feedback direction (Halgren, E. et al., 2003)

A controversy surrounding this initial IC-effect is whether it indexes the segmenting of a region of space (salient region or SR) or the completion of contours per se. Since the LOC is
regularly implicated as sensitive to coherent objects, this initial step could conceivably index a crude segregation of a SR from the background. Stanley and Rubin (2003) modified Kanizsa ICs so that the usual corners of the Pacman inducers were rounded. This set off a region of space to be segregated without specifically inducing contour perception. They compared fMRI effects to the differences between inducing and non-inducing conditions for ICs and SRs, finding the LOC implicated in response to both stimuli. They concluded that the LOC is involved in detection of SRs, but not specifically in IC processing, and inferred that V1 and V2 must process contour-specific information. However, a subsequent EEG investigation using the same stimuli found temporal dissociation between responses for the two stimulus classes (Shpaner, M. et al., 2009). An initial response was measured to ICs during the N1 latency, but only very weakly to the SRs. The IC effect was source-localized to lateral occipital and temporal as well as to medial occipital areas, while source-estimations for the SR effects were exclusively medial, suggesting sources in the dorsal rather than the ventral stream. Responses to SRs during a later period – between 400 and 480 ms – produced stronger activation more consistent with LOC sources, suggesting that the equivalent effects measured for the two stimulus types in the earlier study were a product of the cruder temporal resolution of fMRI, which conflated two unique responses.

This echoes earlier work by Lamme and colleagues (1999) using texture-defined stimuli that dissociate filling-in of regions from the detection of the contours that comprise their boundaries by recording from receptive fields centered on the stimulus border, the interior, or the background. Their recordings from V1 monkey neurons detected a sequence of processing steps beginning with boundary detection at around 80 ms, with surface processing following at 150 ms and continuing until past 400 ms, also suggesting that boundary processing precedes filling-in.
Work with hemispatial-neglect patients whose attention to the left side of space was impaired, showed that they were capable of bisecting bar-shaped Kanizsa stimuli as accurately as they did real bar stimuli, despite the fact that they could not see the inducer when it was located in the left hemifield (Vuilleumier, P. et al., 2001). This suggests that this initial, boundary-completion phase of IC processing is automatic. What emerges from the confluence of evidence is that the LOC is regularly implicated in the earliest responses to IC stimuli, following the arrival of coarse information, likely from dorsal stream structures. This may, in turn, feedback to V2 and V1 (Murray, M.M. et al., 2002; Seghier, M.L. et al., 2006; Shpaner, M. et al., 2013). This rapid, automatic analysis of low-level information in higher cortical areas feeds back to and modulates slower, feed-forward processing of features in lower cortical areas, much like the object processing models discussed earlier, with an early predictive processing in higher cortex reducing the processing burden in lower areas, suggesting why inference in vision is seen as a cognitive efficiency (Murray, S.O. et al., 2004); (Bar, M. et al., 2006; Chen, C.M. et al., 2007).

VEP modulations following IC presentation have also been measured from 200 to 400 ms, (Sugawara, M. & Morotomi, T., 1991; Herrmann, C.S. et al., 1999; Proverbio, A.M. et al., 2002), suggesting that contour completion may occur over multiple phases. VEP effects during such latencies are often described as reflecting higher conceptual-level processes in the object-processing domain. This is reflected in Doniger and colleagues (2000; 2001) perceptual completion work with more complex images than ICs. They first presented a line drawing of a common object that had so many of the pixels removed that identification of the object was rendered impossible. Then they presented successive images, each time adding back more pixels until, although the image was still fragmented, the viewer could fill-in the missing contours and identify the object (Fig 1.8). There was no modulation of VEP amplitude during the N1
timeframe following presentation of these stimuli, but steady increases in the 230 to 400 ms range were measured to each successive presentation of the image, a component termed the negative for closure ($N_{cl}$). The later onset and incremental modulation over an extended timeframe suggested a process that may have been more challenging to the visual system than completion of ICs. However, if one of the original highly fragmented images was presented a second time during a series of images, then not only could participants complete it in its most fragmented version, the VEP modulation now began during the earlier N1 timeframe. This suggests that through repeated viewing a prior had somehow been instantiated, and that the visual system could, via reference to it, rely on more automatic means of completing the image.

Intracranial work in humans has revealed coherent oscillatory activity in the beta bandwidth during the $N_{cl}$ timeframe among the LOC, prefrontal cortex, and hippocampal formation (Sehatpour, P. et al., 2008). This suggests the involvement of a coherent network of distant regions which echoes Bar et al’s (2006) object recognition model. Sehatpour and colleagues posit that the frontal lobe may generate hypotheses, while the LOC might compare incoming feed-forward sensory information with stored object representations in the hippocampal formation, a recursive process that concludes when a match is made. Given reports of long-range underconnectivity in ASD, such processes could be impaired, which may be revealed by differences in the strength or timing of IC processing metrics.

Despite the fact that the two phases marked by the IC-effect and $N_{cl}$ both involve the LOC, they appear to index distinct processes. Impaired processing during the $N_{cl}$ timeframe has been measured following presentation of IC stimuli to schizophrenic patients despite intact effects during the N1 latency (Foxe, J.J. et al., 2005). This dissociation is also evident in a study in comparing VEP response to ICs manipulated by subtly rotating the inducers in the illusion-
inducing condition such that the sides of the square appeared slightly convex (the “fat” condition) or concave (the “thin” condition). Murray and colleagues (2006) asked participants to discriminate between the two conditions. While the N1 effect was unaffected by task performance, the later effect, measured between 330 to 406 ms showed task-related modulations. This suggests that later phase processing must be instantiated for cognitive tasks that require awareness.

Hemispheric Processing

In addition, many studies have reported right hemisphere dominance during IC processing which has typically been explained in terms of classic lateralization of global grouping processes to the right hemisphere and local featural processing to the left (Hirsch, J. et al., 1995; Atchley, R.T. & Atchley, P., 1998; Larsson, J. et al., 1999; Murray, M.M. et al., 2002). However, the effect is not observed consistently (Proverbio, A.M. et al., 2002; Shpaner, M. et al., 2009). Pillow and Rubin also employed a “fat/thin” discrimination task. They manipulated either the horizontal or vertical contours of the IC. In one condition, the contour to be evaluated straddled the vertical meridian, requiring hemispheric integration, and in the other it fell within a single hemifield. They found a significant advantage for task performance in the within-hemifield compared to across-hemifield condition (Pillow, J. & Rubin, N., 2002). This suggests that contour completion of centrally presented ICs requires integration of information from both hemispheres, so, if interhemispheric connectivity differs in ASD (Anderson, J.S. et al., 2011), then IC processing may be different as well.

Theoretical Framework

In an attempt to encompass the above anatomical and temporal evidence in contour completion, grouping, and the wider object-processing literature, our approach to investigating
contour completion in ASD involves the following phases (Fig 1.9). Initially, an early extraction of features begins in lower visual cortices, the information is conveyed in a feedforward manner toward higher regions of visual cortex. The C1 component (60-90 ms) has been measured as an index of this early phase. However, feature extraction should be identical in the two conditions of IC stimuli. Therefore, the subtraction of illusion-inducing and non-inducing stimuli would cancel each other out. The earliest phase of activity related to the difference between IC conditions is proposed to index the automatic filling-in of contour fragments. Evidence suggests that this process conveys information about priors via feedback connections from LOC, integrating it with incoming sensory information. A later process seen in situations of increased perceptual burden, such as difficult to complete objects, judgment tasks, or processes compromised by pathology, is believed to index a more detailed filling-in process, facilitated by recurrent processing among a distributed network involving LOC, prefrontal cortex, and the hippocampal formation (Fig 1.9).

1.11 Typical Development of Object Processing, Grouping, and Completion

If we are to consider the atypical development of the processing of objects and their constituent parts, it is fundamental to look at how such processes develop typically. Is the primacy of global processing hard-wired from the start? Do global and local levels of processing develop in tandem or somewhat independently?

Infant Development

While there are claims that grouping is possible at birth (Farroni, T. et al., 2000) this seems unlikely given the considerable development of the human visual system that occurs post-natally (Zanker, J. et al., 1992). Most studies suggest that sensitivity to object features begin separately
and that somewhere between two and six months of age, infants begin binding features together (Younger, B.A. & Cohen, L.B., 1986; Colombo, J., 2001). Individual difference studies separating infants into those who fixate stimuli for short and for long periods of time suggest that shorter fixators may process global level information first whereas longer fixators begin by processing local-level information sequentially, feature-by-feature. However, this second group did demonstrate the ability to switch to global precedence if first familiarized with the stimulus (Colombo, J. et al., 1991; Frick, J.E. et al., 2000). The different bases for Gestalt grouping emerge at different times of development. While evidence for grouping based on luminance appeared at just 2-months-of-age, it was not measured to shape cues until 4 months, and at 6 months grouping by proximity was still not evident (Quinn, P.C. et al., 2002; Farran, E.K. et al., 2004; Quinn, P.C. & Bhatt, R.S., 2005).

There are strong indications that global perception develops during early “critical” periods. A study of adolescent and adult patients with congenital cataracts showed that those treated after 5-months-of-age took longer to detect, and missed a greater number of ICs within a field of distractors (Putzar, L. et al., 2007). Infant habituation studies have measured consistent differential responses between illusion-inducing and non-illusion inducing conditions of IC stimuli at 7, but not at 5 months of age (Bertenthal, B.I. et al., 1980) and suggest that infants may perceive the illusory figure as a surface superimposed on a background at 8 but not at 4 months of age (Csibra, G., 2001). This developmental trajectory of various types of illusory shape perception could be manipulated by various parameters. Four-month-old infants were more sensitive to ICs if they were moving (Johnson, S.P. & Mason, U., 2002), if support-ratios were increased from 37 to 66% (Otsuka, Y. et al., 2004), or if the absolute extent of the stimulus was decreased from 5.9° to 4.4° of visual angle (Bremner, J.G. et al., 2012). Binocular depth...
perception is not reported to develop until after 5-months of age, so if the inferred edge of an IC suggests that the illusory shape occludes the background, it seems unlikely that an infant could perceive ICs before that time.

A contrast of bilaterally and unilaterally presented matching tasks with face-like configurations in 19 to 23 and 24 to 28-month-old participants, suggested that only the older group benefitted from bilateral presentation (LIEgeois, F. et al., 2000), pointing to possible early development of hemispheric specialization in infancy. Anatomic evidence suggests that the period of 4 to 6 months is likely to be one of significant transformation in communication between left and right visual regions as corpus callosum fibers connecting those areas become myelinated during that time (de Lacoste, M.C. et al., 1985).

**Childhood and Adolescent Development**

For years, the common wisdom has been that children are more ‘parts’ than ‘wholes’ processors. A study of children’s recognition of upright and inverted faces has been widely cited as the evidence for a local to configurational shift in processing at about 10-years-of-age (Carey, S. & Diamond, R., 1977), although face processing may not generalize to all kinds of object processing. In addition, this study assumes that global and local aspects of a stimulus are polar ends of a single continuum rather than separate dimensions developing in parallel. A target search paradigm using either global or local criteria of an array of dots in 6, 8, 10, and 22-year-olds, found strong improvements across age for global targets but little improvement for local targets, suggesting that global and local perception are dissociable late into childhood (Enns, J.T. et al., 2000).
Although children 3 to 6 years of age can integrate spatially separated units of hierarchical stimuli into cohesive wholes, when the difficulty of the task was increased by removing some of the local components of the stimulus, the younger children relied more on local than on global cues to make similarity judgments (Dukette, D. & Stiles, J., 1996), supporting the idea of local bias in childhood. However, 6, 10, 14-year-old, and adult participants were presented pairs of hierarchical stimuli and asked to determine whether they were the same or different on the basis of global or local criteria. All participants demonstrated faster responses to hierarchical stimuli on global trials, but a stronger bias was seen in 6-10-year-olds, diminishing to adult levels prior to 14-years-of-age (Mondloch, C.J. et al., 2003), countering the parts-to-wholes story.

The development of hemispheric biases of global and local processing is equally controversial. A contrast of bilaterally and unilaterally presented matching tasks with face-like configurations involving 10 and 12 to 14-year-olds saw an advantage for bilateral presentation only for children above the age of 12 (Merola, J.L. & Liederan, J., 1985). However, an fMRI study of children 12 to 14 years of age measured activation related to a target detection task at global versus local levels. Slow performers demonstrated greater local level activation overall, equivalent activation of the hemispheres for global tasks, and greater right than left activation for the local task, whereas fast performers showed greater right than left hemisphere activity in the global task and the opposite during the local task (Moses, P. et al., 2002). This adds support to the idea that hemispheric biases are not monolithic. Structural MRI assays of corpus callosum volume suggest steady development from 4 to 18 years-of-age, so interhemispheric communication is likely to continue to develop into adolescence (Giedd, J.N. et al., 1996).

Indeed, a comparison of TD persons from 8 to 30 years of age using hierarchical figures showed just that. Scherf and colleagues (2009) compared few-element with many-element versions of
hierarchical stimuli, finding that while participants of all ages made accurate judgments of similarity between shapes based on global-level information, children and adolescents had slower reaction times than adults, regardless of the manipulation, duration of presentation, or whether stimuli were composed of letters or shapes. Scherf posits that the ability to determine which elements in an array go together (global sensitivity), is dissociated from the binding of those elements as a shape, a process which includes the establishment of object boundaries, and which develops into adolescence. So-called global biases in infancy may simply reflect differences in visual acuity, since infants may be meaningfully processing predominantly low-spatial frequency information. Children do not acquire fully adult-like resolution until approximately age 5 (Zanker, J. et al., 1992). In a detection task requiring contour integration (Kovacs, I. et al., 1999) tiny aligned Gabor stimuli were presented amidst a background of randomly oriented but otherwise identical stimuli (Fig 1.10). So, the local elements conformed to the receptive field properties of primary visual cortex, but the contours could not be detected without integrating elements into a global percept involving horizontal and feedback connections. The experimenters found that children 5 to 14 years-of-age detected contours significantly less accurately than adults, and while adults performance was not changed by varying the spacing between aligned contours, childrens’ performance was. This suggests that processing relying on integration of global and local inputs is still developing into early adolescence. A behavioral IC investigation of contour integration using the fat/thin discrimination paradigm, showed that 6-year-olds were less able to make such discriminations whether real or illusory contour stimuli were used. Only those 12-years-of-age and above are comparable to adults in making the discrimination with ICs (Hadad, B.S. et al., 2010), but, as this paradigm is incapable of determining the timecourse of such processes, the early and late
phases of IC processing may, in fact, have different developmental trajectories, a possibility explored in Chapter 3.

*Development of Processing Associated With Ventral Visual Stream Structures*

Assays of the development of the ventral visual stream point to the gradual maturation of the ability to combine elements into objects. In one study, fMRI activity was measured in response to animals and tools viewed passively in scrambled and unscrambled conditions. While the LOC and fusiform gyrus, typically selective to tools, already showed object category specificity in 6 and 7-year olds, specificity for animals appeared to emerge gradually (Dekker, T. et al., 2011). An fMRI comparison of face, place, and object processing demonstrated adult-like specificity in 5-8-year-olds and 11-14-year-olds in response to houses and objects (in the LOC). However, there was reduced selectivity for faces in areas specific for this purpose in adults. These effects also lateralized differently. Although adult-like specificity was found in the right hemisphere by adolescence, it was not found in the left hemisphere until early adulthood (Scherf, K.S. et al., 2007). A dissociation of the developmental processing for objects with and without social relevance has also been reported, with maturation continuing until at least until 17-years-of-age (Pelphrey, K.A. et al., 2009; Golarai, G. et al., 2010). Such differences have relevance for understanding object processing in ASD given its associated social deficits. The use of ICs in the present studies attempts to investigate processing independently of differences specific to processing socially relevant stimuli.

*Development of Invariance*

In order to identify objects, the brain must not only develop sensitivity to differences between categories, it must also generalize within categories. In a study that measured fMRI activity to animals and tools viewed from typical and atypical perspectives, Dekker et al (2011) found that
recognition improved significantly from 6 to 10 years-of-age and correlated with the MRI signal measured in bilateral fusiform areas. Some additional improvement continued until 20 years of age, but the category selectivity for objects associated with the LOC appears adult-like by somewhere between 5 and 8 years of age (Golarai, G. et al., 2007; Scherf, K.S. et al., 2007). Although the LOC has been shown to be invariant to object size but not reliably to viewpoint (Grill-Spector, K. et al., 1999; Grill-Spector, K. et al., 2001; Golarai, G. et al., 2007), this has not yet been explored developmentally. In a behavioral comparison of generalization to perspective in 8 to 16 year-olds, younger children recognized objects from previously learned perspectives exclusively whereas adolescents could generalize knowledge to new viewpoints (Juttner, M. et al., 2006). In a manipulation of IC support-ratio, all participants 9 years-of-age and above performed better with higher support ratio, however, the 6-year-old group was immune to manipulation of support ratio, suggesting that the neural mechanisms that facilitate scale invariance may still be developing in younger children (Hadad, B.S. et al., 2010). These results are echoed in an observational study comparing incidences of young children using miniature objects in a scale-inappropriate fashion, such as sitting on a miniature chair or trying to get into a toy car. Behavior was coded based on observer judgments of the child’s seriousness and persistence to distinguish true errors from pretend play. Scale errors were seen across the range of 18 to 30 months-of-age, with a peak at 20.5 to 24 months (DeLoache, J.S. et al., 2004), suggesting that there may be a developmental period during which a child’s perception of objects lacks the scale invariance seen in adults.

The above suggests that adult-like object processing in TD persons develops over time, but little ERP work has measured how neural activity differs as these processes develop. Evidence suggests that the visual system’s ability to generalize different sizes or perspectives of identical
objects changes as we develop. To bring the discussion back to ASD, atypical visual processing as well as a general bias away from gist and toward concrete meaning is an often-observed phenotype (Kanner, L., 1943; Frith, U., 1989; Simmons, D.R. et al., 2009). A good deal of evidence points to disordered fronto-temporal connectivity in ASD – connections implicated in the models of object processing detailed above – and disordered interhemispheric connectivity in ASD - implicated in the integration of global and local levels of stimuli, and in the processing of ICs specifically. These differences create the potential for object processing that, as Pellicano describes it, may apply prior knowledge with greater variance to the processing of incoming sensory information (Pellicano, E. et al., 2012). If this is true, we would expect grouping to be different in ASD and this may be visible in differences in contour integration processes.

1.12 Grouping, Binding, Closure, and Object Processing in ASDs

*Paul doesn’t generalize the particulars of his experience into the habitual, the ongoing, as many other people do. Each moment seems to stand out distinctly, and almost unconnected with others, in his mind.* – News From the Border: A Mother’s Memoir of her Autistic Son (McDonnell, J.T., 1993)

*I have no trouble noticing the little details that no one else seems to see, and in fact I have no choice but to see every little detail. I'll see the tiny plants in the concrete cracks, the placement of hair on the people around me, the light damage on cars beside me, the exact words and pictures of all the advertisements... I can't block that out, I can't just glance over it and move on, I have to stop and LOOK at every little thing before the whole scene makes sense. ...This means that I get the overall impressions of the scene in front of me MUCH more slowly than the people around me...*

*Edited Dec 7 to add:*
*This isn't going further, I got interrupted by a bright rainbow outside while I was typing this yesterday... Oh well. :)* - Ari, from her blog Perception (Akari, 2010)
Since Kanner first described autism in 1943 (Kanner, L., 1943; Kanner, L. et al., 1956), an atypical style of processing has been associated with it that lacks the typical bias for making coherent wholes. This global-local processing atypicality has been attributed to an inherent superiority in processing the details (Mottron, L. et al., 2006) and to a deficit in processing configuration (Scherf, K.S. et al., 2008), fuelling a decades-long discussion.

Enhanced Perceptual Functioning & Weak Central Coherence – Local and Global Differences

Laurent Mottron’s attempt to understand the extraordinary abilities of an autistic savant to graphically represent proportions (Mottron, L. & Belleville, S., 1993) was extended to codify differences in such abilities as stimulus detection, pattern recognition, and pitch discrimination seen in persons on the autism spectrum. The result was the Enhanced Perceptual Functioning theory (Mottron, L. et al., 2006). Adolescents with ASD and their TD counterparts were compared on a hierarchical figure task, three grouping tasks, and a task comparing speed of detection of simple shapes alone versus those embedded within more complex shapes. They measured slowing in the TD group for embedded figures but no slowing for the ASD group. They interpreted ASD performance to result from an ability to ignore the context - the more complex shape – something they termed locally-oriented processing. Given that there were no differences found in either grouping or hierarchical figure tasks, they concluded that persons with ASD had superior performance in locally-oriented tasks together with intact global processing (Mottron, L. et al., 2003).

Enhanced local visual performance has been demonstrated on tasks such as the Block Design subtest of the Wechsler Intelligence Scales, most often used in an adapted version which contrasts whole from segmented designs. Individuals with ASD performed better than they did on other subtests, and better than a control group of mildly mentally retarded persons matched
for age and non-verbal IQ (Shah, A. & Frith, U., 1993). This superior performance also predicted high AQ scores, indicating self-report of high incidence of ASD traits in non-diagnosed persons displaying autistic traits (Stewart, M.E. et al., 2009). Persons with ASD can copy impossible figures (think of Escher’s architecture) more accurately than TD persons, suggesting that they can ignore the logic of figures derived from their knowledge to focus exclusively on copying lines (Mottron, L. et al., 1999). Adults and children with autism perform visual search tasks more quickly than TD persons (O’Riordan, M.A. et al., 2001). Persons with ASD exhibit superior performance on the Embedded Figures Task (EFT) (Witkin, H. et al., 1971) – requiring the detection of a geometric shape within a larger complex pattern (Jolliffe, T. & Baron-Cohen, S., 1997; Bolte, S. et al., 2007). This is also true of undiagnosed persons with high AQ scores (Baron-Cohen, S. et al., 2001; Grinter, E.J. et al., 2009), and even of asymptomatic parents of children with ASD (Bolte, S. & Poustka, F., 2006).

However, dysfunctions in such skills as making inferences has led others to believe that superior Block Design performance on items requiring mental segmentation may not result from a locally intensified way of processing but from a weakness in integrating elements into coherent wholes (Shah, A. et al., 1993). Support for the Weak Central Coherence theory also employs the EFT, but cites a weakness in configurational processing as the mechanism driving performance differences (Pellicano, E. et al., 2005). However, studies based on one neuropsychological evaluation or another are intrinsically unsatisfying. There are those who find no differences in EFT performance (Ozonoff, S. et al., 1991; White, S.J. & Saldana, D., 2011; Spencer, M.D. et al., 2012). In addition, although lesion and developmental studies have suggested that the processing of global and local stimulus elements are dissociable (Enns, J.T. et al., 2000; Riddoch, M.J. et al., 2004), advocates for enhanced perception or weak coherence
confusingly conflate the two. Two examples of this include: “The objective of this study was to investigate the tendency for local processing style (weak central coherence)” (Bolte, S. et al., 2006) or “The Weak Central Coherence account: detail focused cognitive style” (Happe, F. & Frith, U., 2006). This exemplifies the need for going beyond conceptual explanations.

Even in cases of equivalent EFT performance, different brain activity has been observed with fMRI. While TD individuals who performed well demonstrated frontal and parietal activation (Walter, E. & Dassonville, P., 2011), those with ASD activated occipital and extrastriate regions more than frontal and parietal (Ring, H.A. et al., 1999; Manjaly, Z.M. et al., 2007), suggesting that the brains of TD and ASD persons employ different circuitry to disembed figures. The involvement of low-level visual cortex sensitive to features is offered as anatomical support for a more local approach at the root of enhanced perceptual processing (Mottron, L. et al., 2006). The use of striate and extrastriate regions for the ASD group, which are relatively close to each other, rather than frontal and parietal regions, which are anatomically distant, suggests greater local connectivity in the context of less connectivity among dispersed regions (Just, M.A. et al., 2004; Courchesne, E. et al., 2005).

Grouping and Binding in ASDs

The findings of Gestalt grouping studies comparing individuals with ASD and control groups vary widely. A comparison of children with ASD to those with moderate learning difficulties in grouping arrays of dots and lines, reported that the ASD group applied Gestalt principles at a level not significantly different from chance, as well as grouping significantly less than the control group. However, this was not reflected in a drawing task. Those in the ASD group drew more Gestalt forms, contradicting the interpretation that global representations are inaccessible in individuals with ASD (Brosnan, M.J. et al., 2004). When performing a task involving
hierarchical figures that could be matched on either a global or local basis, children made more choices based on a local than a global basis than did adults. However, children with ASD showed neither perceptual enhancement at the local level, nor a tendency away from processing at the global level (Plaisted, K. et al., 2006). Results differed when comparing a group of high-functioning (HF) males with autism to schizophrenic, depressed, and neurotypical males (Bolte, S. et al., 2007). Although the principle of similarity was employed less effectively as a cue in comparison to all groups, employing proximity only produced significantly different performance from some of the control groups. This suggests that some Gestalt grouping mechanisms could be shared with persons having mental and mood disorders. ASD and TD males performed equivalently in judging whether elements within shape matrices were grouped by virtue of proximity or alignment (Farran, E.K. & Brosnan, M.J., 2011) However, this paradigm varied task difficulty by introducing distracters into the arrays. In easier conditions, rows or columns were nearly uniform grids, whereas, in more difficult conditions, some elements within a row or column varied. For example, if proximity was the grouping principle, then spacing would vary. ASD participants made more errors than TD on low-difficulty trials for orientation and luminance. These are trials for which grouping could be easily determined by quick global assessment but, with more distractors, participants would benefit increasingly from a feature-oriented approach, and in this case ASD and TD performance was equivalent. The ASD cohort also showed poorer performance in determining grouping on the basis of shape, regardless of difficulty. One can determine proximity simply by looking at the space between elements (configuration). No comparison is necessary. But one cannot determine similarity of shape without attending to local criteria to determine shape and global criteria to determine
configuration. The performance decrement, therefore, could be attributed to a weakened ability to integrate global and local criteria.

In a developmental investigation using hierarchical stimuli in 8-30 year-olds, TD adults displayed typical faster reaction times for the global level, but this did not emerge until adolescence, whereas individuals with ASD never displayed this bias. Their local bias emerged much more gradually, stabilizing in adulthood (Scherf, K.S. et al., 2008). When manipulating task difficulty, TD participants demonstrated typical global advantage and interference effects whether or not they knew that targets would appear at the local or global level. Participants with ASD also demonstrated a global advantage and interference when targets appeared consistently at one level, which belies the account of impaired global processing. But in cases when targets could appear equally probably at either level, persons with ASD demonstrated a local advantage (Plaisted, K. et al., 1999). So, if local processing is the default in ASD, it appears that it can be overcome with specific cueing toward the global stimulus level. Iarocci et al’s (2006) comparison of high-functioning TD and ASD children on two search tasks demonstrates a different effect. The first task biased efficiency of a search toward either a global or a local target but did not explicitly direct attention toward either. In this case, TD and ASD groups accessed targets at global or local levels equally accurately, but the search rate of ASD children was less efficient in difficult global target searches. However, when a global bias was advantageous but the probability of a global or a local target varied, then TD children were much more sensitive to the global bias than the local one, whereas ASD children were equally sensitive to either.

It may sound as though such flexibility should be an advantage as the visual system could chose a strategy on a task-by-task basis. However, this may slow processing down. If our brains
have evolved to manage a surfeit of visual information in complex arrays, then a global default may have facilitated processing stimuli at the highest level possible because it is heuristic. At the global level, visual information is contained in the sparsest encoding, so a global or theory-driven approach can filter out irrelevant detail, allowing us to become competent across a range of tasks. However, the local or data-driven strategy we observe in ASD only appears to be advantageous when the integration of global information interferes with local processing, and presumably these tasks are less common in our visual world.

**Grouping in Autism and Connectivity**

If you recall from an experiment described on page 63, when a target contour is surrounded by collinear contours, cortical response is enhanced, whereas, when the target is flanked by orthogonally oriented contours, inhibition results (Kapadia, M.K. et al., 2000). Comparing TD and ASD in a flanker task, sensitivity to targets increased when the distance between the target and flankers was small and not when it was large, but this enhancement was greater for the ASD group, suggesting altered lateral connectivity (Keita, L. et al., 2011). Using ERP indices of texture-stimulus processing, you may recall that two phases are proposed to occur, much like the temporal model which frames our analysis of IC processing. The first phase correlates with the detection of contours, facilitated by lateral inhibition. It peaks at 150 ms after stimulus presentation. The second is associated with filling-in of the textured surface delimited by the contours, peaking at approximately 260 ms - a process integrating feedback from higher areas (Roelfsema, P.R. et al., 2002). Persons with ASD detected fewer boundaries, performance which correlated with reduced electrophysiological effects at approximately 150ms. The investigators attributed this to abnormal horizontal connections in lower visual cortex causing altered lateral inhibition. An enhancement of effects at 220-240 ms over lateral occipital scalp suggested
compensatory processing at later stages, making possible later phase recurrent processing that was the same as TD participants (Vandenbroucke, M.W. et al., 2008). Our analysis of the relative contributions of feedforward and feedback connections to IC processing is the focus of Chapter 4.

A comparison of coherent motion processing offers additional clues to possible neural mechanisms in grouping. This stimulus is comprised of two dots presented simultaneously at opposite diagonal corners of a square field for 200 ms. They are then turned off and replaced by dots appearing in opposite position, flipping positions back and forth. The flip creates the illusory perception of either vertical or horizontal motion. This is attributed to the binding of the two dots based on the feature of motion either within or across hemifields of vision. David and colleagues (2010) varied the distance between dots comparing the response of TD and ASD viewers. While there was no difference between groups for vertical binding, shorter distances between dots were required for the ASD participants to be able to bind the dots and experience the horizontal motion illusion. Only in the case of horizontal binding is the brain integrating information from both hemifields, implicating differences in interhemispheric connectivity.

The above makes a case for differences in grouping of stimulus features in ASD, differences which implicate lateral or feedback connections and, likely, connectivity between the hemispheres. We believe that IC completion, as one such grouping processes, is likely to reveal similar differences between TD and ASD groups.

Contour Completion in ASDs

Behavioral assessment of whether children with ASD are susceptible to visual illusions, particularly the Kanizsa ICs, has produced conflicting results. In Francesca Happe’s investigation, children with ASD correctly judged illusions to be present less often than their TD
counterparts (Happe, F.G.E., 1996). However, Ropar and Mitchell saw no difference between
groups in discerning illusions. While Happe and colleagues asked their participants to respond
verbally, Ropar and Mitchell asked their participants to adjust one stimulus to physically match
the other, suggesting task demands may have accounted for the difference (Ropar, D. & Mitchell,
P., 1999). When children with ASDs performed the ‘thin/fat’ discrimination task on Kanizsa
rectangles, a task described earlier, they perceived as many ICs as control children did (Milne, E.
& Scope, A., 2008).

There is no developmental and little electrophysiological work on IC perceptual processing in
ASD and most of it employs gamma-band oscillatory activity as a dependent measure. Both
intracranial and surface recordings have associated binding processes with oscillatory activity in
the gamma band (40 hz) (Singer, W. & Gray, C.M., 1995; Tallon-Baudry, C. & Bertrand, O.,
1999) with parietal-occipital effects following the presentation of ICs in TD adults (Tallon-
Baudry, C. et al., 1997) and frontally in 8-month-old infants (Csibra, G., 2001). Yuval-
Greenberg has demonstrated that transient gamma band responses time-lock to micro-saccade
activity, so they may not in fact reflect stimulus processing (Yuval-Greenberg, S. et al., 2008).
Nonetheless, some studies report IC processing-related differences in Gamma in ASD. Gamma
band responses have also been reported to differentiate individuals with Williams syndrome from
those with ASD despite equivalent behavioral responses (Grice, S.J. et al., 2001). Brown and
colleagues (2005) compared adolescents viewing arrays of multiple IC inducers, some with and
some without an induced rectangle present. Participants were asked to respond when they
detected the illusion. Their behavioral responses of ASD and TD groups did not differ, but the
ASD group showed a peak from 80-140 ms not present in the control group and an earlier onset
of a peak present in controls at 250-400 ms. In another study, beta and gamma activity at
occipital and occipital-parietal scalp sites were compared in TD and ASD boys ages 3 to 7 years-of-age who passively viewed ICs. They analyzed phase-locked responses in an 11.5 to 24 hz frequency band for beta and 24 to 48 hz for gamma in an effort to address Yuval-Greenberg’s criticism. The TD group demonstrated significant gamma, but non-significant beta response at occipital scalp sites in the 40-120 ms time window. The gamma power in response to non-inducing was greater than to the inducing condition. A second gamma response at parietal-occipital sites during the 120-270 msec timeframe was greater to inducing than to non-inducing conditions. However, the ASD group showed a single broad timeframe (40 to 270 ms) and, unlike the TD group, showed an inverted relationship of gamma, with the non-inducing condition’s response greater than to the inducing condition (Stroganova, T.A. et al., 2012). The same group’s ERP investigation also demonstrated inverted IC-effects for the ASD group, however, differences between conditions to responses in their ASD group appeared to start before 50 ms, making the validity of their results difficult to evaluate (Stroganova, T.A. et al., 2007).

The timecourse and topography of IC integration effects is well-replicated in neurotypical adults, as well as being a far less controversial metric than gamma oscillations. However, there is little ERP work in individuals with ASD and the developmental trajectory of contour integration has yet to be assessed. We intend the studies covered in Chapters 3, 4 and 5 to begin to close that gap.

*Categorization, analogic reasoning, and what they impart about global processing differences*

Accounts of higher-level cognitive analytic processes speak to a particular way in which global and local processes may interact. There is some evidence that, unlike neurotypical individuals, those with ASDs may not group items into conceptual categories to facilitate
cognitive tasks such as memory. For example, while adults generally recalled related lists of words better than unrelated ones, those with ASDs remembered equal numbers of words from either list (Bowler, D.M. et al., 1997). Prototypes have been defined by Posner and Keele as the average of category exemplars (Posner, M.I. & Keele, S.W., 1968). They are thought to function heuristically, allowing individuals to reference one representation in memory rather than every instance ever experienced. One is thought to acquire the ability to creating prototypes automatically in the first year of life (Strauss, M.S., 1979), but this is not the only means of categorizing. By two years of age, one also develops the ability to remember individual exemplars (Younger, B., 1990), giving one the ability to learn the rules for category membership. However, this second approach is not always advantageous. It is true that most dogs have four legs and a tail, but three-legged dogs are dogs nonetheless, so such complex exemplars challenge the efficacy of the rule-learning approach. Klinger and Dawson’s (2001) comparison in low-functioning persons with ASD trained participants to label objects within categories. They compared the two processes, one using an implicitly acquired prototype and one using rules explicitly taught to them. The ASD group performed no differently overall from controls and all groups did well applying the rules, but those with ASD did not form spontaneous prototypes. They made use of rules even when that was not beneficial. It is possible that task instructions may have introduced a confound in that participants were asked to choose the “best” category exemplar, an ambiguous criterion that may have proven disproportionally challenging to the tendency toward concreteness in ASD (Molesworth, C.J. et al., 2008).

In another classification task conducted with high-functioning adolescents and adults, participants were asked to describe elliptical shapes as ‘narrow’ or ‘wide’ from among 10 varying widths (Soulieres, I. et al., 2007). TD and ASD groups performed nearly identically in
placing a boundary within the continuum of ellipses, and in taking more time to classify stimuli near the boundary. However, they responded differently in discriminating between pairs of same and different ellipses. The TD group showed a peak in performance at the border of the narrow and wide categories they had earlier established. Nothing about the second task explicitly required they use the skills acquired in the first, but TD participants evidenced a performance peak in the area near the boundary, whereas those with ASD appeared to perform the discrimination task autonomously from the first one. Thinking this might be attributed to a need for a longer training period, another study controlled for this. They used random patterns of dots as a prototype, however, they trained participants on slightly distorted versions of the pattern so as to never display the actual prototype. Subsequent testing was conducted on patterns at a variety of levels of distortion which included the prototype. Participants were trained until they reached a minimum performance. Members of both the groups could learn the categories, but the ASD group did so more slowly. ASD categorization was comparable to TD across the distortion manipulation. However, two versions of this experiment were conducted. In the first, all the dot locations were different on testing than they were in training. In the second, a subset of the locations remained the same. In the first, ASD performance was lower compared to TD, even though performance across distortion conditions was comparable. In the second experiment, ASD and TD performance was equivalent. This might be explained by stronger ASD skills in responding to the local stimulus level, that is, they may have achieved their performance by learning the exact location of the dots (Vladusich, T. et al., 2010).

A comparison of analogic reasoning in children 11-16 – using complex non-representational designs, objects, and scenes found no differences between groups (Morsanyi, K. & Holyoak, K.J., 2010). However a factorial analysis on a battery of instruments measuring higher reasoning
produced factors which dissociated concept formation from identification in persons with ASD, but not for the TD group. Identification for those with ASD could be further subdivided into attribute identification and rule learning. So, while it appeared that individuals with ASD were capable of abstract thinking, once they identified the criteria to apply, they used them as fixed rules. Such lack of flexibility in ASD limits ability to generalize (Minshew, N.J. et al., 2002).

Similarly, a comparison of narrative comprehension in four to seven-year-olds was conducted using three categories of questions regarding short paragraphs: detail questions, main idea questions, and inferential questions. TD and ASD groups showed no differences in processing the details of the story, and showed equal capability to extract the main idea when cued to do so. However, children with ASD were not able to use their understanding of the main idea to make inferences about story details as TD children did (Nuske, H.J. & Bavin, E.L., 2011).

Spontaneous use of conceptual prototypes requires both low- and high- level information. It is impacted by both the application of a general relational rule and the interference of individual exemplars, so integration of local and global levels again is key. How might connectivity play into these abstract processes? Fiebelkorn et al (2012) tested categorization using an established electrophysiological index of object-based selective attention. This phenomenon confers processing advantages such as greater accuracy and quicker reaction time in a search task for any stimulus, whether it is declared a target or not, as long as it falls within the boundaries of an attended object. If you recall, earlier we described this effect as providing us with a definition for an object. Enhanced neural processing measured with this effect has been localized to the LOC and the advantage can be seen whether the stimulus falls within real object boundaries or those created by ICs (Egly, R. et al., 1994; Martinez, A. et al., 2006). Like an object – a category functions to generalize the processing of any exemplar which falls within its bounds.
This can be seen in an electrophysiological marker 200 ms following stimulus presentation over lateral occipital scalp locations (Molholm, S. et al., 2004; Molholm, S. et al., 2007). In a target detection task of objects in a category – say correctly responding to a particular breed of dog when presented with images of many dogs – the electrophysiological response is the same regardless of which dog is viewed. This is a neural expression of how categories function to subsume the diverse exemplars under their aegis. While ASD and TD participants demonstrated identical accuracy and reaction times in this task, ASD indices of object-based attention did not generalize to category. Their responses differed at the exemplar level and, unlike TD individuals, were much stronger over right- than left-hemisphere locations, pointing to another example of possible reduced cooperation between hemispheres.

Many of my Asperger’s traits are double-edge swords, gifting me simultaneously with challenges and strengths. Impaired perspective taking? It makes it harder for me to work out people’s intentions but it also makes me nonjudgmental. Trouble with generalizing? That means I have to learn a similar lesson many times over, but gifts me with a dogged optimism and unconventional problem solving skills. – Aspie Strengths and Superpowers, Dec 21, 2012 blog Musings of an Aspie

When Kanner described his first autistic patients, he wrote “a sentence is not regarded as complete if it is not made up of exactly the same elements that were present at the time the child was first confronted with it. If the slightest ingredient is altered or removed, the total situation is no longer the same and therefore is not accepted as such” (Kanner, L., 1943). Without the ability to generalize, every instance becomes its own unique exemplar. We have observed many instances where persons with ASD, although they have the ability to make generalizations based upon prior knowledge, don’t spontaneously apply that knowledge to new scenarios when it would be optimal. If they do, it tends to be in the form of hard and fast rules. A question is, at
what level of cognitive processing is this pattern instantiated? One could say that we see an analogous pattern in sensory processing. There, in cases where incoming sensory stimuli would typically be integrated with and/or modified by prior knowledge, that sometimes does not occur to the same degree or in the same way. At both the sensory and higher cognitive levels, it is feedback that is implicated in the application of prior knowledge. Is feedback a common dysregulated mechanism?

Many autism investigations examine higher cognitive processes – unsurprising, as that is where dysfunction is most visible in daily life. More basic processes such as perception are studied, but so often we are left only with a conceptual framing for the differences we see. Only with electrophysiological measures can we hope to understand the differences on the spatio-temporal scale that they occur in the brain. The experiments that follow use ERP to look at contour completion processes in ICs as a metric of early, automatic feedback contributions to the binding of elements during the formation of objects. We wish to understand:

1) Whether the parameters of the elements that comprise ICs cue contour completion. To the extent that varying contour length, support ratio or inducer size affect the spatio-temporal dynamics of classic completion markers, what can this tell us about feedback contributions to the grouping of visual features? To the extent that they remain stable, what might we infer about invariance to features?

2) How does contour integration develop across childhood and adolescence? Are the dynamics similarly variant or stable in response to a manipulation of contour extent? What does this say regarding the development of feedback processes in vision?

3) Given an atypical integration of global and local information in ASD, do spatio-temporal dynamics of contour completion develop atypically? What does this imply about the
integration of prior knowledge with basic processing of sensory elements? What is the role of feedback processes in potential differences between neurotypical persons and persons with ASDs?
Chapter One – Figures

Figure 1.1 Caption
Grating Stimuli – Luminance-defined (left) and contrast-defined (right)

Figure 1.2 Caption
Texture-defined ‘stack and frame’ stimulus
Figure 1.3 Caption
Hierarchical stimuli

Figure 1.4 Caption
Gestalt grouping examples

Figure 1.5 Caption
Intact image and fragmented scrambled versions
Reprinted from Vision Research 45(13), Hershler O, Hochstein S., At first sight: A high-level pop out effect for faces, pp 1707-24, Copyright (2005), with permission from Elsevier.
Figure 1.6 Caption

Tilt illusion

The original source of this image was Song, C., Schwarzkopf, D.S., Rees, G. (2013) Variability in visual cortex size reflects tradeoff between local orientation sensitivity and global orientation modulation. *Nat Commun.* 2013; 4:2201. Doi: 10.1038/ncomms3201. Copyright (2013). It was reprinted under the terms of the Creative Commons license (Attribution 3.0 Unported (CC BY 3.0))

Figure 1.7 Caption

Color-spreading illusory stimulus

Figure 1.8 Caption

Example of degraded picture stimulus at fragmented and fully filled-in levels from stimulus sets below:


Figure 1.9 Caption
Theoretical framework schematic

Figure 1.10 Caption
Gabor path stimuli

Reprinted from *NeuroImage*, 69(1April 2013), Shpaner M, Molholm S, Forde E, Foxe JJ., Disambiguating the roles of area V1 and the lateral occipital complex (LOC) in contour integration, Pp 146-56, Copyright (2013), with permission from Elsevier.
Figure 1.10
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Chapter Two
Early Electrophysiological Indices Of Illusory Contour Processing Within The Lateral Occipital Complex Are Virtually Impervious To Manipulations Of Illusion Strength.

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Reprinted from NeuroImage 59(4) Altschuler TS, Molholm S, Russo NN, Snyder AC, Brandwein AB, Blanco D, Foxe JJ, Early Electrophysiological Indices Of Illusory Contour Processing Within The Lateral Occipital Complex Are Virtually Impervious To Manipulations Of Illusion Strength, Pp4074-85, Copyright (2012), with permission from Elsevier.
INTRODUCTION

The visual system can readily interpolate object identity under less than optimal viewing conditions, permitting us to bridge gaps in the contours of incomplete or obstructed objects, a process termed “perceptual completion” in the cognitive neurosciences. Using illusory contour (IC) stimuli, first described by Schumann (1900) and subsequently by Kanizsa (1976), a well-studied stimulus class whose processing time-course in humans has been carefully detailed using visually-evoked potentials (VEPs) (e.g., Murray, et al., 2002; Foxe, et al., 2005), we sought to better understand the limits of perceptual completion by explicitly taxing IC processing. In a series of three experiments manipulating key features of this canonical stimulus class – spatial extent, support ratio, and inducer size – we aimed to systematically vary the strength of the illusion while concurrently measuring cortical processing using high-density VEP recordings.

ICs can be induced using Pac-man-shaped disks (Figure 2.1a), oriented so that the contours of their “mouths” are relatively closely aligned. When aligned and placed not too far from one another, typical viewers perceive a two-dimensional object of homogeneous and somewhat increased luminance superimposed upon the background (though no luminance difference physically exists). This illusory object’s contours give the impression that they continue the real contours of the mouths of the inducers, despite a physical gap between them (Peterhans & von der Heydt, 1989; Ringach & Shapley, 1996; Murray, et al., 2002; Halko, et al., 2008). In other words, we perceive a square (or another shape, depending on the configuration of the inducers) even though only four Pac-men exist. The perception of such a shape could be considered an error of processing as it is essentially an inaccurate representation of the existing physical stimulus. However, this error provides an excellent window onto fundamental operations of the visual system as it works to analyze the confusion of inputs impinging on the retina, producing
both different perceptions and different VEPS. This affords researchers the opportunity to parse object processing into its constituent parts.

VEPs, with their exquisitely fine temporal resolution, have been extensively used to study IC processing on a millisecond timescale (Sugawara & Morotomi, 1991; Herrmann, et al., 1999; Murray, et al., 2002; Murray, et al., 2004; Foxe, et al., 2005; Murray, et al., 2006; Shpaner, et al., 2009; Fiebelkorn, et al., 2010). They have revealed two dissociable phases of object processing, comprising what are thought to reflect temporally dissociable perceptual and conceptual modes (Tulving & Schacter, 1990; Doniger, et al., 2001). Sensitivity to ICs is first measurable as a difference between visually evoked potentials (VEPs) during the onset phase of the N1 component, beginning at ~ 90ms and peaking at ~ 150 ms, during which contour-forming configurations (Figure 2.1a) evoke a substantially more negative amplitude over lateral occipital scalp sites than non-contour forming configurations (Figure 2.1b). Hereafter, we will refer to this first phase of IC processing as the “IC-effect” (Figure 2.1c) (Murray, et al., 2002). This effect has been localized to a cluster of ventral stream regions known as the lateral occipital complex (LOC) (Murray, et al., 2002; Sehatpour, et al., 2006; Fiebelkorn, et al., 2010), a system of areas associated with object processing (Malach, et al., 1995; Grill-Spector, et al., 1998; Sehatpour, et al., 2008; Lucan, et al., 2010). It has been associated with automatic completion of object boundaries, accomplished without reference to stored representations (Murray, et al., 2002; Foxe, et al., 2005; Shpaner, et al., 2009).

The second temporally dissociable processing phase associated with completion of IC images and fragmented objects is observed from ~230 extending to 400 ms. This phase is evoked when initial input is insufficient for object recognition, as with objects degraded by obstruction or novel orientation (Doniger, et al., 2000; Doniger, et al., 2001; Doniger, et al., 2002; Foxe, et al.,
During this process, sensory information is believed to be actively compared with existing representations of objects, filling-in the missing information, a completion process historically referred to as “perceptual closure” (Bartlett, 1916; Snodgrass & Feenan, 1990). This second VEP component has been termed the N_{cl} (negativity for closure) (Doniger, et al., 2000). Both the IC-effect and N_{cl} have been source-localized to the LOC (Sehatpour, et al., 2006; Sehatpour, et al., 2008) pointing to the fact that these two separable phases of object processing are achieved within the same cortical structures.

Recent work supports a model of IC processing whereby early object segmentation is accomplished automatically during the perceptual stage, via the completion of contours (Shpaner, et al., 2009). What is less clear, since no complete contours exist in ICs, is upon what parameters boundary completion is dependent. Retinal extent has been measured as influencing the perceived strength of ICs in behavioral studies in adults (Dumais & Bradley, 1976; Banton & Levi, 1992). Inducer size has also been seen to influence illusion strength (Banton & Levi, 1992). Although Shipley and Kellman (1992) observed no relationship dependent upon extent, they and Hadad et al (2010) found that “support ratio”, the proportion of real contour of one side of the induced shape (equal to the diameter of the inducer) to the entire side of that shape (see Figure 2), influences illusion strength measured either by subjective estimate of magnitude (Shipley & Kellman, 1992) or a shape discrimination task (Murray, et al., 2006; Hadad, et al., 2010) requiring clearly perceived contours. As judgment of illusion strength depends upon contour-based information, using electrophysiological measures one might have expected to see an analogous effect during the N1 window when that contour is said to be established. Yet, Murray et al (2006) observed that, when asked to distinguish whether the contours of an IC square were concave or convex, subjects’ accuracy was uncorrelated with magnitude or
topography of the first phase of the electrophysiological signature of IC processing. Instead, the observed effects of support ratio were seen in the later conceptual phase indexed by the N_{cl}, and then only for IC and not control stimuli. In other words, perceptual judgment was temporally dissociable from the laying down of boundaries, a process which appears largely indifferent to any manipulation carried out thus far.

Behavioral studies have manipulated the perception of ICs via masking and varying the spatial extent (Ringach & Shapley, 1996), support ratio (Shipley & Kellman, 1992), occlusion of contours, and whether inducers are moving or static (Halko, et al., 2008). We wished to understand how vulnerable the early phase of object processing is to manipulation of basic contour parameters independent of task obligations. We hypothesized that the limits of the automatic boundary completion phase of object recognition are a function of contour-related parameters and are likely to be revealed as a variation in IC-effect amplitude or latency. VEP paradigms have varied shape, contrast, support ratio, and laterality of presentation (Murray, et al., 2002), but they have not specifically or systematically investigated the impact of these parameters. The following series of three experiments was designed to examine the effect of retinal eccentricity, ratio of real to illusory contours, and inducer diameter while measuring the amplitude and latency of the IC-effect. Shape, luminance, and location of the IC within the visual field were unvarying.

**METHODS & MATERIALS**

This study comprises three experimental manipulations of spatial extent, support ratio, and inducer diameter of Kanizsa-type illusory squares. Details for stimulus manipulations are described in succession (Figure 2.3a). The parameters are inescapably intertwined, e.g., if
eccentricity is parametrically increased, as is true in Experiments 1 and 3, to hold support ratio constant, the third parameter must also vary. Each of the three experiments thus varies two of three variables, holding the third constant. The paradigm time course is depicted in Figure 2.3b.

**Experiment 1: Manipulation of eccentricity and inducer diameter with constant support ratio.**

*Participants*

Twelve neurotypical adults (9 female), compensated with course credit or a modest stipend, aged 19 – 31 years (mean (SD) = 23.3 (3.4)) participated. All were recruited from the City College of New York (CCNY) community, reported normal or corrected-to-normal vision, and had normal color vision (Ishihara, 2008). All but one were right-handed (Oldfield, 1971) and all provided written valid consent. The study conformed to the principles outlined in the Declaration of Helsinki and the CCNY Institutional Review Board approved all procedures.

*Stimuli & Task*

Subjects were comfortably seated in a dimly-lit, sound-attenuated booth 60 cm from a computer monitor. They viewed four black Pac-man-shaped disks, presented against a gray background, arrayed like the number four on a die centered on the screen. These randomly took one of two orientations - either with the 90° angle that comprises their “mouths” pointed toward the center point of the array, equidistant from their vertices, such that they induce in a typical viewer the perception of a Kanizsa-type (Kanizsa, 1976) illusory contour square (IC); or with three of the four inducer mouths rotated away from the center (No-IC). The location of the fourth, non-rotated inducer in the No-IC condition varied randomly. This was done to prevent subjects adopting a spatial strategy to perceive the difference between conditions. The amount
of rotation for the other 3 inducers was generated randomly across a range from 20° - 180° for each of the three inducers. These orientations were held consistent thereafter for all presentations of the No-IC condition. Stimuli were generated in MATLAB 7.4.0. Three parametric levels of retinal eccentricity subtended approximately 4°, 7°, and 10° of visual angle. The inducers were 2.1°, 3.8°, and 5.6° in diameter respectively (approximated as though the inducers were viewed foveally). The resulting support ratio (Ringach & Shapley, 1996) – i.e., the proportion of real contour of one side of the square (equal to the diameter of one inducer) to entire side of that square (the portion between the center of the inducers, see Figure 2.2) – was held constant for the three eccentricity levels at 54%.

Stimuli were presented for 500 ms with a stimulus-onset asynchrony (SOA) varying from 800 – 1400 ms with a square distribution. Subjects were not required to explicitly attend to stimuli as Murray et al (2002) previously showed that explicit attention to IC stimuli is unnecessary to elicit the IC-effect. Ten 3-minute blocks were administered with short breaks, as necessary, to recover from fatigue.

A simultaneously-presented task ensured that participants attended to the center of the screen. This required fixation on a centrally presented red dot, 4 pixels in width and height. The dot changed to green for 160 ms every 1-10 seconds with inter-stimulus-interval (ISI) varied pseudo-randomly on a time-scale uncorrelated with the presentation of the IC stimuli. Random co-occurrence of the color change and IC presentation was < 1%. The 2 colors were selected from a single isoluminant plane of DKL color-space (Derrington, et al., 1984), in which color isoluminance can be approximated via chromatic response of macaque lateral geniculate nuclei neurons. The color shift employed was, for all practical purposes, imperceptible without foveating, due to multiple mechanisms including the relative paucity of cone receptors in
peripheral retina (Moreland & Cruz, 1959). Subjects clicked the mouse button with their right index finger for each perceived color change. Average performance for the fixation task ranged from 94 – 100% (Mean (SD): 98 (2)). Instructions focused exclusively upon the fixation task, making no mention of inducers or the illusion they might produce. No formal measure of participants’ awareness of the IC stimuli was taken, but this was added in Experiments 2 and 3. 25% of the subjects in Experiment 1 participated in Experiments 2 and 3. 100% of the participants in Experiments 2 and 3 demonstrated during debriefing that they could perceive illusory contours without any reference having been made that such an illusion might be induced.

Data acquisition and analysis

Continuous EEG was acquired through a Biosemi ActiveTwo system from 64 scalp electrodes, digitized at 512 Hz and referenced to the Common Mode Sense (CMS) which is actively recorded, and the Driven Right Leg (DRL), a passive electrode, that form a feedback loop that acts as a reference. Epochs of continuous EEG (-150 msec before stimulus onset to 1000 ms after) were averaged from each subject in response to each of the two conditions and three levels of stimulus using BESA 5.1.8 EEG software. An artifact rejection criterion of ± 100 μV was applied to reject trials with eye blinks and movement, electrical signals produced by muscle movement or electromyography (EMG), or other sources of noise. An average of 175 ± 50 trials per condition was accepted per subject. Each of the six conditions was averaged, baseline-corrected across an epoch of -80 to +20 ms, and low-pass filtered at 45 Hz with a 24 db/octave roll-off.

Two analyses were planned at the pair of parieto-occipital electrodes of maximal response (PO3 and PO4, based on previously well-characterized topographies for the IC-effect (Murray, et
al., 2002; Foxe, et al., 2005). The first examined the impact of the parameter manipulation on the amplitude of the IC-effect and the other on the peak latency. As this is a well-described effect which this study explicitly tried to modulate, a 20 ms time window surrounding the effect peak was derived from the grand average waveform of each level of retinal eccentricity using MATLAB 7.4.0. These data were referenced to electrode AFz to maximize visualization of a parietal-occipital effect. The latency analysis compared IC-effect peaks, identified as the negative most point derived from individual subject difference waves in a time window of 120 – 220ms. In response to reviewers’ comments, an additional analysis of peak latency was conducted on separate IC and No-IC conditions in order to distinguish effects specific to ICs from effects on the overall N1. Both were analyzed with a repeated-measures ANOVA in SPSS 15.0 with within-subjects factors of IC condition (IC vs. No-IC), parametric level (eccentricity of 4°, 7°, and 10°), and hemiscalp (PO3, PO4). Significance criteria was α < 0.05.

An estimate of onset latency of the IC-effect was also made using point-wise paired t-tests, calculating the first time point where the t-test exceeded the 0.05 alpha criterion and remained so for 15 consecutive time points. The requirement of 15 consecutive time points controls for inflation of type I error due to multiple comparisons (Guthrie & Buchwald, 1991). Because adjacent time points in EEG do not change arbitrarily fast, they are not independent. Consequently, we computed the temporal autocorrelation of the noise in the baseline at a representative electrode for all subjects to determine the lag at which such dependence does not differ from zero (with 95% confidence). This was 15 time points. Of the three experiments, these data were the noisiest, requiring the highest number of consecutive time points. As this was the most conservative requirement, it was applied across all three experiments. The results are displayed as a statistical cluster-plot, plotting estimated latency and scalp region on the x and
y axes respectively; $t$-test results are color-coded, as indicated in Figure 2.6a. These average onset latencies are more susceptible to the vagaries of signal-to-noise ratio than are the peak onsets and are most usefully interpreted as estimated pictures of onset across scalp regions.

**Experiment 2: Manipulation of inducer diameter and support ratio with constant eccentricity.**

*Participants*

Eleven (5 female) neurotypical adults, compensated with course credit or a modest stipend, aged 20–34 participated, one of whose data was excluded due to excessive noise. Ten subjects (4 female) aged 20 – 34 (mean (SD) = 26.8 (5.5)) data were ultimately analyzed, 25% of whom also participated in Experiment 1. They were recruited from the CCNY community, reported normal or corrected-to-normal vision, and normal color vision (Ishihara, 2008). All but one were right-handed (Oldfield, 1971) and all provided written informed consent. The study conformed to the principles outlined in the Declaration of Helsinki and the CCNY Institutional Review Board approved all procedures.

*Stimuli & Task*

Black Pac-man-shaped inducers oriented in either the IC or No-IC condition, as described for Experiment 1. Three parametric levels of illusory squares, and a non-shape-inducing counterpart, were used. Inducers subtended 2.1°, 3.8°, and 5.6° of visual angle in diameter (approximated as though centered), producing support ratios of 31, 55, and 79%. Eccentricity was held constant at 7° of visual angle.

Stimulus duration, SOA, number and length of blocks were identical to Experiment 1, as was the central fixation task. Experiments 2 and 3 were administered together, their order counterbalanced across subjects. Average performance for the fixation task ranged from 93 –
100% (Mean (SD): 98 (2)). Subjects were not required to explicitly attend to Kanizsa stimuli. At debriefing, participants received a verbally administered questionnaire probing their awareness of any stimulus besides the color dot of the fixation task. All but one of the participants claimed awareness of other visual information besides the colored dot. When specifically prompted for other “shapes” all but one described something that approximated the inducers or illusory squares. When shown printed images of IC and No-IC conditions of induced triangles and asked what they saw, 100% indicated that they perceived triangles regardless of the order of administration of the conditions. When shown printed IC and No-IC conditions in the square configuration and asked to identify the “square,” 100% of participants pointed to the IC stimulus that resembled the one seen in the experiment.

Data acquisition and analysis

Continuous EEG was acquired in an identical manner to Experiment 1. An artifact rejection criterion of ± 100 μV was applied to all but one subject to reject trials with eye blinks and movement, excessive EMG, or other sources of noise. For one subject with particularly noisy data, the threshold was set at ±120 μV. An average of 220 ± 44 trials per condition was accepted per subject. Each of the conditions was separately averaged, baseline-corrected across an epoch of -80 to +20 ms, and low-pass filtered at 45 Hz with a 24 db/octave roll-off.

Data analysis was carried out at the identical electrodes (PO3 and PO4) for identical effects of the new parameter manipulation on the amplitude and latency of the IC-effect, in an identical manner to Experiment 1 for amplitude and peak latency. Both were analyzed with a repeated measures ANOVA in SPSS 15.0 with within-subjects factors of IC condition (IC vs. No-IC), parametric level (support ratios of 31, 55, and 79%), and hemiscalp (PO3, PO4). Onset latency
was estimated via point-wise paired $t$-tests, and depicted as a statistical cluster plot, as described for Experiment 1.

**Experiment 3: Manipulation of eccentricity and support ratio with constant inducer diameter.**

*Participants*

The eleven participants in Experiments 2 and 3 were identical. Data from ten were ultimately submitted to analysis.

*Stimuli & Task*

Black Pac-man-shaped inducers, oriented in either the IC or No-IC condition were presented as described earlier. The manipulation of shape parameters changed again. As in Experiment 1 the retinal eccentricity of the three parametric levels of illusory squares subtended approximately $4^\circ$, $7^\circ$, and $10^\circ$ of visual angle. The corresponding support ratios were 54, 30, and 21%. This time the inducer diameter was constant at $2.1^\circ$ of visual angle.

Stimulus duration, SOA, number and length of blocks were all identical to Experiments 1 and 2, as was the fixation task. Average performance for the fixation task ranged from $95 - 100\%$ (Mean (SD): 98 (.02)) and study instructions confined their focus to this task, making no mention of the IC stimuli or inducers. As this experiment was administered along with Experiment 2, subjects received the debriefing questionnaire described above.

*Data acquisition and analysis*

Continuous EEG was acquired in an identical manner to Experiments 1 and 2. An artifact rejection criterion of $\pm 100 \mu V$ was applied to all subjects to reject trials with eye blinks and movement, excessive EMG, or other sources of noise. An average of $226 \pm 26$ trials per
condition was accepted. Each of the conditions was separately averaged, baseline-corrected and low-pass filtered as above.

Data analysis was carried out at the identical electrodes (PO3 and PO4) for the effects of the third parameter manipulation on the amplitude and latency of the IC-effect as before. Amplitude as well as peak and onset latency analyses were conducted as above. Data was submitted to repeated measures ANOVA using SPSS 15.0, with within-subjects factors of IC condition (IC vs. No-IC), parametric level (4°, 7°, and 10° of visual angle and respective support ratios of 54, 30, and 21%), and hemiscalp (PO3, PO4).

Dipole Source Modeling

We modeled current sources of the IC-effect using the same 20 ms time window used in the original analyses. BESA uses a least squares algorithm which fits signal to dipoles that explain a maximal amount of variance. We constrained the solution to two symmetrical dipoles. Whether they fit LOC location or not, the stability of the best fit model supplied by BESA was challenged by changing locations. Miltner (1994) reports an average 1-2 cm error rate using this method. The average source is reported in Talairach coordinates at the end of the Results section.

RESULTS

Note: significant two-way interactions are only reported if germane to the question of interest. Greenhouse Geiser corrections were applied, as noted, for violations of sphericity.

Experiment 1: Manipulation of eccentricity and inducer diameter with constant support ratio.

The effect of eccentricity on the amplitude of the IC-effect was calculated using the area beneath the curve for the 20 ms window centered on the effect and derived from the grand
average of each eccentricity level. The IC-effect of level 1 of the parameter manipulation (4°
retinal eccentricity/2.1° inducer diameter/54% support ratio) peaked at 164 ms; a window of 154
– 174 ms was used. For level 2 (7° retinal eccentricity/3.8° inducer diameter/54% support ratio)
the window was 155-175 ms, and for level 3 (10° retinal eccentricity/5.6° inducer diameter/54%
support ratio) 153 – 173 ms. These data were submitted to a 2 x 3 x 2 repeated-measures
ANOVA with within-subjects factors of IC condition (IC vs. No-IC), parametric level (4°, 7°,
and 10° of retinal eccentricity), and hemiscalp (PO3, PO4). A main effect of IC condition was
observed ($F(1, 11) = 82.35; p < 0.0000019; \eta^2_{\text{partial}} = 0.88$) (Figure 2.4a) confirming the presence
of the IC-effect (Murray, et al., 2002). There were no main effects of hemiscalp or retinal
eccentricity (Figure 6d). Of most relevance to the experimental question, the IC condition x
eccentricity interaction was not significant ($F(2,22) = 1.46; p = 0.25; \eta^2_{\text{partial}} = 0.12$) (Figure 2.4d)
indicating no measurable effect of eccentricity on the amplitude of the IC-effect.

Peak latency comparisons were calculated on the basis of the peak amplitudes of individual
subject difference waves between the IC conditions. These were submitted to a 2 x 3 repeated-
measures ANOVA with factors of hemiscalp and eccentricity level. No main effects or
interactions were observed. Specific to the question of interest, there was no main effect of
eccentricity ($F_{(2, 22)} = 2.22; p = 0.13; \eta^2_{\text{partial}} = 0.17$) suggesting no effect of eccentricity on peak
latency of the IC-effect. In addition, estimation of onset latency of IC conditions was conducted
using point-wise paired t-tests (see Methods). The near equivalence of the three onset latencies
of the IC-effect is evident in the statistical cluster-plots (Figure 2.5a) (~ 135 – 140 ms across the
3 manipulations) and mirrors the stability of the peak latency. A comparison of peak latency
effects for IC and No-IC conditions yielded no interaction of IC condition x eccentricity ($F(2,22)$)
suggestion that absence of peak latency differences is equivalent in the overall N1 versus the *IC-effect*.

**Experiment 2: Manipulation of support ratio and inducer diameter with constant eccentricity.**

The effect of support ratio on amplitude used the area beneath the curve for the 20 ms window centered on the peak amplitude of the *IC-effect*, calculated from the grand average of each manipulation level. The peak amplitude of level 1 (30% support ratio/2.1° inducer diameter/7° retinal eccentricity) differed by hemisphere, peaking at 191 ms in the left and 186 ms in the right. The amplitude for a 20 ms window centered on the average peak amplitude of the two hemispheres - 178 – 198 ms - was submitted to analysis. For level 2 (54% support ratio/3.8° inducer diameter/7° retinal eccentricity) the peak amplitudes were 180 ms and 188 ms for the left and right hemispheres respectively. The window applied was 174-194 ms. For level 3 (80% support ratio/5.6° inducer diameter/7° retinal eccentricity), the peak amplitude was 164 ms at both electrodes and a window of 154 – 174 ms was used. These data were submitted to a 2 x 3 x 2 repeated-measures ANOVA with within-subjects factors of IC condition (IC vs. No-IC), parametric level (30%, 54%, and 80% support ratio and 2.1°, 3.8°, and 5.6° diameter inducers), and hemiscalp (PO3, PO4). A main effect of IC condition was observed ($F_{(1, 9)} = 45.08; p < 0.000087; \eta^2_{\text{partial}} = 0.83$), again confirming the presence of the *IC-effect* (Figure 2.4b) (Murray, et al., 2002). A main effect of parametric level was also observed (Figure 2.6d) ($F_{(2, 18)} = 18.82; p < 0.000039; \eta^2_{\text{partial}} = .68$), reflecting an overall increase in VEP amplitude relative to support ratio and inducer diameter. No main effect of hemiscalp was observed. Of primary interest, the IC condition x level interaction was not statistically significant (Figure 4d) ($F_{(2, 18)} = 1.04; p = 0.37; \eta^2_{\text{partial}} = .10$).
Post-hoc pairwise comparisons with a Bonferroni correction to adjust for Type I error inflation were conducted to unpack the main effect of parametric level (Figure 2.6d). As it is collapsed across IC conditions, this likely reflects ongoing extrastriate processing of basic sensory characteristics typically visible at N1 latency rather than object identification per se (Murray, et al., 2001; Foxe & Simpson, 2002). It is the presence of a main effect in the absence of an interaction with the IC-effect that makes more distinct the mechanism that may underlie the IC-effect, and is the subject of more thorough treatment in our discussion. The comparisons of level 1 vs. level 3 ($t_9 = 4.78; p < 0.003$) and level 2 vs. level 3 ($t_9 = 4.68; p < 0.003$) were significant. Increasing support ratio and inducer volume increases the amplitude of the N1 but has no impact upon the IC-effect.

Peak latency comparisons were calculated on the basis of individual subject peaks from IC minus No-IC differences waves submitted to a 2 x 3 repeated-measures ANOVA with the factors of hemiscalp and eccentricity level. The effect of interest – a main effect of parameter - was significant (Figure 4d) ($F_{(2,18)} = 9.74; p < 0.003; \eta^2_{\text{partial}} = 0.52$). No interactions were observed. Post-hoc pairwise comparisons with a Bonferroni correction applied to adjust for Type I error inflation revealed significance for the comparison of level 2 vs. level 3 ($t_9 = 3.10; p = 0.038$) and level 1 vs. level 3 ($t_9 = 4.24; p = 0.007$). The latency of the IC-effect, collapsed across hemiscalp, decreased as support ratio and inducer volume increased. The more divergent 3rd condition, with a support ratio of 79% in the IC condition, was mainly responsible for driving this effect. Onset latency of IC conditions, as represented in the statistical cluster-plots (Figure 2.5b), covers only an 11 ms range: ~152 ms for level 1, ~144 ms for level 2, and ~141 ms for level 3. The difference is small, but mirrors the direction seen in peak latency. A 2 x 3 x 2 repeated-measures ANOVA with within-subjects factors of IC-Condition, parametric level, and
hemiscalp was conducted to disambiguate the origin of peak latency effects. The interaction of IC-condition x level proved nearly significant: $F(2,18) = 3.25; \ p = 0.06$. While it would be inappropriate to run apply post-hoc analyses to the individual conditions, it is evident from a glance at the mean differences between parameter levels that the IC-forming condition drives this effect (IC1: 1 vs 2 = 8.4; 2 vs 3 = 5.3; 1 vs 3 = 13.7; No-IC: 1 vs 2 = 7.8; 2 vs 3 = 0.7; 1 vs 3 = 8.5). The overall N1 varies only 8.5 ms between parameter levels at its maximum, however the IC-forming condition varies nearly 14 ms.

**Experiment 3: Manipulation of eccentricity and support ratio with constant inducer diameter.**

The effect of eccentricity and support ratio on amplitude used the area beneath the curve for the 20 ms window centered on the peak amplitude of the IC-effect, derived from the grand average of each level of the manipulation. Level 1 peak amplitude (54% support ratio/4° retinal eccentricity/2.1° inducer diameter) differed slightly between hemispheres, peaking at 168 ms in the left and 170 in the right. The amplitude for the 20 ms window centered on the average peak of the two hemispheres - 159 – 179 ms - was submitted to analysis. For level 2 (30% support ratio/7° eccentricity/2.1° inducer diameter) the peak amplitudes were 186 ms and 189 ms for left and right hemispheres respectively. The window applied was 178-198 ms. For level 3 (21% support ratio/10° eccentricity/2.1° inducer diameter), the peak amplitude was 199 ms and 197 ms for left and right hemispheres respectively; a window of 188 – 208 ms used. These data were submitted to a 2 x 3 x 2 repeated-measures ANOVA with within-subjects factors of IC condition (IC vs. No-IC), parametric level (54%, 30%, and 21% support ratio and 4°, 7°, and 10° retinal eccentricity), and hemiscalp (PO3, PO4). As expected, a robust main effect of IC condition was observed (Figure 2.4c) ($F_{(1, 9)} = 64.88; \ p < 0.000021; \ η^2_{\text{partial}} = 0.88$). A main effect of parametric level was also observed (Figure 2.6c) ($F_{(2, 18)} = 24.61; \ p < 0.00020$ (Greenhouse
Geisser corrected); \( \eta^2_{\text{partial}} = 0.73 \). There was no main effect of hemiscalp and no interactions were significant. Of the greatest interest to us, the IC condition x level interaction was not significant (Figure 2.4d) \((F_{(2,18)} = 2.15; \ p = 0.15; \ \eta^2_{\text{partial}} = 0.19)\).

Post-hoc pairwise comparisons with a Bonferroni correction were conducted to unpack the main effect of the parametric manipulation collapsed across IC-condition and hemiscalp. As described in Experiment 2, this likely reflects ongoing extrastriate processing of basic sensory characteristics visible at N1 latency independent of IC condition, not object identification per se. It is relevant to our question in that a main effect of these parameters on N1 amplitude in the absence of a modulation of the IC-effect helps clarify the significance of the lack of interaction we originally explored. Statistical significance was revealed for every contrast. Level 1 vs. level 2 \((t_9 = -4.87; \ p < 0.003)\), level 2 vs. level 3 \((t_9 = -3.09; \ p < 0.039)\), and level 1 vs. level 3 \((t_9 = -5.31; \ p < 0.001)\). Thus, increasing eccentricity while decreasing support ratio decreases N1 magnitude but has no detectable impact upon the IC-effect.

Peak latency comparisons were calculated on the basis on individual subject peak amplitudes. No main effect of hemiscalp was observed, but a main effect of parameter was (Figure 2.6d) \((F_{(2,18)} = 16.78; \ p < 0.000077; \ \eta^2_{\text{partial}} = 0.65)\). There were no significant interactions. Post-hoc pairwise comparisons with a Bonferroni correction were conducted to unpack the main effect of parametric level collapsed across hemiscalp. This revealed significance when comparing level 1 with level 2 \((t_9 = -3.42; \ p < 0.023)\) and level 1 with level 3 \((t_9 = -5.40; \ p < 0.001)\), with peak IC-effect latency increasing as support ratio decreased and retinal eccentricity increased. A 2 x 3 x 2 repeated-measures ANOVA with within-subjects factors of IC-Condition, parametric level, and hemiscalp was again conducted to disambiguate the origin of peak latency effects. The interaction of IC-condition x level proved significant: \( F(2,18) = 4.30; \ p = 0.03 \). An analysis of
the individual mean differences, Bonferroni adjusted, showed that, the manipulation was significant between two of the three comparisons in the IC-condition, but was not significant for any comparison in the No-IC condition. IC-condition: 1 vs 2 ($t_9 = 4.4; p = 0.20$); 2 vs 3 ($t_9 = 9.3; p = 0.02$); 1 vs 3 ($t_9 = 13.7; p = 0.01$). No-IC condition: 1 vs 2 ($t_9 = 3.4; p = 0.30$); 2 vs 3 ($t_9 = 2.7; p = 0.93$); 1 vs 3 ($t_9 = 6.1; p = 0.27$). We find no evidence for significant changes in overall N1 latency, but IC-effect latency clearly does change as a function of the manipulation.

Onset latency is represented in statistical cluster-plots (Figure 2.5c). In this case, the largest support ratio (level 1) onset at ~137 ms, level 2 at ~145 – 150 ms, although some fronto-central activity is evident as early as 140 ms. For the smallest support ratio - level 3, parietal and occipital-parietal IC-sensitive activity is not seen until ~175 – 180 ms, however, frontal and fronto-central activity is evident to the greatest degree in this condition, and onsets at ~140 ms. Onset latency thus increased as support ratio decreased and eccentricity increased, mirroring the pattern of peak latency, in all but frontal scalp regions.

**Signal-to-Noise Ratio Analysis**

In response to a reviewer’s comments, we measured SNR as a means of comparing sensitivity of our measures across experiments. We used the pre-stimulus period as an estimate of background noise, and a window encompassing the N1 and the range of the IC-effect (90- 200 ms) as an estimate of signal. Amplitudes were averaged across the conditions and levels of each experiment and squared to yield a rectified value for each subject. These were averaged across time points and electrodes of interest. Signal was divided by noise and converted to decibels in order to be scale-invariant. The resulting SNRs were compared using a two-sample Kolmogorov-Smirnov test. The mean (SD) of SNRs across the subjects of each experiment
were: Experiment 1 = 19.03 (3.75); Experiment 2 = 23.60 (4.01); Experiment 3 = 21.83 (3.30).
All three SNRs are extremely robust, pointing to the high sensitivity of our measures. The comparison of SNRs for Experiments 1 and 2 did reach significance \( p = 0.05 \), however, the comparison of Experiment 1 and 3 \( p = 0.49 \) and Experiments 2 and 3 \( p = 0.68 \) did not. In latency comparisons for all experiments, our effect size \( \eta^2 \) exceeded Cohen’s threshold for a large effect (0.1379) (Cohen, 1988) in every case.

**Dipole Source Model**

The average of the modeled dipoles of the IC-effect (averaging the solutions across conditions and experiments) are depicted in transparent cartoon brains as well as superimposed on an MRI representation of an axial slice within Talairach space (Figure 2.7). The colored dots correspond to modeled locations. For reference, Mendola et al (1999), Murray et al (2002), and Wu et al’s (2011) coordinates from their fMRI experiments of LOC response to Kanizsa-type ICs across multiple configurations, and Spiridon et al’s (2006) study of object vs. scrambled object stimuli, which differentiates anterior and posterior portions of the LOC, are depicted in black. The LOC is generally described as composed of both dorsal-caudal (lateral occipital) and ventral-anterior (posterior fusiform with possible overlap of ventral occipital areas) regions. It is situated in the lateral occipital sulcus extending into the posterior inferior temporal sulcus (Grill-Spector, et al., 2001; Grill-Spector & Malach, 2004). As can be seen in the composite diagram, our averaged coordinates fall well within the bounds described in the fMRI literature. The average distance (SD) between each condition’s coordinates and the average is 1.54 (0.57) cm. Taking into account the spatial resolution of ERP and the error rate of such estimates, these data support our interpretation of the modeled locations as within lateral occipital complex.
DISCUSSION

We set out here to investigate the extent to which early electrophysiological signatures of illusory contour processing in humans were modulated or delayed as a function of parametric manipulations associated in numerous studies with perception of illusion strength. The stimulus class we employed is a much-used proxy of basic object processing because, while providing two equivalent conditions at the physical stimulus level which differ only in their configuration, one induces perception of an object and the second does not. This perceptual contrast is indexed by a highly robust electrophysiological difference between signals that peaks at ~150 ms - the IC-effect. It is associated with the automatic establishment of object boundaries, and has been definitively localized to visual object processing regions of the human lateral occipital complex.

What precisely does this processing stage represent? Recent VEP work specifies the mechanism behind this earliest object processing stage as specifically reflecting contour integration processes (Shpaner, et al., 2009). We therefore hypothesized that manipulation of the basic contour parameters of retinal extent and support ratio would be reflected in a variation of the amplitude and/or latency of the IC-effect. With this information we hoped to better understand the processes underlying the effect and what they explain about the limits of the visual system’s ability to interpolate object contours from incomplete information at this automatic stage of processing. We remind the reader that the participants in Experiment 1 overlapped 25% with the identical samples of Experiments 2 and 3. Our comparisons of results are interpretive; explicit statistical comparisons among the three experiments were not conducted.
Parametric variations of illusion strength and the amplitude of early IC processing effects

Much to our surprise, no matter which manipulation was applied, the IC-effect was observed under all studied conditions. This was so despite subjects’ attention to an orthogonal task, and the fact that no explicit mention of the illusion was ever made. Still, decreasing support ratio (i.e. increasing the relative extent of illusory contour to be interpolated) delayed the latency of the IC-effect but not the overall N1, whereas its amplitude was invariant to manipulation of absolute or relative spatial extent of contours. This was so notwithstanding concurrent large-scale changes in the overall VEP amplitude during the same processing time frame, independent of IC condition, which rules out potential explanations of the current findings based on a lack of sensitivity of the measures used.

Two retinal eccentricity variations were explored. In one, inducer volume changed to hold support ratio constant and in the other support ratio varied, leaving inducer volume constant. As the extent of a perceived contour increases, one might expect a greater number of cells to be activated and a concomitantly larger VEP to result. Yet despite increasing across a wide range of visual angles - from 4° to 10° – there was no measured change in IC-effect amplitude. These electrophysiological findings are in accord with the behavioral finding that length of contours does not affect judgment of illusion clarity (Shipley & Kellman, 1992).

However, illusion strength has been observed to change relative to support ratio (Shipley & Kellman, 1992; Hadad, et al., 2010). We manipulated support ratio in two ways. In one case, the inducer volume changed, holding retinal eccentricity constant. Support ratio varied greatly from 30% to nearly 80%. In the second, with inducer volume held constant, the eccentricity varied inversely with support ratio that spanned 21% to 54%. The range encompassed in six
manipulations in two experiments with identical samples varied from nearly complete squares, requiring only 20% of contour length to be filled-in, to a condition in which 80% of the contour was missing. Remarkably, in no case was a significant modulation of the magnitude of the IC-effect measured.

What can explain the invariance of amplitude of the IC-effect to contour manipulation, and how should these results be interpreted in light of previous assertions that the strength of edge interpolation of ICs is determined by support ratio? Whether varying literal contour length or length of real to illusory contour, these quantitative differences are not matched by differences in the amplitude of the IC-effect. It is worth restating that no square actually exists until its contours are induced, and even then its perception is illusory. These results offer a different interpretation from Shipley and Kellman’s because, at the onset of the IC-effect, no object yet exists. Doniger et al’s (2001) temporally distinct perceptual and conceptual modes of object processing offer a reasonable explanation of the present results. They reflect the pre-semantic contribution of sufficient sensory information to suggest that an object exists, but prior to the time when that sensory information is actively compared with semantic memory representations, accomplishing the conceptual identification of the object. The IC-effect appears to capture the binding of the inducers as a single object. Only following the establishment of boundaries relative to the statistical properties of the inducers is the enclosed region segmented from background (Shpaner, et al., 2009). Murray et al (2006) further suggested that the contribution of conscious judgments made about object parameters, such as judgment of illusion strength, occur subsequent to that object’s segmentation from the rest of space. The present study supports this contention. The IC-effect seems to reflect a binary process – contours are completed or they are not. The amplitude of the effect appears to contain no quantitative
information about how much contour is completed, and the perception of a square where only Pac-men exist results because a statistical estimate determines the outcome of this binary process.

But the IC-effect reflects more than an estimate which sometimes produces an “error” in representing nature. Vision permits recognition of a single object from multiple perspectives. This quality of invariant object processing is remarkable given that the sensory imprint of the multiple perspectives on our retina can be vastly different. Previous fMRI and electrophysiological work has linked the LOC to such invariant recognition (Malach, et al., 1995; Grill-Spector, et al., 1998), the same complex of structures to which the IC-effect and the Ncl have been localized (Foxe, et al., 2005; Sehatpour, et al., 2006). The binding of objects from discrete components as reflected by the IC-effect does not vary parametrically as contour parameters are varied, at least not within the ranges explored in these experiments. We see this invariant neural response as a prerequisite for the invariant object processing that is subserved by the LOC.

Changes in the timing of contour processing as a function of the distances to be interpolated

Support ratio did modulate the latency of the IC-effect, perhaps because the amount of missing contour relative to real contour determines how much closure must occur. This is reflected in the amount of time that binding takes. As Experiment 1 held support ratio constant, no significant modulation was observed in peak (Figure 2.4d) or onset (Figure 2.5a) latency. However differences were observed in Experiments 2 and 3, 75% of whose participants differed from Experiment 1. Increasing support ratio and inducer diameter was met with a speeding up of the IC-effect peak latency but the overall N1 was not impacted to the same degree (Figure 2.4d).
this case, the extent of the illusory square did not change but the amount of real contour did.
Thus, the smaller the gap to be bridged relative to real contour, the less processing is required to bind the inducers, and the sooner initial establishment of the boundaries is completed. T-tests reveal that the latency difference between a support ratio of 30% and 55% was just 2 ms, however, level 3 – with a support ratio of 80%, nearly a complete square – was 20 ms faster, driving this effect. The same was true for varying support ratio inversely with eccentricity: the larger the gap to bridge, the later the peak latency. The alternative explanation that we are witnessing a change in the overall N1 is not supported by our comparison of peak latency for IC and non-IC-forming conditions, which show latency differences to be driven by the IC-condition. Inspection of the waveforms further clarifies this (Figure 2.4d).

Analysis of onset latencies in Experiments 2 and 3 indicated that the initiation of IC-sensitivity over lateral occipital scalp regions varied with support ratio: the smaller the ratio the later the onset. One can also observe that relatively large support ratios (> 50%) induce more punctate IC-effects with less subsequent processing, whereas smaller support ratios (< 31%) tend to result in increased object processing in the 300 – 400 ms time window, associated with later conceptual closure processes (Doniger, et al., 2001; Foxe, et al., 2005). This suggests that, with larger relative gaps, more object processing is required following contour completion. It is worth noting that, as support ratios decline, more frontal and fronto-central activity is apparent, onsetting at ~140 ms, suggesting that, as the statistical cues for object presence are less robust, frontal processing is recruited to mediate binding. This finding is highly consistent with previous work suggesting frontal cortex facilitation of object recognition on the basis of context (Bar, et al., 2006; Oliva & Torralba, 2007), as well as work by our own group using intracranial recordings in human epilepsy patients, where a clear role for frontal regions in conceptual-level
object recognition processes was established (Sehatpour, et al., 2008). In this latter study, we found robust beta-band coherence across a network of regions that comprised lateral prefrontal cortex, the hippocampus, and the LOC when participants were processing fragmented but recognizable images.

Statistical cluster plots for three pairs of identical stimuli across experiments evidence nearly equivalent onset latencies, but peak latencies for Experiment 1 level 2 and Experiment 2 level 2 vary by 20 ms. In addition, the amount of processing associated with the later conceptual time frame varies in all three pairs. This could be the result of different samples in Experiment 1 versus 2 and 3, however, it could also be the result of the contextual effects, i.e., the same parameters will not necessarily be identically processed if they are experienced in different contexts – a subject for future studies.

**Modulation of ongoing visual processing independent of contour induction**

Despite the invariance of IC-effect amplitude as a function of the parametric manipulations employed across the three reported experiments, clear effects were apparent during the N1 processing timeframe when responses were collapsed across IC condition for the second and third experiments. The presence of these modulations makes clear that the parametric variation in inducer size and spatial extent did result in systematic modulations of the VEP during the N1 processing timeframe, attesting to the sensitivity of our measures to the stimulus manipulations. We begin with Experiment 1 in which retinal eccentricity and inducer diameter were varied but no modulation of the VEP was observed. It is apparent to the eye (Figure 2.3a) that in this case, larger inducers create more contrast relative to the background than smaller ones, and on the face of it one might expect this to result in activation of more sensory neurons and a concomitant
increase in cortical neural activity. However, since the inducers move outward from central space as they grow in this experiment, the so-called cortical magnification factor comes into play (Tootell, et al., 1988). That is, as the neural representation of foveal visual space is considerably magnified in the cortex relative to the periphery (Rovamo & Virsu, 1979; Qiu, et al., 2006), as the inducers occupy increasingly peripheral space, relatively fewer neurons are likely to fire. Hence, a plausible explanation for the lack of modulation of the VEP during the N1 processing timeframe in Experiment 1 (Figure 2.6d) is that the increased neural activation to be expected from larger inducers was counteracted by their decreased representation as they moved outward from central space. This was likely further impacted by the fact that the regions of early visual cortices that process peripheral locations are located deeper and deeper along the calcarine sulcus, and therefore further and further from the sensors at the scalp surface. In Experiment 2, varying support ratio and inducer diameter, the inducers’ position in space does not vary between conditions. Without offsetting the decrease in activation due to cortical representation, increased activity due to increased inducer size would be expected (whereas support ratio, which only exists in one IC condition and not the other, is irrelevant here). The modulation of the VEP as a result of the experimental manipulation in Experiment 2 bore this out (Figure 2.6d). As inducer size increased, so did VEP amplitude. In Experiment 3 in which there was manipulation of eccentricity and support ratio, progressively decreasing neural representation resulted from increasingly peripherally located inducers that was not counteracted by a change in inducer size as in Experiment 1. A decrease in VEP amplitude as inducers moved outward from central space was indeed what was observed (Figure 2.6d).

In contrast to these inducer related modulations of the amplitude of the N1 as a function of inducer size or spatial extent, none of the manipulations altered the amplitude of the IC-effect.
This lends support to the speculation that the mechanism underlying the *IC-effect* reflects the binding of the inducers as *objects* (in this case, squares), and is blind to any variations in contour related parameters.

**Conclusion.** In summary, the present results offer further support for dissociable perceptual and conceptual phases of early object processing. During the first of these, indexed by the *IC-effect*, it appears that components determining object contours may be bound as long as minimal statistical characteristics of contour extent relative to object size are satisfied. It is apparent that these processes take longer when a gap of greater relative extent must be bridged. Possible contextual effects are suggested and remain to be examined in future studies.

**Acknowledgements**

This study was supported by a grant from the U.S. National Institute of Mental Health (NIMH) to JJF and SM (RO1 - MH085322). Mr. Altschuler is supported by a Robert Gilleece Fellowship through the Program in Cognitive Neuroscience at City College of New York. Mr. Snyder is supported by a Ruth L. Kirschstein National Research Service Award (NRSA) pre-doctoral fellowship from the NIMH (F31 – MH087077). The authors would like to express their gratitude to Dr. Hilary Gomes, Ms. Snigdha Banerjee, Drs. Manuel Gomez-Ramirez, Hans-Peter Frey and John Butler for their valuable support and input during this study.
FIGURES

Figure 2.1 Caption
(a) Kanizsa type Illusory-contour square in contour-forming configuration (IC). (b) Non-contour forming configuration (No-IC). (c) Example of IC-effect from Experiment 1 Level 2.

Figure 2.2 Caption
Support ratio definition
Figure 2.1

(a) IC = (b) No-IC =

(c) IC-effect

Figure 2.2

Support ratio = \[ \frac{\text{Real contour}}{\text{Illusory contour}} \]
Figure 2.3 Caption
a) Three Experimental manipulations.  b) Paradigm time-course.
Figure 2.3

(a) Experiment 1  Experiment 2  Experiment 3

Level 1

- Eccentricity: 4°, 7°, 4°
- Inducer Diameter: 2.1°, 2.1°, 2.1°
- Support Ratio: 54%, 30%, 54%

Level 2

- Eccentricity: 7°, 7°, 7°
- Inducer Diameter: 3.8°, 3.8°, 2.1°
- Support Ratio: 54%, 64%, 30%

Level 3

- Eccentricity: 10°, 7°, 10°
- Inducer Diameter: 5.6°, 5.6°, 2.1°
- Support Ratio: 54%, 79%, 21%

(b)
Figure 2.4 Caption
Main Effect of IC-Condition (IC-effect) & Interaction of IC-Condition x Manipulation - Main effect wave forms show IC condition (black) & No-IC condition (red) from -150 to +500 ms. Electrode PO4 is shown in all cases as it is maximal and representative and there is no statistical difference between hemispheres. Waves are referenced to electrode AFz
(a) Experiment 1 IC condition main effect. (b) Experiment 2 IC condition Main effect. (c) Experiment 3 IC condition main effect. (d) IC condition x manipulation interaction for three experiments.
Figure 2.4
Figure 2.5 Caption
Statistical Cluster Plots Comparing IC Conditions - Color values indicate the result of point-wise paired t-tests for 15 consecutive points (see Methods), comparing IC Conditions over a -15 to +500 ms time period (x-axis) and scalp region (y-axis). $\alpha = 0.05$. baselined from -80 to +40 ms, referenced to AFz. The red line aids in comparing onset latencies. Statistically significant peak latency comparisons were observed in Experiment 2 between levels 2 & 3 and 1& 3 and in Experiment 3 between levels 1 & 2 and 1 & 3. There were no significant peak latency differences in Experiment 1.
Figure 2.6 Caption
Main Effect Of Manipulation Collapsed Across IC Condition - Main effect manipulation collapsed across IC Condition from -150 to +500 ms. Electrode PO4 is shown in all cases as it is maximal and representative; there is no statistical difference between hemispheres. Waves are referenced to electrode AFz. (a) Experiment 1 manipulation main effect topography. (b) Experiment 2 manipulation main effect topography. (c) Experiment 3 manipulation main effect topography. (d) Three levels collapsed across IC condition.

Figure 2.7 Caption
Dipole Source Analysis - “Glass brain” dipole model depictions (modeled dipoles represented in red and blue; reference studies in black); dipoles modeled in MRI axial slice (bottom right quadrant); Table with Talairach coordinates, this study’s model is highlighted in blue.
Figure 2.6

(a) EXPERIMENT 1
Eccentricity &
Inducer Volume

Parameter Manipulation
Level 1

154 ms

(b) EXPERIMENT 2
Support Ratio &
Inducer Volume

Parameter Manipulation
Level 2

165 ms

(c) EXPERIMENT 3
Eccentricity &
Support Ratio

Parameter Manipulation
Level 3

163 ms

(d) Manipulation Level
Collapsed across 1C- condition

Level 1
Level 2
Level 3

Figure 2.7

<table>
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<th>Studies</th>
<th>Talairach Coordinates</th>
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<td>Average Least Squares Dipole Model</td>
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Bibliography


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Chapter Three
The effort to close the gap: Tracking the development of illusory contour processing from childhood to adulthood with high-density electrical mapping

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INTRODUCTION

von Helmholtz observed that vision relies on more than stimulation of the retina, “reminiscences of previous experiences act in conjunction with present sensations to produce a perceptual image.” (von Helmholtz, H., 1910). Poor lighting, occlusion, and the fact that the retina is a variegated and somewhat discontinuous surface produce incomplete, two-dimensional low-level representations of objects. Changes in perspective or viewing distance of a given object result in projection of vastly different images onto this surface. Indeed, the retina contains a so-called blind-spot of nearly 2 mm in diameter where the axons of the optic nerve exit (Quigley, H.A. et al., 1990), and yet, the visual system seamlessly “fills in” the missing information (Pessoa, L. & De Weer, P., 2003). As Helmholtz inferred, perception might be more reasonably characterized as an interaction between relatively impoverished sensory representations and internally-generated representations that have been encoded through experience. Such interpolation of visual input has been observed electrophysiologically during the automatic filling-in of certain types of fragmented contours, with related modulations of brain activity observed within 90-150 ms of stimulus presentation (Murray, M.M. et al., 2002; Proverbio, A.M. & Zani, A., 2002; Foxe, J.J. et al., 2005; Brodeur, M. et al., 2006; Li, W. et al., 2006; Shpaner, M. et al., 2009). The bulk of this processing occurs prior to the viewer’s awareness of the object (Vuilleumier, P. et al., 2001) or the application of semantic knowledge to identify it or make judgments regarding its characteristics (Murray, M.M. et al., 2006). These automatic completion processes have been extensively studied in adults using psychometrics, electrophysiology, and neuroimaging (e.g., Ffytche, D.H. & Zeki, S., 1996; Ringach, D. & Shapley, R., 1996; Mendola, J.D. et al., 1999; Ohtani, Y. et al., 2002; Halko, M.A. et al., 2008). Developmental explorations have studied this process in infancy (e.g., Csibra, G., 2001; Otsuka, Y. et al., 2004; Bremner, J.G. et al., 2012), but the use of fixation duration in such studies allows...
only an implied measure of neural processing. A behavioral study in children suggests that completion processes are still developing from 6 until at least 12 years-of-age (Hadad, B. et al., 2010), however, no one has characterized neural processing using electrophysiology across multiple stages of development. We don’t know whether completion processes are similarly automatic to adults, whether their timecourse is the same, or whether the same regions of the brain are implicated in children.

One of the primary approaches to understanding these contour integration processes has involved the use of a class of stimuli with incomplete contours that nonetheless induce perception of complete contours, known as Illusory contour (IC) stimuli (Schumann, F., 1900; Kanizsa, G., 1976). These stimuli have proven very useful for studying contour completion specifically and the binding of features into objects more generally (Csibra, G. et al., 2000) because simple rearrangements of elements of identical stimulus energy give rise to considerably different percepts (Figure 3.1). In the illusion-inducing configuration, viewers describe continuous contours between inducing elements, contours which form a two-dimensional object that appears to be superimposed on the background. In the non-inducing arrangement, they describe only the inducers. Robust modulation of the visual-evoked potential (VEP) time-locked to the presentation of these conditions provides an index of the neural contributions underlying this perceived change in contour completeness (Sugawara, M. & Morotomi, T., 1991; Herrmann, C.S. et al., 1999; Murray, M.M. et al., 2002; Foxe, J.J. et al., 2005; Fiebelkorn, I.C. et al., 2010).

Electrophysiological investigations have pointed to a two-phase model of contour completion with two temporally distinct phases of processing (Foxe, J.J. et al., 2005; Murray, M.M. et al., 2006). These conform to Tulving and Schacter’s (1990) dissociation of a perceptual phase of functioning from a higher-level conceptual phase (see also Doniger, G.M. et al., 2001; Doniger,
The “perceptual” phase has been associated with a modulation of VEP amplitude during the timeframe of the N1 component (occurring between 90 and 200 ms in adult observers). This manifests as a response of increased negativity for illusion-inducing compared to non-illusion-inducing conditions over lateral-occipital scalp locations. Referred to as the IC-effect, this negative modulation is associated with automatic filling-in of object boundaries (Shpaner, M. et al., 2009). The second “conceptual” phase lasts from approximately 230 to 400 ms and has been seen in response to peripherally presented IC stimuli or to the presentation of fragmented objects that are difficult to identify (Doniger, G.M. et al., 2000; Doniger, G.M. et al., 2001; Foxe, J.J. et al., 2005; Sehatpour, P. et al., 2006) (Figure 2). This latter phase is thought to reflect more effortful processes that rely on active comparison with existing neural representations of objects (Murray, M.M. et al., 2002; Sehatpour, P. et al., 2008). The VEP component associated with this phase is the Ncl (closure-related negativity). Murray et al (2006) differentiated these phases functionally, finding the IC-effect was correlated only with accurate detection of boundary completion and not with discerning differences between ICs of varying shape. Shape judgments were only associated with modulations of the later Nc1l. Both of these processing phases have been source-localized to the lateral occipital complex (LOC) (Pegna, A.J. et al., 2002; Foxe, J.J. et al., 2005; Sehatpour, P. et al., 2006; Sehatpour, P. et al., 2008), a system of ventral visual stream brain regions long-associated with visual object processing (Grill-Spector, K. et al., 1998; Murray, M.M. et al., 2002; Murray, M.M. et al., 2004; Foxe, J.J. et al., 2005; Murray, M.M. et al., 2006; Shpaner, M. et al., 2009; Fiebelkorn, I.C. et al., 2010; Altschuler, T.S. et al., 2012; Knebel, J. & Murray, M.M., 2012; Shpaner, M. et al., 2012).

The main question driving the present study is whether early IC processing is similarly automatic throughout childhood or whether more effortful processes, like those employed by
adults in processing ambiguous stimuli, must be relied upon until some point in childhood. Gamma-band oscillations, thought to index the binding of stimulus features of ICs, have been measured in infants as young as 8 months old (Csibra, G. et al., 2000). This finding seems to indicate that contour integration is in place very early in development. However, subsequent work strongly suggested that gamma-band response measures are often confounded by subtle saccadic eye movements (Yuval-Greenberg, S. & Deouell, L.Y., 2009). Such effects are only likely to be magnified in infancy. In our view, electrophysiology has not yet offered clear evidence as to whether contour completion processes mature with age.

If automatic contour integration relies on reference to global stimulus configuration in the processing of discrete elements, this may reflect a bias that Navon, D. (1977) observed in adult visual processing in general. Adults detect configuration-based differences in visual stimuli more often than differences between local elements. Carey, S. and Diamond, R. (1977) suggested that adults’ ability to encode configuration results in an advantage over children in recognizing previously-seen versus novel faces. This suggests that this strategy may develop from a focus on local elements in childhood to one on global information in adulthood. For example, Mondloch, C.J. et al. (2003) observed that faster processing of global relative to local processing of hierarchical figures (larger shapes composed of the arrangement of smaller shapes) emerged between 10 and 14 years of age. Scherf et al’s (2009) developmental comparison of hierarchical figure processing detected a local bias in children and adolescents through 17 years-of-age, but this could be manipulated by cueing attention to local or global information. Taken together, these paradigms offer a strong suggestion that global versus local strategies for object processing change over childhood, but an unclear picture of the trajectory. This suggests to us that contour completion processing is also likely to alter.
The goal here is to trace the developmental trajectory of perceptual contour completion from 6 years-of-age to adulthood using a cross-sectional sampling approach. A number of clear predictions can be made. If perception of ICs relies on later more effortful processing in earlier childhood, then Phase-one processing (the IC-Effect) may be absent until later in development and IC-processing may instead rely exclusively on later N\textsubscript{cl}-related processes. Perhaps a more likely scenario is that early automatic processing emerges relatively early in development, but is found to be weaker in early childhood with Phase-two N\textsubscript{cl} processing playing a more prominent role for younger children.

Additionally, visual filling-in processes are not impervious to experimental manipulations of inducer parameters. Variations in, for example, retinal extent relative to the size of the shape they induce, have been shown to influence the subjective perception of illusion strength (Shipley, T.F. & Kellman, P.J., 1992; Ringach, D. et al., 1996) and the timing of the IC-effect (Murray, M.M. et al., 2002; Altschuler, T.S. et al., 2012). In Altschuler et al (2012), we systematically manipulated contour length, inducer diameter, and the proportion of real contour to illusory contour – known as support ratio (see Figure 2 in Altschuler et al (2012)). The latency of the IC-effect changed, but only in response to the manipulation of support ratio. Somewhat to our surprise, the amplitude of the IC-effect was entirely invariant to manipulations previously associated with illusion strength. Functional neuroimaging work has associated the LOC with visual processing of objects that is invariant with regard to their size or the perspective from which they are viewed (Malach, R. et al., 1995; Grill-Spector, K. et al., 1998). This is in contrast to hierarchically earlier retinotopic regions which do show sensitivity to variations in stimulus energy, as reflected in amplitude modulations of the C1 and P1 components of the VEP (Di Russo, F. et al., 2002; Foxe, J.J. et al., 2008). In our 2012 study, images of different size,
projecting different images upon the retina, produced indistinguishable activations in LOC neuronal populations. As long as the gap between inducers was not too large relative to the overall size of the potential object, the contour fragments were bound, leading to the perception of a single object. The two-phase model would posit that this occurs via automatic reference to the viewer’s knowledge of similar stimulus configurations.

In the present study, as in our adult study, we manipulated the absolute length of illusory contours (referred to here as “extent”) across a range of 4°-10° of visual angle (Figure 3.1). Although this manipulation resulted in no variation of the IC-effect whatsoever in adults, we reasoned that the human brain does not come “ready-made” to execute such instantaneous references to spatial groupings. Rather, these would likely be tuned via multiple exposures across development to ultimately produce reliable inferences. This is supported by the experience-dependent development of size-invariant object representation in the inferior temporal cortex of non-human primates (Li, N. & DiCarlo, J.J., 2010).

METHODS & MATERIALS

Participants

63 neurotypical individuals (34 female) in four age cohorts participated: 6-9 years of age (N = 16), 10-12 years of age (N= 17), 13-17 years of age (N = 18), and 19-31 years of age (N = 12). Mean ages and standard deviations for each cohort are summarized in Table 3a. All participants reported normal or corrected-to-normal vision, normal hearing, and were tested for normal trichromatic vision (Ishihara, S., 2008). Adults gave written informed consent and those younger than 18 provided assent, with their parent or guardian giving informed consent. The City
College of New York, Montefiore Medical Center, and Albert Einstein College of Medicine Institutional Review Boards approved all procedures and all procedures were conducted in accordance with the tenets of the Declaration of Helsinki (Rickham, P.P., 1964).

All child and young adult participants had a Full Scale IQ > 85 (Wechsler, D., 1999), see Table 3a for summary. They were also screened for receptive (Dunn, L.M. & Dunn, D.M., 2007) and expressive language (Semel, E. et al., 2003), and social communication and daily living skills (Sparrow, S. et al., 2005). Head trauma, seizures, Attention Deficit Disorder, psychiatric, learning, or developmental disorders, or having a first-degree relative with a developmental disorder constituted exclusionary criteria. Adults were not formally assessed but were functioning as undergraduate or graduate students and reported no significant neurological, psychiatric or developmental histories.

Stimuli & Task

Subjects sat in a dimly-lit, sound-attenuated booth 60 cm from a monitor with 1280 x 1024 pixel resolution or 75 cm from a monitor with 1680 x 1050 pixel resolution. They viewed four black Pacman-shaped disks, presented equidistant from central fixation, against a gray background, arrayed like the number four on a die (Figure 3.1). Either the 90° angle that comprised the “mouths” pointed toward the center, such that the perception of an illusory square was induced (IC Condition), or three of the mouths were rotated away from the center (No-IC Condition). These conditions were presented in random order and equiprobably. In the No-IC condition, the location of the non-rotated inducer varied randomly. For the other inducers, the amount of rotation was generated randomly in a range from 20° - 180° and thereafter held
constant for all presentations. Retinal eccentricity was manipulated, with stimuli subtending 4°, 7°, and 10° of visual angle, (calculated for the IC condition) presented in pseudo-random order equiprobably over each block. To hold support ratio (Ringach, D. et al., 1996) constant for the three levels at 54%, inducers were 2.1°, 3.8°, and 5.6° in diameter respectively (Figure 3.1).

Stimuli were presented for 500 ms with an 800-1400 ms stimulus-onset asynchrony varying according to a square wave distribution. Ten to fifteen 3-minute blocks (as necessary to acquire sufficient trials) were administered, with breaks to accommodate fatigue. Task instructions referred only to an orthogonal color detection task which focused participants on the center of the display monitor. Murray et al (2002) have shown that explicit attention to ICs is unnecessary to elicit the IC-effect in adults. These procedures were undertaken to encourage a passive relationship to IC presentation, and avoid biasing participants towards perception of the illusion. Color detection stimuli consisted of a centrally-presented red fixation-square 4 pixels in area. Every 1-10 seconds, the dot changed to green for 160 ms with the inter-stimulus-interval varying pseudo-randomly on a time-course uncorrelated with that of the Pacman stimuli (Figure 3.1). Subjects clicked the mouse button with their right index finger for each perceived color change. The changes were effectively imperceptible without foveating, providing a good measure of fixation. Average accuracy for the fixation task is summarized in Table 3a. 6-9-year-olds performed slightly more poorly than other age groups. Once this became apparent, an Eyelink 1000 eye-tracking camera (SR Research Ltd., Ottawa, Ontario) was used for as many members of the 6-9-year-old cohort as possible (7) to ensure that fixation was not more than 2° from center.

A debriefing questionnaire assessed participants’ ability to perceive the illusion. Printed images of IC and No-IC triangles with an open-ended request to “describe what you see” elicited
an indication that triangles were seen in the IC condition in 93% of participants, regardless of the order of administration of the conditions. When shown IC and No-IC conditions in a square configuration and asked to identify the square, 100% of participants pointed to the IC condition resembling the one seen during the experiment.

Data acquisition

Continuous EEG was acquired through a Biosemi ActiveTwo system from a 72-electrode montage, digitized at 512 Hz and referenced to the Common Mode Sense (CMS) and the Driven Right Leg (DRL). Continuous EEG epochs from -150 ms before stimulus onset to 1000 ms after were averaged for each subject for each condition and level of manipulation using BESA 5.1.8 EEG software (Gräfelfing, Germany). Trials were baseline-corrected across an epoch of -80 to +20 ms and low-pass filtered at 45 Hz with a 24 db/octave roll-off. Given that children’s evoked responses are of larger amplitude and that they also typically show greater levels of background noise, artifact rejection criteria were chosen on an individual participant basis within a range of ±100-150 μV and applied via a BESA-generated algorithm to reject trials with eye or muscle movement, as recommended by Luck (2005). Average number of trials per condition is shown by age cohort in Table 1. Channels with excessive noise were interpolated and three external electrodes were so consistently noisy in younger subjects that they were turned off in all participants and excluded from further analysis. These were the two mastoid leads (M1 and M2) and the nosetip electrode, which wasn’t well tolerated by younger children.

Statistical analyses

Statistical analyses were guided by previous ERP work on IC processing in adults (e.g., Murray, M.M. et al., 2002; Shpaner, M. et al., 2009) which has produced the two-phase model described earlier. Accordingly, the primary analyses were focused relative to the IC-effect over
scalp regions where the visual N1 response was largest in amplitude (lateral occipital scalp represented best at scalp-sites PO3 and PO4), and the early time window was centered on the peak latency of the N1. The later time window was defined relative to the N_{cl}, typically spanning ~230-400 ms and also largest at lateral occipital scalp locations (Doniger, G.M. et al., 2000; Doniger, G.M. et al., 2001; Foxe, J.J. et al., 2005; Murray, M.M. et al., 2006; Shpaner, M. et al., 2012).

Specifically, the first window encompassed the 30 ms window centered on the N1 of the grand average waveform of each age cohort and level of extent. This was identified as the most negative point between 100 and 250 ms averaged across IC conditions (IC and No-IC) and hemiscalp (PO3 and PO4). A 300-400 ms window was chosen to encompass the N_{cl}. Waveforms were re-referenced to an anterior midline frontal scalp site (AFz). These two time windows were subjected to 2x2x3 repeated-measures ANOVAs in SPSS 15.0 with a between-subjects factor of age cohort (6-9, 10-12, 13-17, 19-31), and within-subjects factors of IC condition (IC vs. No-IC), hemiscalp (PO3, PO4), and eccentricity (4°, 7°, and 10°). Significance criterion was set at an α < 0.05. Differences between IC conditions at both latencies were also regressed upon age as a continuous variable and the resulting R^2 values tested for significance. The results are depicted as a scatter plot.

To assess whether our measures were sensitive to the range of contour extent manipulation, a P1 analysis was conducted on the 30 ms window surrounding the first positive peak of the grand average waveforms between 60 and 150 ms for each age group and extent condition at electrodes PO3 and PO4. This employed the same methods as above.
Additionally, we observed that, although the IC-effect was statistically equivalent across age groups, it varied greatly in proportion to the overall amplitude of the VEP. To assess the significance of this relative difference, we ran an additional post-hoc ANOVA on the ratio of the difference between IC and No-IC during the N1 timeframe (the IC-effect) and P1 amplitude.

Onset latency of VEP responses were calculated using point-wise paired t-tests collapsed across eccentricities for each age cohort. This identified the first time point where the t-test exceeded the 0.05 alpha criterion for 11 consecutive time points at 3 adjacent electrodes. The consecutive time points approach is a conservative control for inflation of type I error due to multiple comparisons (Guthrie, D. & Buchwald, J.S., 1991; Foxe, J.J. & Simpson, G.V., 2002). The requirement of 3 adjacent electrodes controls for spurious effects based on the fact that activity at any channel should be correlated with activity at adjacent channels. The results are displayed as a statistical cluster-plot, with latency on the x axis, scalp region on the y axis. T-test results are coded by color. The white dotted line roughly divides scalp areas which are posterior to center from those which are anterior to center.

Dipole source modeling

The intracranial sources of effects were modeled using BESA’s least squares algorithm, fitting two symmetrical dipoles to explain the maximal amount of variance in the overall signal. The latencies analyzed were based on the maximal amplitude effects with the N1 and N_{cl} timeframes, as determined from subtraction waveforms. The stability of the model was challenged by altering the location of the dipoles and re-fitting. Results for the difference between IC and No-IC conditions collapsed across contour extent are shown along with their goodness-of-fit (i.e., percent variance explained) for each age cohort in Talairach coordinates (mm) and the Brodmann Area in which they are estimated to be situated.
Signal-to-Noise (SNR) ratio

SNR was measured by comparing amplitude in a pre-stimulus period as an estimate of noise, to amplitudes in a window of 90-200 ms to allay concerns that any differences between conditions or group might be due to differences in signal strength. Methods are summarized in (Altschuler, T.S. et al., 2012) and results displayed in Table 3a.

RESULTS

N1 Analysis

The maximum negative deflection in the 100-250 ms period averaged across IC conditions and hemiscalp was selected as the N1 peak for each extent in each age cohort. This latency decreased with age as has been previously observed (Brandwein, A.B. et al., 2011; Brandwein, A.B. et al., 2012). The integrated amplitude over a 30 ms window centered on this latency (Table 3b) was submitted to analysis to compare the amplitude of the difference between IC conditions across the four age cohorts, two hemiscalps, and three levels of retinal eccentricity (extent) (Figure 3.3).

A main effect of IC condition ($F_{(1,59)} = 51.506; p <0.001; \eta^2_{\text{partial}} = 0.47$) indicated the presence of an IC-effect collapsed across age cohort, hemiscalp, and extent manipulation (Table 3c; Figure 3). A main effect of age cohort ($F_{(3,59)} = 3.612; p = 0.02; \eta^2_{\text{partial}} = 0.16$) indicated a difference in VEP magnitudes collapsed across IC condition, hemiscalp, and extent (Table 3c). This main effect is driven by significant mean differences between adults (-3.2 µV) and the two youngest groups: 6-9-year-olds (1.1 µV; $p = 0.04$) and 10-12-year-olds (1.1 µV; $p = 0.03$). No interactions attained significance.
The regression of IC difference (i.e., IC-effect) upon age as a continuous variable was not significant whether data were fitted linearly ($R^2 = 0.015$, $F_{(1,61)} = 0.92; p = 0.34$) or quadratically ($R^2 = 0.016$, $F_{(2,60)} = 0.48; p = 0.62$) (Figure 3.4).

Considering the differences in overall VEP magnitude across age groups, we compared the IC-effect magnitude as a proportion of P1 magnitude collapsed across hemiscalp for each condition and age group. Voltages increased with age: 6-9 = -0.087 µV; 10-12 = - 0.137 µV; 13-17 = - 0.348 µV; 19-31 = -1.167 µV (Table 3) but did not emerge as significant ($F_{(3,59)} = 1.49; p = 0.23; \eta^2_{\text{partial}} = 0.07$).

$N_{cl}$ Analysis

The integrated amplitude across the period from 300-400 ms was submitted to analysis to compare the amplitude of the difference between IC conditions (i.e. the $N_{cl}$ component) for the four age cohorts, two hemiscalps, and 3 levels of extent.

A main effect of condition ($F_{(1, 59)} = 48.254; p < 0.001; \eta^2_{\text{partial}} = 0.45$) indicated a difference between IC conditions collapsed across age cohort, hemiscalp, and extent manipulation (Figure 3.3). A main effect of age cohort ($F_{(3,59)} = 24.118; p < 0.001; \eta^2_{\text{partial}} = 0.55$), indicated a difference of VEP magnitude collapsed across IC conditions, hemiscalp, and extent. This was driven by significant mean differences between all age contrasts except 10-12-year-olds vs. 13-17-year-olds. In contrast to the effect during the N1 processing timeframe, a significant interaction of IC condition x age cohort was present ($F_{(3, 59)} = 5.284; p = 0.0027; \eta^2_{\text{partial}} = 0.21$). The comparison of differences between IC conditions (Bonferroni adjusted) was significant through childhood and adolescence but not in adulthood (Table 3c) 10-12-year-olds: - 2.015 µV ($p < 0.001$); 6-9-year-olds: -1.669 µV ($p < 0.001$); 13-17-year-olds: -0.638 µV ($p = 0.047$); 19-
178-year-olds: -0.4 µV (p = 0.30). This was echoed by the regression of IC difference upon age as a continuous variable, which was significant whether modeled linearly ($R^2 = 0.141, F_{(1,61)} = 9.98; p = 0.002$) or quadratically ($R^2 = 0.145, F_{(2,59)} = 5.105; p = 0.009$) (Figure 3.4).

**P1 Analysis**

In the absence of any magnitude differences during the N1 and N_cl timeframes as a function of the extent manipulation, the P1 timeframe for each age group and condition was submitted to analysis. The P1 component is thought to reflect early registration of spatial stimulus parameters and has shown systematic modulation to the manipulation of stimulus extent in adults (Di Russo, F. et al., 2002; Murray, M.M. et al., 2002; Snyder, A.C. et al., 2012). A main effect of extent ($F(2,59) = 4.985; p = 0.013$ (Greenhouse-Geisser corrected); $\eta^2_{\text{partial}} = 0.078$ confirmed our participants’ sensitivity to the range of manipulation (Figure 3.5). This was driven by a significant contrast between the 4° and 10° conditions (6.8 µV versus 6.1 µV; p = 0.011). The contrast between 7° and 10° approached significance (6.7 µV versus 6.1 µV; p = 0.056).

**Onset latencies**

Paired $t$-tests between IC conditions revealed the overall spatio-temporal patterns of IC-related activity (Figure 3.6). The oldest cohort displayed one significant and relatively punctate phase of IC processing prior to 400 ms which onset at ~155ms and continued for ~90 ms, with activity confined mainly to occipital and parietal-occipital scalp locations. Later modulations of much smaller amplitude occurred after 430 ms and included central scalp locations (a white dotted guideline divides regions anterior to central regions from those posterior to central regions). 13-17 year olds displayed an early phase onsetting at ~175ms and continuing until ~270. Processing resumed after ~300 ms and was measured across a greater extent of the scalp
than in the adults. 6-9 year olds showed some occipital activity as early as 140 ms with parietal occipital activity onsetting at ~150 ms and continuing until ~250 ms. This early phase included central scalp locations. Activity resumes only 20 ms later and continued past 500 ms, with a very wide scalp distribution, including over frontal regions. 10-12 year olds proved to be the most divergent from adults, showing almost one continuous processing phase onsetting at ~205 ms with sustained activity apparent until at least 500 ms.

**Topographies**

Spline-interpolated potential maps depict voltage across the scalp surface for the difference between IC and No-IC conditions (Figure 3.7). Posterior views for each age cohort and extent showed the greatest voltage over occipital and/or occipito-temporal regions. Seven representative latencies across the epoch are presented, including average N1 latencies for the two oldest age cohorts (171 ms), two youngest (228 ms), and three spanning the N_{cl} (300, 350, 400 ms). Activity was apparent in the N1 time frame for all age groups. While activity was restricted to this latency for adults, the two younger groups show activity that continues into the N_{cl} time-window that is of even greater magnitude. 13-17-year-olds lie in between, with more discrete activity during the N1, similar to that observed in adults, as well as activity in the N_{cl} time-frame in 6-9 and 10-12 year olds. Anterior views collapsed across extent (Figure 3.8) show activity over frontal and fronto-central regions for every group except adults in the N_{cl} timeframe.

**Dipole Models**

Two symmetrical dipole current sources were modeled for the 30 ms window centered on the N1 (IC-effect) and the 40 ms window centered on the N_{cl} derived from the global field power
(GFP) (Skrandies, W., 1995) of the subtraction of IC and No-IC conditions averaged across contour extent. Separate color-coded maps show solutions for each age group, with the color of the dipole cartoon matching the color of the Talairach coordinates given (Figure 3.9). During the N1, solutions for all groups overlap and fits exceed 92% of explained variance. The coordinates for all age groups fall approximately within Brodmann Area (BA) 19 which encompasses lateral occipital cortex as estimated on Talairach Client software (Lancaster, J.L. et al., 1997; Lancaster, J.L. et al., 2000). Solutions for the Ncl processing time-frame overlap roughly for 6-17 year-olds falling in BA 19 and 37 - lateral occipital and occipito-temporal areas. The fits of these estimates exceed 94% explained variance. There was no peak in GFP during the Ncl time-frame in adults, obviating the logic of fitting a dipole solution. However, we attempted a model for the sake of consistency. The solution accounting for the greatest amount of variance was estimated to fall close to the inferior temporal gyrus in BA 20. Only 76% of the variance was explained by this model.

**DISCUSSION**

To investigate the developmental trajectory of contour completion processes, we presented stimuli composed of non-continuous contours. One condition induced the illusory perception of continuous contours whereas a second control condition did not. Neurotypical participants ranged from 6-31 years of age. Extent and inducer diameter were varied to hold support ratio constant with the idea that presenting contour fragments over increasing spatial extents would reveal the limits of the visual system’s ability to interpolate said contours, and that those limits might change with age if this ability is experience-dependent. We worked from a well-tested theoretical model that has identified temporally and functionally dissociable processing phases
using electrophysiology— the first was an automatic, perceptual phase occurring between 100-200 ms (associated with the N1 processing timeframe), and the second later conceptual phase (230-400 ms) which has been associated with the analysis of higher-level ambiguous objects.

**Early Perceptual Phase Processing of Illusory Contours**

An adult-like difference between contour conditions was observed during the “perceptual” phase in all the four age groups, including the youngest group tested (6-9 year olds). This analysis was constrained to the timeframe of the N1 of each age group for each extent condition, since the N1 is a stable component of the VEP (Di Russo, F. et al., 2002; Foxe, J.J. et al., 2003) and has a stereotypical morphology by age two (Lippe, S. et al., 2007). N1 latency varied inversely with age, from approximately 226 ms in 6-9-year-olds to 165 ms in adults (Table 3b). This shortening of N1 latency is an already well-characterized effect (Lippe, S. et al., 2007; Brandwein, A.B. et al., 2011).

Posterior topographies of the IC-Effect (Figure 3.7) showed voltage distributions focused over lateral occipital scalp areas. Dipole models were nearly identical in every age group (Figure 3.9), estimating generators of this effect to be located in the region of Brodmann Area 19, a lateral occipital region which corresponds very well with previous fMRI studies identifying the LOC as sensitive to IC processing (Mendola, J.D. et al., 1999; Murray, M.M. et al., 2002).

Overall VEP magnitude, as indexed by P1 amplitude (Table 3c), was quite large in the youngest sample, decreasing rather dramatically with age. This is a common finding in developmental ERP studies (Gomes, H. et al., 2001; Brandwein, A.B. et al., 2011). To our knowledge, there is as yet no widely accepted explanation for this difference across age-groups.
One highly plausible cause, however, may be found in the properties of the volume conductor itself – that is, the nature of the intervening structures between the electrodes and the neural tissue generating the measured currents. Children have thinner more immature skulls that continue to thicken across childhood (e.g., Adeloye, A. et al., 1975), and this thickening undoubtedly increases the intervening resistivity (Cuffin, B.N., 1993; Akhtari, M. et al., 2002). The skull, which is a relatively poor conductor, plays an especially large role in attenuating EEG signals (Lanfer, B. et al., 2012). Thus, in comparing responses between adults and children, one might suppose that concentrating on relative changes in amplitude (i.e. ratios) makes the most sense. In adults, the ratio of IC difference during the perceptual phase to the P1 was ten times that of the youngest children. This represents a substantial modulation of ongoing activity in adults, whereas it obviously represents a more moderate modulation in younger children. However, when ratios were assessed statistically rather than absolute amplitudes, the difference was not robust, leaving this observation and the methodological question of whether the use of ratios or absolute values represent the more meaningful approach for future investigations. We would nevertheless argue that this difference is suggestive of the relative immaturity of this automatic early-phase contour-integration mechanism in younger children.

Later Conceptual Phase Processing of Illusory Contours

Key differences between adults and children emerged during the “conceptual” processing timeframe. Unlike the early phase, differences between contour-forming and non-contour-forming conditions varied significantly with age during this timeframe, with the greatest amplitude modulations apparent in the two youngest groups (6-9 and 10-12 year-olds), followed
by the 13-17-year-old group. In contrast, no significant difference was observed during this timeframe in adults. Although the developmental trajectory did not follow an entirely neat step-like decrease across age groups, since the 10-12 year-old group showed slightly greater modulations during this timeframe than the youngest cohort, the overall pattern across age groups suggests amplification of conceptual-phase relative to perceptual-phase processing in younger children, a pattern that begins to reverse during adolescence and is fundamentally different by adulthood. In adults, only the automatic perceptual-phase appears obligatory for analysis of this stimulus class. This general pattern points to a protracted developmental trajectory whereby contour-integration processes involve multiple temporal phases of processing within object-recognition areas during childhood, but as visual experience is acquired across childhood, the encoding of these stimuli becomes ever more automatic, shifting from a reliance on later processing to a consolidation of processing into early automatic processing - a late-to-early consolidation model.

Inverse source localization produced strong fits within lateral occipital and occipito-temporal regions for all three childhood age groups. On the other hand, adults, who showed no effect during the conceptual timeframe, showed no second peak in global field power, and unsurprisingly, source analysis produced a poorly fitted model (Figure 3.9). In addition, more distributed networks appeared to be implicated in children than in adults (Figure 3.6). Topographic mapping for both of the younger groups showed greater activity over fronto-central scalp (Figure 3.8), suggesting possible recruitment of conceptual-level mechanisms (Sehatpour, P. et al., 2008). Alternatively, it is possible that this fronto-central voltage represents the inverse of the lateral occipital dipoles, but then it is not clear why such activity is not seen more consistently across conditions.
What Do These Developmental Differences Mean?

The present results point to significantly more protracted contour closure processes in childhood than adulthood. Two phases of amplitude modulation occurred in the period between approximately 150-400 ms in children and adolescents in contrast to the single discrete and relatively punctate early process observed in adults (~150-220ms). Moreover, prior to adolescence, the second processing phase appears to have been of greater magnitude than the first, although we did not make a direct statistical comparison.

In considering boundary completion of Kanizsa type illusory contours, we considered what may be the simplest version of completion processes. These stimuli, which rely on only a few inducers to drive contour integration mechanisms, could be considered impoverished in terms of their ‘objectness’ relative to the objects typically encountered by the visual system. Certainly, prior work has investigated the neural mechanisms of object closure for considerably more complex objects from highly fragmented inputs. This latter case of completion may be closer to the parsing of an everyday visual scene in which many of the objects we view are partially occluded by other objects, or otherwise degraded due to poor viewing conditions. For example, Doniger et al. (2000) presented participants with line drawings of common objects in a recognition task where they employed the so-called ‘ascending method of limits’ design. They began by presenting participants with line-drawings of everyday objects (airplanes, dogs and the like), but on initial presentation, only 30% of the pixels of the original drawing were displayed. With this few pixels, object-identification is impossible. They then repeated presentation with an additional 10% of the pixels added back, and continued this process of adding pixels until the participant could successfully “close” (or recognize) the object. This procedure allowed for examination of the VEP to the fragmentation level at which the image was ultimately
recognized, which in neurotypical individuals is still quite fragmented, and for comparison of this response to the responses to the preceding fragmentation levels when the objects were not explicitly recognized. This revealed gradual increases in activity in the LOC in the 230-400 ms timeframe, with no evidence for modulation during the earlier N1 processing timeframe, contrasting with the modulations seen for simple Kanizsa figures. This later onset and more protracted timeframe suggested a less automatic process – one that appeared to present a greater challenge to the visual system. Subsequent intracranial work in humans (Sehatpour, P. et al., 2008) revealed the involvement in this process of a distributed network involving not only the LOC, but also prefrontal cortex, and the hippocampal formation. This lead Sehatpour and colleagues to propose a model whereby the LOC facilitates on-line matching of incoming sensory stimuli to mnemonic object representations stored in the hippocampal formation, while the prefrontal cortex limits the matching options by generating hypotheses.

In a subsequent version of the fragmented picture study, certain objects were shown to participants a second time. With repeated images participants could successfully close the image in its most degraded version, and when they did, a VEP difference was also seen during the earlier N1 latency (Doniger, G.M. et al., 2001). It is presumed that rather than accessing object representations at the “conceptual” level, the visual system can begin closure sooner because it has access to a sensory trace laid down when closure was achieved on the previous presentation of the image. It is conceivable that the automatic closure seen in the present study is, similarly based on lower-level cues derived from contour extent (hence our reference to it as “perceptual”) and therefore relies on a certain amount of exposure. When the limits of such processes are taxed or sufficient expertise has not yet been acquired, the system cannot rely on parametric cues to complete contour fragments automatically. Studies in higher primates have pointed to size-
invariant object processing as a mechanism that is tuned over multiple exposures (Li, N. et al., 2010). An interpretation was put forth in a study of closure processes in schizophrenia patients whereby deficiencies in posterior visual processing were compensated for by additional frontal activity during the later timeframe (Foxe, J.J. et al., 2005). The general lack of exposure that children have to even simple stimulus configurations such as the Kanizsa stimuli may be similarly compensated for here.

The greater recruitment of fronto-central regions pointed to by anterior topographies (Figure 3.9) suggests that children may employ so-called conceptual-level processes to accomplish the closure adults achieve with low-level perceptual mechanisms. However, the characterization of the later phase as “conceptual” stems from a decade of work during which participants executed tasks demanding their attention to stimuli that required closure. Here, although no explicit manipulation of attentional load was included, an orthogonal task at the fixation point appeared to require the continuous attention of participants, and there was never any explicit need for participants to pay attention to the Kanizsa inducers throughout the experiment. Indeed, if anything, they would likely have acted as potential distracters from the central task. Thus, the present data suggest that second stage conceptual-level processing and recruitment of more distributed networks also occurs relatively automatically, at least in children and adolescents. Seghier and Vuilleumier (2006) offer a similar early, fast, low-level/late-high level framing of IC processing in their review of the MRI literature.

Anatomical Considerations Concerning Conceptual Phase Processing of Illusory Contours

The magnitude of conceptual phase processing across the developmental period measured here generally decreases from the youngest to oldest participants, but not in a linear fashion. It is
in the second period – that of late childhood to early adolescence (9-12 years old) – where we measured the largest magnitude. Parallel non-linear effects in the anatomical development literature may point to some of the mechanisms underlying this pattern. Histological analyses suggest that pruning of excess synapses doesn’t begin until late childhood or early adolescence (Huttenlocher, P.R., 1990). Childhood increases in gray matter volume as measured by MRI are followed in adolescence by decreases, peaking at approximately 11-12 years of age and decreasing thereafter (Caviness, V.S., Jr. et al., 1996; Giedd, J.N. et al., 1999). The use of resting-state fMRI as an index of functional connectivity suggests a shift in processing modes during the transition from late childhood to young adulthood, from segregated processing within local nodes to processing across more distributed nodes (Fair, D.A. et al., 2009). Diffusion tensor imaging (DTI) assays of white matter development also suggest that late childhood into adolescence is a highly dynamic period (Barnea-Goraly, N. et al., 2005; Schmithorst, V.J. & Yuan, W., 2010; Lebel, C. & Beaulieu, C., 2011). For example, Qiu et al. (2008) showed that while overall measures of white matter structural integrity increased from 6-23 years-of-age, only 9-12 year-olds demonstrated regressive as well as progressive changes in measures of diffusivity. A great deal of the observed structural changes occurred in frontal, right-temporal, and occipital regions. Schmithorst et al (2010) have suggested that understanding of the structural changes occurring during this period would be well-served by not limiting analyses to linear models and by breaking out 9-12 year olds as their own group, and the current results accord well with this suggestion.

**Response Invariance as a Function of Spatial Extent Manipulations**

In a previous study conducted in adults, we manipulated the absolute spatial extent of ICs and revealed invariance in the magnitude and latency of the IC-effect as well as the overall VEP
during the perceptual timeframe (Altschuler, T.S. et al., 2012). These effects are replicated here. Also in that earlier study, the IC-effect was invariant to manipulations of relative contour length. However, in that case, the early sensory-evoked VEP (i.e. the N1) did vary in amplitude, since manipulating relative contour length involved changing the absolute size of the inducing elements (i.e. the Pacmen). The current study did not compare manipulations of absolute and relative contour but we do see adult-like invariance of both the IC-effect and overall VEP amplitude to the manipulation of absolute contour extent in children from 6-years-of-age on.

Realizing that invariance to the extent manipulation could be interpreted as the visual system’s lack of sensitivity to the range of the manipulations employed here, we also compared amplitudes during the earlier P1 timeframe (approximately 60-150 ms) since activity during this timeframe is thought to index early spatial processing within dorsal and ventral visual stream sources (Foxe et al 2005; Molholm et al, 2006). Indeed, previous manipulations of spatial extent have resulted in changes in P1 amplitude (Murray, M.M. et al., 2002; Snyder, A.C. et al., 2012), although the direction of that change is in dispute. Here, extent varied inversely with P1 amplitude in accord with Snyder et al (Snyder, A.C. et al., 2012). This demonstrates that, despite the invariance of either the early or late contour completion phases or the overall N1 to systematic manipulation of extent from 4° to 10°, the measures used here are sufficiently sensitive to measure the visual system’s encoding of such a manipulation.

Children older than 6 years of age were remarkably like adults in that the amplitude of both the early and late effects were invariant to the manipulation of contour extent. DeLoache, J.S. et al. (2004) observed that children between 18-30 months-of-age made frequent attempts to perform actions with miniature versions of familiar objects without taking into account their actual size – for example, trying to enter a toy car. These observations suggest that the
developmental trajectory of visual object processing in early childhood includes a point at which children may be less efficient at integrating their knowledge of an object with their perception of its scale. At that point in development, we posit that the contour extent manipulation might well tax the limits of contour integration processes – a question for future exploration.

CONCLUSION

We sought to better understand the developmental trajectory of contour completion processes in a cohort of children of schooling age because these processes contribute to the most elemental steps of delimiting objects from the rest of space. Our approach was to probe the vulnerability of electrophysiological markers of these processes across a range of contour integration extents. The data suggest a generally less efficient, more effortful, and more protracted set of contour completion processes that mature across childhood. Even in adolescents, the data suggest that these processes have not yet reached adult-like patterns of maturity.

Evidence of atypical boundary detection (Vandenbroucke, M.W.G. et al., 2008), an atypical bias toward processing global stimulus configurations (Fiebelkorn, I.C. et al., 2012), and delays in the development of other sensory processes (Foxe, J.J. et al., 2009) in persons with an autism spectrum disorder suggest to us that these differences in contour integration may have application toward understanding the broad phenotype of this wide-spread syndrome. These data offer a developmental baseline from which we can begin to make comparisons.
ACKNOWLEDGEMENTS

This study was supported by a grant from the U.S. National Institute of Mental Health (NIMH) to J.J. and S.M. (RO1 - MH085322). The Human Clinical Phenotyping Core, where the children enrolled in this study were recruited and clinically evaluated, is a facility of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (IDDRC) which is funded through a center grant from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD P30 HD071593). Ongoing support of The Cognitive Neurophysiology Laboratory is provided through a grant from the Sheryl and Daniel R. Tishman Charitable Foundation. Mr. Altschuler is supported by a Robert Gilleece Fellowship through the Program in Cognitive Neuroscience at The City College of New York. The authors would like to express their gratitude to Drs. Hilary Gomes, Hans-Peter Frey, Juliana Bates, Natalie Russo, and Adam Snyder for their valuable input and to Ms. Sarah Ruberman and Mr. Frantzy Acluche for their many hours of work in support of this study. We also extend our heartfelt gratitude to the children and families that have so graciously contributed their time to participate in this research.
Chapter Three – Tables & Figures

Table 3a - Participant Descriptive and Behavioral Data

<table>
<thead>
<tr>
<th></th>
<th>Number of Participants (# female)</th>
<th>Mean Age (SD)</th>
<th>Mean Full Scale IQ Score (SD)</th>
<th>Mean Fixation Task Perf. (SD)</th>
<th>Mean Trials per condition (SD)</th>
<th>Signal-to-Noise Ratio (SD) in dBs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6-9 year olds</strong></td>
<td>16 (9)</td>
<td>8.03 (0.86)</td>
<td>113.07 (12.23)</td>
<td>81.78 (18.44)</td>
<td>151.42 (32.06)</td>
<td>27.02 (4.69)</td>
</tr>
<tr>
<td><strong>10-12 year olds</strong></td>
<td>17 (7)</td>
<td>11.56 (0.91)</td>
<td>116.50 (12.97)</td>
<td>93.56 (6.57)</td>
<td>155.16 (42.26)</td>
<td>24.96 (5.35)</td>
</tr>
<tr>
<td><strong>13-17 year olds</strong></td>
<td>18 (9)</td>
<td>15.01 (1.12)</td>
<td>112.18 (13.87)</td>
<td>95.56 (3.94)</td>
<td>194.94 (48.99)</td>
<td>24.20 (5.29)</td>
</tr>
<tr>
<td><strong>19-31 year olds</strong></td>
<td>12 (9)</td>
<td>23.25 (3.44)</td>
<td>Not assessed</td>
<td>97.73 (1.78)</td>
<td>175 (50.32)</td>
<td>22.69 (2.96)</td>
</tr>
</tbody>
</table>

Table 3b - N1 Latencies across Age Group and Condition

<table>
<thead>
<tr>
<th></th>
<th>Condition 1 (4°)</th>
<th>Condition 2 (7°)</th>
<th>Condition 3 (10°)</th>
</tr>
</thead>
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<td><strong>6-9 years-old</strong></td>
<td>209-239 ms</td>
<td>216-246 ms</td>
<td>209-239 ms</td>
</tr>
<tr>
<td><strong>10-12 years-old</strong></td>
<td>217-247 ms</td>
<td>210-240 ms</td>
<td>218-248 ms</td>
</tr>
<tr>
<td><strong>13-17 years-old</strong></td>
<td>171-201 ms</td>
<td>167-197 ms</td>
<td>166-196 ms</td>
</tr>
<tr>
<td><strong>19-31 years-old</strong></td>
<td>152-182 ms</td>
<td>150-180 ms</td>
<td>148-178 ms</td>
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</table>

Table 3c - Component & Effect Amplitudes across Age Group

<table>
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<tr>
<th></th>
<th>P1 Amplitude (uV)</th>
<th>N1 Amplitude (uV)</th>
<th>N1 IC Condition Mean Diff (uV)</th>
<th>Ncl IC Condition Mean Diff (uV) &amp; Significance</th>
<th>Ratio of IC Condition Mean Diff (N1) to P1 Amplitude (uV)</th>
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<tbody>
<tr>
<td><strong>6 - 9</strong></td>
<td>12.453</td>
<td>1.1362</td>
<td>-1.082</td>
<td>-1.669 (p = 0.0000052)</td>
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<tr>
<td><strong>10 - 12</strong></td>
<td>7.739</td>
<td>1.1251</td>
<td>-1.064</td>
<td>-2.015 (p = 0.000000052)</td>
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<tr>
<td><strong>13 - 17</strong></td>
<td>4.408</td>
<td>-0.7821</td>
<td>-1.534</td>
<td>-0.638 (p = 0.047)</td>
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<tr>
<td><strong>19 - 31</strong></td>
<td>1.474</td>
<td>-3.2067</td>
<td>-1</td>
<td>-0.4 (p = 0.30)</td>
<td>1.167</td>
</tr>
</tbody>
</table>
Figure 3.1 Caption
Stimuli & Paradigm - A. Stimuli in illusion-inducing (IC) condition with 3 experimental manipulations of contour extent. B. Paradigm time-course.

Figure 3.2 Caption
Figure 3.1

A. IC Stimuli

Level 1
- Eccentricity: 4°
- Inducer Diameter: 2.1°
- Support Ratio: 54%

Level 2
- Eccentricity: 7°
- Inducer Diameter: 3.6°
- Support Ratio: 54%

Level 3
- Eccentricity: 10°
- Inducer Diameter: 5.6°
- Support Ratio: 54%

B. Paradigm timecourse

Figure 3.2
Figure 3.3 Caption
VEP Waveforms - IC versus No-IC and subtraction waves for each condition and age group (A – D). Effect wave forms show IC condition (blue) & No-IC condition (red) from -150 to +600 ms at electrodes PO3 and PO4. Waves are referenced to electrode AFz. Difference waves depict each condition of contour extent 4° (green), 7° (orange), 10° (burgundy).
Figure 3.3

A.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3a.png}
\caption{IC vs No-IC}
\end{figure}

B.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3b.png}
\caption{Difference waves}
\end{figure}

C.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3c.png}
\caption{Guideline at 200 ms}
\end{figure}

D.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3d.png}
\caption{Guideline at 200 ms}
\end{figure}
Figure 3.4 Caption
Regression analysis - Difference amplitudes during N1 (blue) and N_{cl} (red) latencies regressed upon age. Data are collapsed across hemiscalp and contour extent. Quadratic regression is significant for N_{cl} but not for N1 latency.
Figure 3.4
Figure 3.5 Caption
P1 Main Effect of Extent Manipulation - A. Bar graph: P1 magnitude (uV) collapsed across age and IC conditions for each extent. ** The significant contrast between 4° and 10° (p = 0.011) drives the effect. *The contrast between 7° and 10° approaches significance (p = 0.056). B. The average waveforms of IC conditions and age groups is shown for each extent condition 4° (green), 7° (orange), and 10° (burgundy) from -150 - +250 ms. Electrode PO3 was chosen as representative. Waves are referenced to electrode AFz.
Figure 3.5

A.

![Graph showing P1 Magnitude (μV) for 4 degrees, 7 degrees Extent, and 10 degrees. Error bars indicate ±2 SE.]

B.

![Graph showing waveforms for PO3'.]
**Figure 3.6 Caption**

T maps of difference between IC and No-IC conditions collapsed across extent - Color values indicate the result of point-wise paired t-tests for 10 consecutive points a 3 consecutive electrodes (see Methods), over a -50 to +500 ms time period (x-axis) and scalp region (y-axis). \( \alpha = 0.05 \). baselined from -80 to +40 ms, referenced to AFz. A. 6 - 9 year-olds. B. 10 – 12 year-olds. C. 13 – 17 year-olds. D. 19 – 31 year-olds.
**Figure 3.7 Caption**
Topographical Voltage Maps – Posterior View - Voltage across the scalp surface for the difference between IC and No-IC conditions across age groups (A – D), contour extent, and time 100 – 400 ms. Average N1 latencies are shown for the two youngest age groups (6-9 and 10-12-year-old: 228 ms – blue outline) and the two oldest age groups (13-17 and 19- 31-year-old: 171 ms – green outline). Three latencies during the $N_{cl}$ processing-time frame are shown (red outline).
Figure 3.7

<table>
<thead>
<tr>
<th>Age Group</th>
<th>100 ms</th>
<th>171 ms</th>
<th>228 ms</th>
<th>250 ms</th>
<th>300 ms</th>
<th>350 ms</th>
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<tbody>
<tr>
<td><strong>A. 6-9 years</strong></td>
<td></td>
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<td><strong>B. 10-12 years</strong></td>
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<td><strong>C. 13-17 years</strong></td>
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<td><strong>D. 19-31 years</strong></td>
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**Figure 3.8 Caption**
Topographical Voltage Maps – Anterior View - Voltage across the scalp surface for the difference between IC and No-IC conditions across age groups (A – D), collapsed across contour extent. The N1 peak latency for each age group and the center point of the window encompassing the $N_{cl}$ processing timeframe are shown. D (left panel) illustrates electrode positions. Voltage recordings were restricted to the area where electrodes were placed.
Figure 3.8
Figure 3.9 Caption
Dipole Models - “Glass brain” and MRI dipole models for A. N1 time window (averaged across condition for each age group) and B. N_{cl} window (365 - 405 ms). Dipole colors correspond to age cohorts as indicated. Only right-hemisphere locations are shown as model is symmetrical.
Figure 3.9

<table>
<thead>
<tr>
<th>Age Cohort</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Latency (ms)</th>
<th>BA</th>
<th>GOF</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Latency (ms)</th>
<th>BA</th>
<th>GOF</th>
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Bibliography


Chapter Four
It’s all in the timing: Delayed feedback in autism spectrum disorders may weaken predictive mechanisms during contour integration

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INTRODUCTION

There are abundant reports of associations between autism spectrum disorders (ASDs) and disordered neural connectivity. Compared to neurotypical persons, increased diffusion of frontal white matter has been measured (Barnea-Goraly, N. et al., 2010), as has reduced connectivity between frontal and posterior areas (Cherkassky, V.L. et al., 2006) and between hemispheres (Just, M.A. et al., 2007). Impaired feedback (Vandenbroucke, M.W. et al., 2009), and horizontal connections within lower visual cortex have also been implicated (Bertone, A. et al., 2005; Vandenbroucke, M.W. et al., 2008). While an increased short-range/reduced long-range pattern has been suggested (Barttfeld, P. et al., 2011), the picture of connectivity in ASDs remains murky.

Individuals with ASDs are notable for an atypical cognitive style emphasizing parts rather than wholes (Kanner, L., 1943; Frith, U., 1989). Enhanced perceptual processing of features (e.g., Mottron, L. et al., 2006) a weakness in global processing (Happe, F.G. & Booth, R.D., 2008) or more recently, increased variance in the application of prior knowledge to processing incoming sensory data, known as hypo-priors (Pellicano, E. & Burr, D., 2012), have been offered as an explanation of this characteristic imbalance. Here we report on delayed feedback in the context of unaltered feedforward contributions to early perceptual processing, proposing this as a neural mechanism of hypo-priors.

Creating a visual representation of an object confronts two inconveniences. 1) Missing information – the retina has a 2mm hole where the optic nerve exists (Quigley, H.A. et al., 1990). 2) Ambiguity - one object viewed from different angles projects different shapes upon the retina.
The poverty or ambiguity of incoming signals is thought to be resolved via its combination with prior knowledge (Helmholtz, H., 1860/1962; Pollen, D.A., 1999).

Although the mammalian visual system is characterized as a hierarchy, with lower cortex encoding the most basic features, inputting to successively higher areas which encode ever more complex combinations (Hubel, D.H. & Wiesel, T.N., 1968), information moves both up and down the system (Rockland, K.S. & Pandya, D.N., 1979). Feedforward pathways are proposed to play a key role in extracting sensory data (DeYoe, E.A. & Van Essen, D.c., 1988) and feedback to convey statistical predictions based upon prior experience (Grossberg, S., 1980; Rao, R.P. & Ballard, D.H., 1999). The predictions shape the feedforward information – and a rapid back and forth process disambiguates the representation of incoming data (Grossberg, S., 1994; Lee, T.S. et al., 1998).

Feedforward and feedback projections in non-human primates originate and target different layers of cortex (Rockland, K.S. et al., 1979) and crucially, they develop over different timecourses (Barone, P. et al., 1995). Humans also show prolonged maturation of feedback projections (Burkhalter, A., 1993) establishing a neural basis for their selective vulnerability to pathology.

Binding of elements in the formation of visual object representations has been associated with feedback in non-human primates (Hupe, J.M. et al., 1998; Super, H. & Lamme, V.A., 2007). In humans, delays specific to feedback connections have been associated with visual binding deficits in schizophrenia independently of altered timing in feedforward connections (Kemner,
Contour integration, involving the filling-in between fragments of contours, is one such binding task (Lee, T.S. & Nguyen, M., 2001; Murray, M.M. et al., 2002; Murray, M.M. et al., 2004; Shpaner, M. et al., 2013). Completion has been studied using Kanizsa illusory contours (IC) (Kanizsa, G., 1976; see Figure 2.1). A modulation of the visually evoked potential (VEP) indexes this process in neurotypical adults and children (Murray, M.M. et al., 2002; Proverbio, A.M. & Zani, A., 2002; Foxe, J.J. et al., 2005; Altschuler, T.S. et al., 2012). This index onsets within 90 to 100 ms and peaks around 150 ms after stimulus presentation in neurotypical adults. Seen most prominently over lateral-occipital scalp, it has been termed the IC-effect, and is associated with automatic filling-in of object boundaries (Vuilleumier, P. et al., 2001; Shpaner, M. et al., 2009).

IC completion and the IC-effect have been localized to the lateral occipital complex (LOC) (Murray, M.M. et al., 2002) an extrastriate group of regions which encodes information about coherent objects independent of the features of which they are comprised (Grill-Spector, K. et al., 2001). Primary visual cortex (V1) receives feedback projections from inferior temporal cortex (the location of the LOC) in non-human primates (Barone, P. et al., 2000). Furthermore, magnetic resonance imaging work in humans has demonstrated that as coherence of features increase, increased activation of the LOC is accompanied by reduced activation of V1 (Murray, S.O. et al., 2004). This suggests that as the influence of global feedback predominates, the influence of feedforward local information lessens.

Initial afferent input to visual cortex can be detected using VEPs at between 50 and 70 ms post-stimulation (Foxe, J.J. & Simpson, G.V., 2002; Molholm, S. et al., 2002; Kelly, S.P. et al., 2008). Presumably, this initial volley is dominated by representation of local features processed in lower
visual areas, feeding forward through the system. Whereas by N1 latency, higher cortices including LOC have not merely been active, but have been conveying information about the global scene back to lower levels (Foxe, J.J. et al., 2002; Bar, M. et al., 2006). We propose, then, that the IC-effect, emerging between 90 and 120 ms is likely dominated by feedback simply by virtue of its timing. Hence, we make use here of an exquisitely time-sensitive metric, VEP, to investigate the onset of feedback dominated binding processes in 6-17-year-olds with ASDs. Our central thesis is that the delay of this process would point to a mechanism of hypo-priors.
MATERIALS AND METHODS

Participants

48 neurotypical and 48 ASD individuals ages 6 to 17 years-of-age participated. Their sex, age, non-verbal IQ scores, and other pertinent descriptive data are provided in Table 4a. Average age (p = 0.46) and average non-verbal IQ (PRI) scores did not differ between groups (p = 0.48). Data from an additional 10 neurotypical and 11 ASD participants were excluded due to poor trial numbers or performance, more than 5 channels with excessive artifacts or no signal, failure to report seeing the illusion, neuropsychological diagnoses uncovered following recording, or signal-to-noise ratios that fell more than two standard deviations below the mean for their age cohort. Participants provided informed assent and their parent or guardian gave informed consent. The City College of the City University of New York, Montefiore Medical Center, and Albert Einstein College of Medicine Institutional Review Boards approved all procedures, which were conducted in accordance with the tenets of the Declaration of Helsinki. (Rickham, P.P., 1964).

Exclusionary criteria for both groups included a history of seizures, head trauma, a psychiatric or learning disorder, or a neurological diagnosis of known etiology. Additional criteria for neurotypical participants included Attention Deficit Disorder, a developmental disorder or history of a developmental disorder in a first-degree relative. Participants were screened for normal or corrected-to-normal vision, hearing, and color vision. Diagnoses of ASDs were made on the basis of the Autism Diagnostic Observation Schedule (Lord, C. et al., 1999) and Autism Diagnostic Interview-R (Lord, C. et al., 1994) using DSM-IV criteria. 26 participants received a diagnosis of autism, 18 of Asperger’s, and 4 of pervasive developmental disorder not otherwise
specified (PDD-NOS). Parents were requested to refrain from giving stimulant medication to their children in the 24 hours preceding participation.

*Stimulus and Task*

Participants viewed four black Pacman disks against a gray background (Fig 2.1). Each disk occupied one of four corners of a square-shaped array. Each had a 90° angle cut out of them - their “mouth.” When the mouths are angled such that their contours are collinear, the gap between the mouths appears to fill-in, inducing the perception of a square (IC condition). When the mouths are not aligned, no illusion is induced (No-IC condition). In the No-IC condition, three of four inducers are rotated away from the center, the fourth inducer’s location varied randomly and equiprobably. Retinal eccentricity of illusory squares was manipulated randomly and equiprobably within blocks among 3 conditions subtending 4°, 7°, and 10° of visual angle (extent). Inducers for the three extents were 2.1°, 3.8°, and 5.6° diameter respectively, holding support ratio (the proportion of actual to perceived contour extent) constant. For the present analysis, data is collapsed across these parameters.

Participants sat in a dimly-lit, sound-attenuated room, 60 cm from a LCD monitor with 1280 x 1024 pixel resolution or 75 cm from a monitor with 1680 x 1050 pixel resolution. Stimuli duration was 500 ms with 800 – 1400 ms onset asynchrony, varied on a square wave distribution. Ten to fifteen 3-minute blocks were presented, with breaks as needed, until sufficient trials had been collected. Explicit attention to ICs is not required to elicit electrophysiological indices of IC processing in TD adults (Murray, M.M. et al., 2002) or children (Altschuler, T.S. et al., In submission). Task instructions made no mention of stimuli or the illusion. Participants attended to a color-detection task involving the central fixation dot. Every 1-10 seconds, the dot changed
from red to green for 160 ms on a random timecourse uncorrelated with IC presentation. As the colors were chosen for an isoluminant plane of the DKL color-space (Derrington, A.M. et al., 1984) the change was imperceptible without foveating. Participants were asked to click a mouse button for each color-change. Performance is summarized in Table 4a. All groups performed well above chance, but participants with ASD performed less well ($t_{(93)} = 3.05; p < 0.01$). 6-9-year-old participants were observed to ensure fixation.

Following administration, a debriefing questionnaire assessed IC perception. Printed images of illusory triangles with a request to “describe what you see,” elicited a response indicating a triangle in the illusion-inducing condition in 98% of participants. When shown square inducing stimuli like that used in the experiment, 100% of included participants identified the IC-condition as the “square.” Failure to give such a response constituted an exclusion criterion.

**Data Acquisition and Processing**

Continuous EEG was recorded via a Biosemi ActiveTwo system from a 70-electrode montage. This was digitized at 512 Hz and referenced to the Common Mode Sense (CMS) and Driven Right Leg (DRL). Data were pre-processed using BESA 5.1.8 software (Gräfelfing, Germany). Epochs from -150 before stimulus onset to 1000 ms after were low-pass filtered at 45 hz with a 24 db/octave roll-off and baseline-corrected across an epoch of -80 to +20 ms for each participant and condition. Artifact rejection criteria were chosen on an individual participant basis within a range of 100 – 150 uV and were applied by means of a BESA-generated algorithm on an epoch of -150 to 750 ms to reject trials with eye or muscle movement. Average number of trials per condition is shown in Table 4a. Channels generating electrical artifacts or failing to record a signal were interpolated when possible. External electrodes M1, M2 and the nose were
tolerated poorly by younger children and became the source of such consistent noise that they were excluded from analysis in all participants. These data were then imported for analysis in MATLAB.

**Statistical analysis of IC-effect onset latencies**

Analyses were guided by previous IC work (Murray, M.M. et al., 2006; Shpaner, M. et al., 2009; Altschuler, T.S. et al., In submission) which identified ERP effects sensitive to the difference between IC conditions during time windows associated with the visual N1. We focused on electrodes over lateral occipital scalp sites (PO3, PO4, PO7, and PO8) where the strongest responses are seen during this latency (Foxe, J.J. et al., 2005; Murray, M.M. et al., 2006; Altschuler, T.S. et al., 2012; Shpaner, M. et al., 2013). Data were initially collapsed across all sensors of interest and diagnostic groups. From this grand mean waveform, a difference wave was computed as IC minus No-IC. The most negative data point in the time-window of the N1 timeframe was found to be 186 ms and a symmetric window of ±20 ms around this point was used to search for onset latencies in the subsequent analyses.

Because difference waves necessarily have a lower signal-to-noise ratio, we used a jackknife-based method to estimate onset latencies. This method has been shown to outperform methods based on the selection of onset latencies at the single participant level (Miller et al., 1998; Ulrich and Miller, 2001; Keisel et al., 2008). It proceeds as follows: for all n subjects in a given group, 1 subject is omitted, and the average computed over the remaining n - 1 subjects. n averages are computed, each subtracting 1 subject’s data. For each of these n jackknife waveforms, an onset latency is computed. For each jackknife waveform, we determined the minimum voltage within the predefined window outlined above (186±20 ms). Onset latency was defined as the point at which the voltage reached 50% of the minimum, a well-accepted estimate of onset previously
used with difference-wave measures (Luck, S.J. et al., 2009). Since the jackknife waveforms are digitally sampled, and thus discrete, we rarely possessed a sampled latency value that corresponded precisely with the 50% criterion. As such, we linearly interpolated between the nearest two latency values (above and below) the precise 50% voltage value.

The jacknife latency values were submitted to a mixed model ANOVA with between-groups factors of Diagnosis (ASD, TD) and within-groups factor Hemisphere (left, right). Ulrich and Miller (2001) rigorously demonstrated that the jackknife technique artificially reduces the error variances in the ANOVA, and since this is likely to inflate $F$ values, the following corrects for such inflation $F_c = \frac{F}{(n-1)^2}$, where $F_c$ is the corrected $F$ value.

Statistical analysis of VEP onset latencies

In order to assess that any changes in feedback-associated processes during the N1 latency were not due to differences at the onset of cortical activation of the visual system, we compared the global field power (GFP) for each group. The GFP is the mean standard deviation of the potential at each electrode, yielding a single value for each timepoint. In estimating the onset of overall cortical activity, this method is not biased by the location of maximum or minimum activity (Skrandies, W., 1995). Each group’s average data were re-baselined across an epoch of -50 to +20 ms. As GFP are positively skewed, these data were log-transformed to normalize their distribution. Each time point from 20 to xx (signal) was compared to a randomly chosen time point between -150 and -51 ms (noise). These were subjected to a paired $t$-test. The first time point where the $t$-test exceeded the 0.05 alpha criterion for 11 consecutive time points was determined to be the onset of cortical signal for each group. This criterion is adopted from Guthrie and Buchwald (1991) to control for Type I error due to multiple comparisons. The log-
transformed GFPs were subjected to a pointwise $t$-test to determine at what latencies the groups’ onset latencies were significantly different from each other.
RESULTS

IC-effect onset latency

Onset latency of the IC-effect was estimated at 164.56 (0.77) ms for participants with ASD and 145.60 (0.57) ms for TD participants (Figure 4.1). This 19 ms delay yielded a main effect of diagnosis ($F_{(94, 1)} = 18,825.49; F_c = 8.52; p < 0.01$) (Figure 4.2). A main effect of hemisphere ($F_{(94, 1)} = 8911.32; F_c = 4.03; p < 0.05$) showed that right hemisphere latency (159.27 (6.82) ms) was later than left (150.90 (12.31) ms). The interaction of diagnosis x hemisphere did not reach statistical significance.

VEP onset latency

Onset latency of the VEP was estimated at 66.78 ms for TD participants and 68.73 ms for participants with ASD. This difference was not statistically significant. TD participant’s IC processing was feedforward-dominated for approximately 79 ms, whereas participants with ASDs was feedforward-dominated for 96 ms.
DISCUSSION

To investigate feedback contributions to visual processing in ASDs, we compared a well-tested metric of automatic contour completion in 6-17 year-olds with ASDs and their neurotypical counterparts. We measured a delay of 19 ms in individuals with ASDs despite simultaneous onset of visual cortical activity of the two groups. No latency differences related to contour integration had been measured in earlier VEP work with 3 to 6 year-old boys with ASD (Stroganova, T.A. et al., 2007).

Feedforward and feedback connections in human visual cortex develop from segregated populations of neurons (Burkhalter, A., 1993). While feedforward axons grow toward their target directly (the dendritic spines of pyramidal cells) reaching them by approximately 4 months of age, feedback fibers appear to grow past their target, sending out multiple buds from the axon (O'Leary, D.D. & Terashima, T., 1988) and have still not reached their targets by this time. Density of targets is still increasing five months postnatally and is followed by pruning back of cell density later in infancy. This is presumed to make space for feedback inputs to reach their targets (Rabinowicz, T., 1986; Burkhalter, A., 1993). Brain overgrowth prior to three-years-of-age is a consistently replicated finding in ASD. It has been connected to increased gray matter volume (Hazlett, H.C. et al., 2005), neuron count (Courchesne, E. et al., 2011), and density (Hutsler, J.J. & Zhang, H., 2010). One possibility is that initial overexuberant feedforward connections cause feedback fibers to encounter greater obstacles to reaching their intended targets. Protracted development of feedback circuitry would likely alter the predictive function of feedback circuitry in sensory processing (Rao, R.P. et al., 1999) particularly if it is dependent on exposure gained through the earlier maturing feedforward circuitry (Berezovskii, V.K. et al., 2011).
Typically, ambiguous sensory inputs are shaped by statistical predictions about configuration acquired through prior exposure. One proposal suggests that the input might be thought of as representing multiple possible outcomes. As predictions based on priors are fed back to lower areas, those representations not matching the hypotheses are eliminated or “explained away” (Lee, T.S. & Mumford, D., 2003). Later onset of feedback dominated activity suggests that perceptual representations remain less shaped by such internal input. Local features influence initial perceptual processing for a longer time – in this case for 20% longer – offering a possible neural mechanism for the reduced influence of priors on processing of local stimulus elements.

Regarding ICs, configural information is thought to cue the filling-in of gaps in contour elements (Altschuler, T.S. et al., 2012), implying that the ambiguity of incoming features is resolved later or that subsequent processing receives more feedforward-dominated input. Such input may explain why individuals with ASD excel in tasks like the copying of geometrically impossible figures (Mottron, L. et al., 1999), where delayed feedback may mean that copying is less influenced by prior knowledge. Assuming this pattern predominated over childhood, this could foster development of experience-dependent visual processes that rely less on predictive mechanisms overall. In such a system it may be adaptive to place greater reliance on sensory details than on information about wholes – a characteristic of the ASD phenotype. It is possible to extrapolate that if irrelevant information is not “explained away,” the sensory processing systems of individuals with ASDs may be overloaded with an abundance of potential representations.

We are not the first to propose connectivity differences related to contour processing in ASDs but in prior work, within-region horizontal connectivity has most often been implicated (Bertone, A. et al., 2005; Vandenbroucke, M.W. et al., 2008). However, there is considerable experimental
support for the involvement of feedback in contour-associated processes, even in primary visual cortex (Gilbert, C. et al., 2000; Li, W. et al., 2008). Additionally, 10 to 20% of feedback connections impact pyramidal neurons via connections to GABAergic neurons (Gonchar, Y. & Burkhalter, A., 2003), so it is possible that the delayed FB measured here helps shape incoming sensory information via inhibitory horizontal connections.

Here, a 19 ms delay in the onset of feedback-dominated visual processing suggests to us a mechanism of hypo-priors (Pellicano, E. et al., 2012), an account of sensory processing in ASDs whereby increased variance in the application of prior knowledge disrupts the predictive apparatus relied on for rapid, automatic grouping of incoming sensory information. This has support in accounts of connective pathology in ASD, as well as the developmental anatomy specific to feedback circuitry in mammals. Additionally, it offers a hypothetical neural mechanism for aspects of the broader ASD phenotype.
Chapter Four – Tables & Figures

Table 4a – Participant Descriptive Data

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<th>Group &amp; Age Cohort</th>
<th>N (f)</th>
<th>Mean Age (SD)</th>
<th>Mean PRI (SD)</th>
<th>Mean Trials per condition (SD)</th>
<th>Mean Orthogonal Task Perf (SD)</th>
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<td>TD</td>
<td>48 (22)</td>
<td>11.7 (2.9)</td>
<td>108.3 (12.1)</td>
<td>172.2 (26.8)</td>
<td>90.8 (12.6)</td>
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<td>ASD</td>
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<td>11.7 (2.8)</td>
<td>106.4 (14.8)</td>
<td>177.6 (32.8)</td>
<td>81.7 (16.5)</td>
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</table>
Figure 4.1 Caption

IC-effect grand average waveforms – average across electrodes PO3, PO4, PO7, PO8, and topographies. Gray bar indicates timeframe of N1 collapsed across groups.
Figure 4.1

ASD

TD

Amplitude (μV)

Time (ms)

Amplitude (μV)

Time (ms)

IC
NO IC

0 μV

0.5

0.5

0 μV

0.5

0.5

1

1

1.5

1.5

0

0

-0.5

-0.5

-1

-1

-1.5

-1.5
Figure 4.2 Caption

IC-effect difference wave (IC minus No-IC). Onset from jackknifed scores of ASD (red) and TD (blue) groups. Circles/diamonds indicate 50% of minimum for A) electrodes PO3 and PO7 (solid lines) and B) PO4 and PO8 (dotted lines). Inset of 100 to 180 ms timeframe with C) 95% confidence intervals, and D) topographies.
Figure 4.2
Bibliography

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Electrophysiological indices of illusory contour show typical amplitude but delayed timing in autism spectrum disorders

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INTRODUCTION

Autism spectrum disorders (ASDs) are neurodevelopmental disorders of social communication, restricted interests and repetitive behaviors (American Psychiatric Association, 2013). They are characterized by an “inability to experience wholes without full attention to the constituent parts” (Kanner, L., 1943). This is manifested in such behaviors as focusing on the literal meaning of a phrase rather than its gist (Dennis, M. et al., 2001) or weaknesses in categorizing objects (Fiebelkorn, I.C. et al., 2012), which might be summarized as dysfunctions in generalizing.

Although ASDs present as disorders of complex behavior, there is evidence that they may originate at more basic levels of processing. ASDs are frequently associated with disordered neural connectivity. Reduced frontal-parieto-occipital connectivity has been correlated with atypical visuospatial performance as well as structural differences in connectivity between the hemispheres (Damarla, S.R. et al., 2010). Impaired feedback (Vandenbroucke, M.W. et al., 2009) and horizontal connectivity (Bertone, A. et al., 2005; Vandenbroucke, M.W. et al., 2008) has also been implicated in sensory processing differences in ASDs. Sensory atypicalities are more common in ASDs than other developmental disorders, and they correlate with severity of social symptoms in children (Dakin, S. & Frith, U., 2005; Kern, J.K. et al., 2007; Leekam, S.R. et al., 2007; Ben-Sasson, A. et al., 2009; Simmons, D.R. et al., 2009; Marco, E.J. et al., 2011; Frey, H.-P. et al., 2013). Reported differences in the visual domain include superior processing of details (Bertone, A. et al., 2005) impairments of gaze direction (Senju, A. et al., 2005), and aberrant perception of motion coherence (Milne, E. et al., 2006; Spencer, J.V. & O'Brien, J.M.D., 2006).

Enhanced processing of local stimulus features (e.g., Mottron, L. et al., 2006) or a disinclination toward processing global properties (e.g., Happe, F.G. & Booth, R.D., 2008;
Scherf, K.S. et al., 2008) is characteristic of persons with ASDs, although they can make use of configural properties when explicitly asked to (Plaisted, K.C. et al., 1999). This processing bias contrasts with neurotypical persons default towards organizing the details of their world into cohesive wholes, as characterized by the Gestalt psychologists (Koffka, K., 1935). This bias is seen as, for instance, faster reaction time to global- relative to local- information in a stimulus (Navon, D., 1977). Pellicano and Burr (2012) proposed that increased variance in the application of prior knowledge to processing of sensory information, known as hypo-priors, might be responsible for this processing bias.

Neurotypically, knowledge acquired through exposure to stimulus configurations can be integrated with incoming sensory signals. Typical scenes include obstructed objects or movement. The retinal surface is interrupted by vasculature and the optic disc (Quigley, H.A. et al., 1990). Viewing the same three-dimensional object from different perspectives can project completely very shapes upon the retina (Kersten, D. et al., 2004). So, sensory signals are both impoverished and ambiguous, suggesting that integration with prior knowledge would be integral to perception (Pollen, D.A., 1999).

Feedfoward pathways in the sensory systems are proposed to carry data extracted from environmental sources, and feedback to convey predictions based upon prior experience. The feedback shapes the feedforward information via back-and-forth volleys known as recurrent processes, disambiguating the representation of incoming data. Recurrent processing between higher and basic visual cortex is thought to be a requirement for the induction of visual perception (Pascual-Leone, A. & Walsh, V., 2001; Super, H. et al., 2001), and for visual recognition of novel images (Camprodon, J.A. et al., 2010). The filling-in of gaps in impoverished sensory signals, termed perceptual closure or contour integration, is one such
predictive process. It is hypothesized to function via feedback which facilitates inferences about whether sensory fragments are part of the same object or not (Lee, T.S. & Nguyen, M., 2001; Murray, M.M. et al., 2002; Altschuler, T.S. et al., 2012; Shpaner, M. et al., 2013). If, as Pellicano and Burr propose, the impact of priors is more variant in persons with ASDs, then their processing might be characterized as more influenced by sensory elements or “less interpreted.” However, Brock has countered that reduced noise in the sensory signal could cause differences in the measures of perception that look identical (Brock, J., 2012). The accuracy of either description will likely be born out via investigation of underlying neural mechanisms.

Modulations of the visually evoked potential (VEP) offer electrophysiological markers of contour integration in neurotypical adults and children (Sugawara, M. & Morotomi, T., 1991; Murray, M.M. et al., 2002; Proverbio, A.M. & Zani, A., 2002; Foxe, J.J. et al., 2005; Brodeur, M. et al., 2006; Altschuler, T.S. et al., 2012). These processes begin within 90 ms of stimulus presentation in neurotypical adults (Murray, M.M. et al., 2002; Li, W. et al., 2006; Altschuler, T.S. et al., 2012). Kanizsa-type illusory contour (IC) figures (Kanizsa, G., 1976 see Figure 2.1) have been useful for studying closure in that they are composed of fragmented contours which, in certain configurations, induce the perception of continuous contours – the visual system fills-in the gaps between fragments.

While some investigations of perceptual closure in ASDs using subjective measures have reported that children with ASDs have less susceptibility to the illusion (Happe, F.G., 1996) although, this has been contradicted (Ropar, D. & Mitchell, P., 1999; Milne, E. & Scope, A., 2008). Electrophysiology allows for direct measure of neural processing irrespective of behavioral differences, so using event-related-potentials (ERPs) to measure differences in contour completion may help uncover the mechanisms underlying global/local processing.
differences in ASDs. Previous work revealed atypical IC-related VEPs in 3-6-year-old boys with ASDs (Stroganova, T.A. et al., 2007).

A recent ERP study of neurotypical IC closure (Altschuler, T.S. et al., In submission) described a developmental trajectory across four age groups (6 to 9, 10 to 12, 13 to 17, 19 to 31). That investigation is framed in terms of a two-phase model of contour completion, dissociating earlier automatic (Murray, M.M. et al., 2002; Proverbio, A.M. et al., 2002; Shpaner, M. et al., 2009) from later higher-level contributions (Foxe, J.J. et al., 2005; Murray, M.M. et al., 2006). The first phase is evident as an increase in VEP amplitude occurring between 100 to 200 ms after stimulus presentation in response to the illusion-inducing condition seen most prominently over lateral-occipital scalp sites. It has been termed the IC-effect, and is associated with automatic filling-in of object boundaries (Vuilleumier, P. et al., 2001; Murray, M.M. et al., 2002; Shpaner, M. et al., 2009). This effect did not differ significantly between neurotypical children and adults (Altschuler, T.S. et al., In submission). The second change in VEP amplitude onsets 230 ms after stimulus presentation. It is seen in adults in lieu of the earlier effect, when processing more complex objects than ICs. This later phase, called the negativity for closure (N_{cl}), extends past 400 ms and is thought to reflect recurrent processes during which fragmented elements of complex objects are gradually filled-in (Foxe, J.J. et al., 2005; Sehatpour, P. et al., 2008). While adult VEPs only show the first effect when passively viewing centrally-presented ICs, children revealed a second period of difference during the N_{cl} timeframe (Altschuler, T.S. et al., In submission). The neurotypical developmental trajectory of contour closure suggests protracted processing over two phases in children, the second of which resembles the processes adults use in closing more complex stimuli.
The lateral occipital complex (LOC) has been implicated in the generation of both the IC-effect and $N_{c1}$ (Murray, M.M. et al., 2002; Sehatpour, P. et al., 2006). The LOC is a group of ventral stream visual areas which responds more strongly to images of objects than to control stimuli such as scrambled objects. The LOC appears to encode information about objects regardless of their individual qualities such as size, luminance, and color – a property called cue-invariance (Grill-Spector, K. et al., 2001). In our developmental study, a manipulation of contour extent tested invariance to size during the early and late phases of contour completion across the four age groups. No significant difference was detected in the amplitude of the VEP for any age group during either phase (Altschuler, T.S. et al., In submission).

Studies demonstrating that children with ASDs were less able to make shape similarity judgments when viewing perspective varied (Ropar, D. & Mitchell, P., 2002) or that they categorized everyday objects differently (Fiebelkorn, I.C. et al., 2012) suggest differences in their ability to generalize among similar classes of objects. However, it is unknown whether this is a dysfunction in higher conceptual or more basic sensory-level processing. We reasoned that if it is the latter, this might be reflected in the absence of cue-invariant IC responses in individuals with ASDs.

Here, we investigated the dynamics of closure processes in 6-17-year-olds with ASDs. We hypothesized that if Pellicano and Burr’s (2012) hypo-priors accurately reflects visual processing in ASDs, this would result in reduced binding of visual elements in ICs, which would be reflected in the magnitude of closure-related effects. We also manipulated contour extent to investigate whether electrophysiological indices of contour completion display cue invariance, as previously reported, in neurotypical children (Altschuler, T.S. et al., In submission).
MATERIALS AND METHODS

Participants

48 neurotypical and 48 ASD individuals between the ages of 6 and 17 years-of-age participated. They were divided into three cohorts: 6-9, 10-12, 13-17 years-of-age. Sex, age, non-verbal IQ, and other descriptive data are provided in Table 5a. Average age collapsed across cohorts \( (p = 0.46) \), or among cohorts \( (p = 0.58) \), did not differ significantly between neurotypical and ASD groups. Average non-verbal IQ (PRI) scores did not differ between diagnostic groups \( (p = 0.48) \) or age groups \( (p = 0.32) \). Data from 10 neurotypical and 11 ASD participants were excluded due to unusually poor trial numbers or task performance, more than 5 channels with excessive artifacts or no signal, failure to report seeing the illusion, possible psychological or neurological diagnoses uncovered following recording, or a signal-to-noise ratio that fell more than two standard deviations below the mean for their cohort. Participants provided informed assent and their parent or guardian gave informed consent. The City College of the City University of New York, Montefiore Medical Center, and Albert Einstein College of Medicine Institutional Review Boards approved all procedures, which were conducted in accordance with the tenets of the Declaration of Helsinki. (Rickham, P.P., 1964).

Exclusionary criteria for study enrollment for both groups included a history of seizures, head trauma, a psychiatric or learning disorder, or a neurological diagnosis of known etiology. Additional criteria for neurotypical participants included Attention Deficit Disorder, a developmental disorder, or a history of a developmental disorder in a first-degree relative. Participants were screened for normal or corrected-to-normal vision, hearing, and color vision. Diagnoses of ASDs were made on the basis of the Autism Diagnostic Observation Schedule (Lord, C. et al., 1999) and Autism Diagnostic Interview-R (Lord, C. et al., 1994) and the
experienced judgment of a licensed clinician using DSM-IV criteria. 26 participants received a diagnosis of autism, 18 of Asperger’s, and 4 of pervasive developmental disorder not OTHERWISE specified (PDD-NOS). Parents were asked to refrain from giving stimulant medication to their children in the 24 hours preceding participation.

Stimulus and Task

Participants viewed four black Pacman disks against a gray background (Fig 2.1a). Each disk occupied one of four corners of a square-shaped array, equidistant from a central fixation dot, and each had a 90° angle cut out of them - their “mouth.” When the mouths face the center of the array and their contours were collinear, the gap between the mouths appears to fill-in for typical viewers, inducing the perception of a square (the illusion-inducing or IC condition). When the mouths are not aligned, no illusion is induced (the No-IC or non-inducing condition). This was accomplished by rotating three of four inducers away, the fourth inducer’s location varied randomly and equiprobably. Retinal eccentricity of illusory squares was manipulated randomly and equiprobably within blocks among 3 conditions subtending 4°, 7°, and 10° of visual angle (extent). Inducers for the three extents were 2.1°, 3.8°, and 5.6° diameter respectively, holding support ratio (the proportion of actual to perceived contour extent) constant.

Participants sat in a dimly-lit, sound-attenuated room, 60 cm from a LCD monitor with 1280 x 1024 pixel resolution or 75 cm from a monitor with 1680 x 1050 pixel resolution. Stimuli duration was 500 ms with 800 – 1400 ms onset asynchrony, varied on a square wave distribution. Ten to fifteen 3-minute blocks were presented, with breaks as needed, until sufficient trials had been collected. Explicit attention to ICs is not required to elicit electrophysiological indices of IC processing in TD adults (Murray, M.M. et al., 2002) or children (Altschuler, T.S. et al., In
submission). Task instructions encouraged a passive relationship to IC presentation, making no mention of stimuli or the illusion. Instead participants were directed to attend to a color-detection task involving the central fixation dot. Every 1-10 seconds, the dot changed from red to green for 160 ms on a random timecourse uncorrelated with IC presentation. As the colors were chosen for an isoluminant plane of the DKL color-space (Derrington, A.M. et al., 1984) the change was imperceptible without foveating. Participants were asked to click the mouse button for each color-change. Performance is summarized in Table 5a. Groups performed well above chance, but ASD performance was less strong (p < 0.01), and 6-9 year olds performed more poorly than other age groups (p < 0.01). This group was observed throughout recording to ensure fixation.

Following administration, a debriefing questionnaire assessed participant’s perception. Printed images of illusory triangles with an open-ended request to “describe what you see,” elicited a response indicating a triangle in the illusion-inducing condition in 98% of participants. When shown the same stimulus as that used in the experiment, 100% of included participants identified the IC-condition as the “square.” Failure to give such a response constituted exclusion criteria.

Data Acquisition and Processing

Continuous EEG was recorded via a Biosemi ActiveTwo system from a 64-electrode montage, with six external electrodes to monitor eye movements and serve as possible reference electrodes post-processing. This was digitized at 512 Hz and referenced to the Common Mode Sense (CMS) and Driven Right Leg (DRL). Using BESA 5.1.8 software (Gräfelfing, Germany), epochs from -150 before stimulus onset to 1000 ms after were low-pass filtered at 45 hz with a 24 db/octave roll-off and baseline-corrected across an epoch of -80 to +20 ms for each subject, condition, and level of extent manipulation. Artifact rejection criteria were chosen on an
individual participant basis within a range of 100 – 150 uV was applied by means of a BESA-generated algorithm on an epoch of -150 to 750 ms to reject trials with eye or muscle movement. Average number of trials per condition is shown in Table 5a. Channels generating electrical artifacts or failing to record a signal were interpolated when possible. External electrodes M1, M2 and the nose were tolerated poorly by younger children and became the source of such consistent noise that they were excluded from analysis in all participants.

Statistical Analyses

Analyses were guided by previous IC processing work in TD adults and children (Murray, M.M. et al., 2006; Shpaner, M. et al., 2009; Altschuler, T.S. et al., In submission) which identified ERP effects sensitive to the difference between IC conditions during time windows associated with the visual N1 and, in some cases, Ncl components. The P1 was also identified, serving as an index of overall VEP amplitude. These were focused at electrodes over lateral occipital scalp sites (PO3, PO4, PO7, and PO8) where the response was largest (Doniger, G.M. et al., 2001; Foxe, J.J. et al., 2005; Murray, M.M. et al., 2006; Altschuler, T.S. et al., 2012; Shpaner, M. et al., 2013). Peak P1 latency was identified for each age group and extent level as the most positive point between 110 and 200 ms. Peak N1 latency was identified for each age group and extent level as the negative-most point between 120 and 270 ms of the grand average waveform, averaged across IC conditions (IC and No-IC) and electrodes. Magnitude was averaged over a 30 ms window centered on these peaks. A 300-400 ms window encompassed the Ncl. Data were re-referenced to anterior-midline-frontal site AFz. Differences between IC conditions averaged across time windows were subjected to a repeated-measures ANOVAs in SPSS 20 with between-subjects factors of Diagnostic Group (TD vs ASD) and Age Cohort (6-9, 10-12, and 13-17) and within-subjects factors of IC condition (IC vs No-IC), hemiscape (Left and
Right), and extent (4°, 7°, and 10°). Significant interactions were subjected to pairwise \( t \)-tests Bonferroni-corrected to control for multiple comparisons. Significance criteria for all comparisons was set at \( \alpha < 0.05 \). Additionally, differences between IC conditions during the N1 and N_{cl} latencies were regressed upon age as a continuous variable and the \( R^2 \) values tested for significance. To further understand processing differences between groups and their relationship to diagnosis, exploratory ANOVAs of identical within-subjects factors and a between-subjects factor of age cohort were conducted within TD and ASD groups separately.

Usually, IC-effect magnitude is compared relative to some group or stimulus-driven difference however, as we observed that the overall amplitude of the VEP varies across age groups (Gomes, H. et al., 2001; Brandwein, A.B. et al., 2011; Altschuler, T.S. et al., In submission). To control for the influence of this difference, we performed an additional ANOVA on the ratio of P1 amplitude (as an index of overall VEP size) to the IC-difference during the N1 timeframe. P1 latency was defined for each age group and extent level as the most positive point between 90 and 160 ms of the grand average waveform, average across IC conditions and electrodes. Magnitude was averaged over a 30 ms window centered on the peak latency.

**Dipole Source Modeling**

Estimated intracranial sources of effects were modeled using BESA’s least squares algorithm. At the latencies of maximal amplitude in the subtraction waveforms during N1 and N_{cl} timeframes, two symmetrical dipoles were fit to explain the maximal amount of variance in the overall voltage across the scalp. The stability of the model was challenged by altering the location of the dipoles. Results collapsed across extent are displayed in Talairach coordinates (mm) and the Brodmann Area in which they are situated.
Signal-to-Noise (SNR) Ratio

To ensure that the difference between diagnostic groups was not due to SNR, an estimate was calculated by dividing average amplitude for each subject and condition during the baseline period (noise) by amplitude across a window spanning 90-200 ms (signal) and submitting them to an independent samples t-test. That difference was not significant ($t_{(94)} = 1.69; p = 0.09$).

RESULTS

N1 Timeframe – IC-Effect

Neurotypical and ASD participants viewed centrally presented IC stimuli to assess the spatio-temporal dynamics of the IC-effect, occurring during the N1 latency in TD adults and in children 6-9, 10-12, and 13-17, are the same for persons with ASD.

There was a main effect of IC condition ($F_{(90, 1)} = 76.426; p < 0.01; \eta^2_{\text{partial}} = 0.459$), indicating an IC-effect for both TD and ASD groups collapsed across all other factors (Fig 5.1). In neurotypical persons of the same ages, the IC-effect was invariant to a manipulation of extent. An interaction of IC x hemiscalp x extent ($F_{(180, 2)} = 6.02; p < 0.01; \eta^2_{\text{partial}} = 0.063$) demonstrated a difference in extent collapsed across diagnostic group (Table 5b). This appeared to be driven by a relatively small, but still significant, effect over right-hemisphere in the 7° condition according to pairwise comparisons (Bonferroni corrected). A marginally significant interaction of IC x hemiscalp x extent x diagnosis ($F_{(180, 2)} = 2.95; p = 0.055; \eta^2_{\text{partial}} = 0.032$) shows this right hemiscalp difference in the 7° condition to be driven by the TD participants (Table 5c).
IC-effect amplitude does not vary directly with extent in the TD group, as we have shown previously (Altschuler, T.S. et al., In submission), but it trends in that direction in the ASD group. Amplitude increases directly with extent for both left and right hemiscalps (Fig 5.2).

A regression of IC-Effect magnitude on age as a continuous variable shows no significant difference from ages 6 – 17 in TD individuals (Linear R² = 0.001; F(46,1) = 0.38; p = 0.85). In individuals with ASDs the IC-effect decreases as participants age, but not this effect is not statistically significant (Linear R² = 0.066; F(46,1) = 3.27; p = 0.08) (Fig 5.3).

It is a common finding to see overall ERP magnitudes decrease as children mature (Brandwein, A.B. et al., 2011), so we performed a post-hoc analysis on IC-effect amplitude as a proportion of P1 amplitude. This approach measured a significant increase as children mature collapsed across diagnostic group (F(90,2) = 3.68; p < 0.05; η² partial = 0.076). This is driven by the TD group, as seen in an interaction of age x diagnosis (F(90,2) = 3.17; p < 0.05; η² partial = 0.066). There is a direct relationship of age and IC-effect in TD children. Differences between age cohorts prove significant in pairwise comparisons between the 13-17-year-olds and 6-9-year-olds (p < 0.01) and 13-17-year-olds and 10-12-year-olds (p = 0.01), but in children with ASD, the effect is largest in 10-12-year-olds (0.224 uV) and differences between cohorts are not significant (Fig 5.4).

N1 Timeframe – Overall VEP

Main effects of hemiscalp and extent were also measured during the N1 latency collapsed across IC-conditions. While this does not address the main hypothesis, which employs IC-difference as an index of perceptual closure, it reflects visual processing differences in the overall VEP. There was a main effect of hemiscalp (F(90, 1) = 8.69; p < 0.01; η² partial = 0.088),
with a larger VEP over the right (-2.03 µV) than the left (-1.04 µV). Pairwise comparisons (Bonferroni corrected) revealed two statistically significant comparisons: 4° versus 7° (0.582 µV; p = 0.02) and 4° versus 10° (0.770 µV; p < 0.05).

A main effect of extent (F(180,2) = 6.89; p < 0.01 (Greenhouse-Geisser adjusted); η² partial = 0.071) demonstrates that participants are sensitive to the extent manipulation. Extent varied directly with amplitude: 10° -1.93 µV; 7° = -1.62 µV; 4° = -1.04 µV. Given that our developmental investigation of neurotypical participants showed no such effect (Altschuler, T.S. et al., In submission), we did a post-hoc exploration of the ASD group whose N1 varies significantly with contour extent (F(45, 2) = 6.0; p < 0.01 (Greenhouse-Geisser); η² partial = 0.118, whereas the TD participants’ does not (Table 5d).

Nycl Timeframe

Maturing neurotypical children showed an IC-effect during a second, later timeframe, an effect which decreased as they matured, and was no longer present in adulthood (Altschuler, T.S. et al., In submission). TD and ASD groups were compared to see if a similar response exists in children with ASD. Most notably, no effects of diagnostic group were measured during the Nycl timeframe. Responses in TD and ASD participants appeared largely equivalent (Fig 5.1).

Differences between IC conditions are significant collapsed across diagnostic group and age (F(90, 1) = 207.571; p < 0.01; η² partial = 0.698) but in the opposite direction from that measured during the N1 timeframe: IC (4.03 uV) < No-IC (5.60 uV). The difference decreases significantly as participants age, regardless of diagnosis. This is reflected in an interaction of IC x age (F(90, 2) = 13.97; p < 0.01; η² partial = 0.237). Follow-up pairwise t-tests (Bonferroni corrected) are significant for every age group 6-9 (p = 1.2 x 10⁻¹⁶), 10-12 (p = 1.7 x 10⁻¹⁷), and
13-17 (p = 0.00009). The results of the regression of IC difference upon age bears out the same progression: TD quadratic $R^2 = 0.284; F_{(45,2)} = 8.9; p < 0.01$ and ASD quadratic $R^2 = 0.269; F_{(45,2)} = 8.29; p < 0.01$ (Fig 5.5).

In addition, a main effect of extent ($F_{(180,2)} = 21.19; p < 0.01$ (Greenhouse-Geisser adjusted); $\eta^2_{\text{partial}} = 0.191$) reflects differences in the overall VEP magnitude relative to the extent manipulation collapsed across age and diagnostic group. In contrast to the N1 timeframe, the VEP varies inversely with extent during the N_{cl} timeframe $4^\circ = 5.60 \mu V, 7^\circ = 4.92 \mu V, 10^\circ = 4.52 \mu V$. Follow-up pairwise $t$-tests are significant for every comparison (Table 5e).

**Dipole analyses**

Two symmetrical dipole sources were modeled for the 30 ms window centered on the N1 and the 40 ms window centered on the N_{cl} of the global field power (GFP) of the differences between IC and No-IC conditions, collapsed across extent. Color-coded maps show dipole solutions for each age cohort and group (Fig 5.7). Fits exceed 91% of variance in every case. All N1 solutions are estimated to fall within Brodmann Area (BA) 19 as estimated on Talairach Client software (Lancaster, J.L. et al., 1997; Lancaster, J.L. et al., 2000) which encompasses LOC. In the N_{cl} timeframe, solutions were more variable. They were estimated to fall in BA 19, BA 22, which includes the temporal lobe, and BA 37, encompassing occipital-temporal cortex and fusiform gyrus.
DISCUSSION

The hypo-priors account proposes that increased variance in the integration of prior knowledge with incoming sensory stimuli underlies perceptual differences in ASDs (Pellicano, E. et al., 2012). To test this, we investigated contour completion of ICs – a process whereby the visual system fills-in gaps in fragmented contours. Contour extent and inducer size were manipulated, on the premise that contour completion across larger gaps would be more taxing for the visual system and could reveal impairment in integrating priors. We employed a well-tested theoretical model describing two phases of IC processing using VEPs - an automatic phase occurring between 100 and 200 ms, and a second phase from 230 to 400 ms seen in children and adolescents, but only in adults when integrating contours under more challenging conditions.

The Early Phase

Changes in perceived illusion strength have been associated with the manipulation of IC size parameters for neurotypical persons (Watanabe, T. & Oyama, T., 1988; Shipley, T.F. & Kellman, P.J., 1992), but these were not reflected in the VEP amplitude of neurotypical children (Altschuler, T.S. et al., In submission). In the present study, a manipulation of the distance between inducers and inducer size produced a difference between ASD and TD groups. Although the IC-effect was present for each condition, age cohort, and group, it was significantly smaller over right hemisphere in the TD group in the middle sized (7°) condition. Outliers did not explain this effect, nor could it be accounted for given current knowledge about the stimuli, development, or ASDs. The possibility of obtaining a false-positive result increases with the number of interaction terms in an ANOVA, so it is not unlikely that this result is a false positive. Except for this difference in one condition out of 12, there appeared to be no difference in IC-
effect amplitude related to extent manipulation or age between ASD and TD groups, a similarity echoed by topographies and dipole source models.

We were struck by a pattern of results that differentiated ASD from TD groups but did not reach statistical significance. The amplitude of the IC-effect for individuals with ASD varied directly with contour extent. We reported in Chapter 4 that feedback-dominated processing, as indexed by the IC-effect, occurred significantly later for individuals with ASD than for their neurotypical counterparts. The completion of contours is a process combining incoming information about the inducers feeding up the visual hierarchy with information about configuration feeding back down (Murray, M.M. et al., 2002; Wokke, M.E. et al., 2013), resolving the question of whether the empty space between the inducers should be filled-in. We suggested that delayed feedback in ASD might result in processing dominated by locally oriented, feedforward information for a longer time. The trend towards a direct relationship of extent and IC-effect amplitude in persons with ASDs suggests the visual system could maintain representation of lower-level information longer than neurotypical persons do. However, it is not statistically significant so we must interpret our outcomes to suggest that the IC-effect in persons with ASDs is similarly cue-invariant to that of neurotypical persons.

**Overall VEP Amplitude Differences During N1 Latency**

Significant differences relative to extent are seen in the overall N1 amplitude collapsed across other conditions. This is notable for two reasons. It demonstrates sensitivity to the range of the manipulation within our participants. Past manipulations of extent revealed no difference in the N1 for neurotypical adults, adolescents, or children (Altschuler, T.S. et al., In submission), so this effect may be driven by the addition of ASD participants. A post-hoc exploration within each group bore out this interpretation. This is also an indication that the visual system of
persons with ASDs may keep lower-level information actively encoded during a timeframe when it is been become irrelevant for their neurotypical counterparts.

We replicated a commonly observed difference whereby overall VEP amplitude decreased noticeably in relation to age (Gomes, H. et al., 2001; Brandwein, A.B. et al., 2011; Altschuler, T.S. et al., In submission). Some have attributed this effect to volume conduction differences due to age-related changes in skull thickness (Adeloye, A. et al., 1975) but this difference is not fully understood. The consequence of these variant VEP amplitudes is that an identical difference between conditions will represent a larger effect relative to a smaller VEP, as is seen in 13 to 17-year-olds, than to a larger VEP, as is measured in 6 to 9-year-olds. We conducted a post-hoc analysis comparing the ratio of the IC-effect to the P1 amplitude for each group and age cohort (Fig 5.4). Using this approach, a significant increase in IC-effect is seen in neurotypical persons as they age, but not in participants with ASD, suggesting that contour completion mechanisms develop differently in ASD and TD groups.

**The Later Phase**

While neurotypical adults appear to process passively viewed, centrally presented ICs in a single early timeframe indexed by the IC-effect, neurotypical children and adolescents reveal additional processing during a later timeframe typically associated with perceptual conditions of increased burden such as completing objects of increased complexity (Doniger, G.M. et al., 2000), discrimination tasks (Murray, M.M. et al., 2006), or processing compromised by pathology (Doniger, G.M. et al., 2002). In the neurotypical group, the amplitude of this phase peaked between 10 and 12 years-of-age and tapered off in adulthood. The developmental trajectory of this second phase appeared no different up to 17-years-of-age in individuals with
ASD, but dipole model solutions were more variant. Sources were estimated to be localized more widely throughout temporal and occipital-temporal areas.

**Contour Completion and ASD**

We have observed that for children with ASD, the amplitude of electrophysiological responses following IC completion across an array of contour extents is not measurably different from that of TD persons. Null results may seem unspectacular, but they are hardly trivial if you have an autism diagnosis. Despite some indications that processing continues to be influenced by lower level aspects of the stimulus for a longer time in ASD, neurophysiological contour integration effects are intact. This is key not because it is adaptive to complete IC contours, but because this ability suggests that the visual system completes impoverished or ambiguous signals, a ubiquitous component of everyday object processing.

The delayed onset of feedback-dominated processing suggests an account where visual processing in ASD is less reliant on predictive processes, yet the IC-effect remains significant, why might this be? In a study of adult IC contour completion, we suggested that invariance to manipulation of extent constituted a binary test of ‘objectness.’ As long as contour parameters exceeded a minimal threshold, the outcome signals that the contour fragments belong to the same object and the gap between them is filled-in (Altschuler, T.S. et al., 2012). One possibility is that thresholds for the test of ‘objectness’ in persons with ASDs may be tuned to accommodate a more feedforward-dominated signal.

Early automatic contour completion based upon parametric cues is sufficient for adults, but IC contour processing in typical children and those with ASD is more protracted. The additional
processing has been measured during a timeframe associated with completing objects under conditions of greater difficulty. For example, in a neurotypical adult investigation, participants were shown line drawings of everyday objects with so many gaps in their contours that the images were unrecognizable. Each successive showing added back a little more of the missing contours until recognition was achieved. This resulted in no IC-effect but a gradual modulation in the VEP between 230 and 400 ms (Doniger, G.M. et al., 2000). However, if the originally unrecognizable image is shown a second time soon after the first viewing, then participants recognize it even in its most fragmented version. The VEP response is seen in the case of this repeat viewing, during the earlier timeframe (Doniger, G.M. et al., 2001). The reliability of the predictions generated during the earlier phase may be tuned over multiple exposures as reported for other instances of priors (Thomas, R. et al., 2010), for cue-invariant object processing in non-human primates (Li, N. & DiCarlo, J.J., 2010), and in other accounts of IC processing (Bertenthal, B.I. et al., 1980; Putzar, L. et al., 2007). Intracranial work in humans has suggested that, when the limits of the early automatic IC processes are reached, the LOC becomes part of a network implicated in recurrent process facilitating matching between the prefrontal cortex, which generates conceptual-level hypotheses, and the hippocampal formation, which may function as a reservoir of mnemonic object representations (Sehatpour, P. et al., 2008).

Foxe et al (2005) have proposed that later frontal activity in IC processing in schizophrenic individuals may compensate for impairments in earlier activity. Work with adolescents and young adults with ASDs using texture stimuli, demonstrated reduced VEP amplitude between 121 – 203 ms correlated with impaired contour detection (Vandenbroucke, M.W. et al., 2008). These investigators measured intact recurrent processing from 242 to 320 ms, but they posited enhanced lateral occipital activity around 225 ms as a possible compensatory mechanism. Given
delayed onset of early IC processing in ASD peaking at 232 ms in 10 to 12 year olds and 250 ms in 6 to 9 year olds (Chapter 4), it is possible that early processing overlaps with later compensatory processes, facilitating an IC-effect with typical amplitude.
Table 5a - Participant descriptive data

<table>
<thead>
<tr>
<th>Group &amp; Age Cohort</th>
<th>N (f)</th>
<th>Mean Age (SD)</th>
<th>Mean PRI (SD)</th>
<th>Mean Trials per condition (SD)</th>
<th>Mean Orthogonal Task Perf (SD)</th>
<th>Mean ADOS Calculated Severity Score (# of scores)</th>
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<tbody>
<tr>
<td>TD</td>
<td></td>
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<tr>
<td>6-9</td>
<td>15 (8)</td>
<td>8.0 (0.86)</td>
<td>109.1 (11.6)</td>
<td>155.6 (28.2)</td>
<td>82.6 (18.8)</td>
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<tr>
<td>10-12</td>
<td>16 (6)</td>
<td>11.6 (0.91)</td>
<td>109.6 (9.9)</td>
<td>157.9 (41.8)</td>
<td>94.3 (6.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>13-17</td>
<td>17 (8)</td>
<td>14.9 (1.1)</td>
<td>106.5 (14.7)</td>
<td>203.2 (39.9)</td>
<td>95.5 (4.1)</td>
<td>n/a</td>
</tr>
<tr>
<td>total</td>
<td>48 (22)</td>
<td>11.7 (2.9)</td>
<td>108.3 (12.1)</td>
<td>172.2 (26.8)</td>
<td>90.8 (7.1)</td>
<td>n/a</td>
</tr>
<tr>
<td>ASD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td>15 (0)</td>
<td>8.3 (0.76)</td>
<td>106.6 (12.9)</td>
<td>139.8 (44.3)</td>
<td>72.5 (21.0)</td>
<td>8.4 (14)</td>
</tr>
<tr>
<td>10-12</td>
<td>17 (3)</td>
<td>11.8 (0.82)</td>
<td>99.8 (17.9)</td>
<td>199.6 (51.2)</td>
<td>84.0 (13.7)</td>
<td>8.5 (15)</td>
</tr>
<tr>
<td>13-17</td>
<td>16 (2)</td>
<td>14.8 (1.3)</td>
<td>112.9 (10.4)</td>
<td>193.3 (68.7)</td>
<td>87.9 (10.4)</td>
<td>7.6 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (5)</td>
<td>11.7 (2.8)</td>
<td>106.4 (14.8)</td>
<td>177.6 (32.8)</td>
<td>81.5 (8.0)</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Table 5b - Interaction of IC x hemiscalp x extent

<table>
<thead>
<tr>
<th></th>
<th>4° (µV)</th>
<th>p value</th>
<th>7° (µV)</th>
<th>p value</th>
<th>10° (µV)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>1.21</td>
<td>7.1 x 10^-7</td>
<td>1.43</td>
<td>2.9 x 10^-9</td>
<td>1.33</td>
<td>7.5 x 10^-8</td>
</tr>
<tr>
<td>Right</td>
<td>1.56</td>
<td>2.86 x 10^-12</td>
<td>0.91</td>
<td>0.00001</td>
<td>1.32</td>
<td>4.5 x 10^-7</td>
</tr>
</tbody>
</table>

Table 5c - Interaction of IC x hemiscalp x extent x diagnosis

<table>
<thead>
<tr>
<th></th>
<th>4° (µV)</th>
<th>p value</th>
<th>7° (µV)</th>
<th>p value</th>
<th>10° (µV)</th>
<th>p value</th>
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</thead>
<tbody>
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<td>TD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1.23</td>
<td>0.0002</td>
<td>1.36</td>
<td>0.00003</td>
<td>1.04</td>
<td>0.002</td>
</tr>
<tr>
<td>Right</td>
<td>1.75</td>
<td>3.3 x 10^-9</td>
<td>0.50</td>
<td>0.08</td>
<td>1.13</td>
<td>0.001</td>
</tr>
<tr>
<td>ASD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1.18</td>
<td>0.0004</td>
<td>1.50</td>
<td>0.00005</td>
<td>1.62</td>
<td>0.00002</td>
</tr>
<tr>
<td>Right</td>
<td>1.29</td>
<td>0.000004</td>
<td>1.33</td>
<td>0.00007</td>
<td>1.51</td>
<td>0.00003</td>
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</table>
Table 5d – VEP magnitude during N1 latency x extent

<table>
<thead>
<tr>
<th></th>
<th>TD (µV)</th>
<th>ASD (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4°</td>
<td>-0.61</td>
<td>-1.48</td>
</tr>
<tr>
<td>7°</td>
<td>-0.89</td>
<td>-2.36</td>
</tr>
<tr>
<td>10°</td>
<td>-1.06</td>
<td>-2.80</td>
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</tbody>
</table>

Table 5e – VEP magnitude during N_{cl} latency x extent

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mean difference (µV)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4° vs 7°</td>
<td>0.68</td>
<td>0.00005</td>
</tr>
<tr>
<td>4° vs 10°</td>
<td>1.07</td>
<td>9.9 x 10^{-7}</td>
</tr>
<tr>
<td>7° vs 10°</td>
<td>0.39</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Figure 5.1 Caption - VEP grand average waveforms

IC (blue) and No-IC (red) and subtraction waves for each diagnostic group, age group, and extent. Epoch of -150 to +600 ms at electrodes PO3 and PO4 are shown as representative. Waves are re-referenced to electrode AFz. Difference waves depict each contour extent 4° (green), 7° (orange), 10° (burgundy).
Figure 5.1

A. 6-9
N = 15

B. 10-12
N = 16

C. 13-17
N = 17

D. 6-9
N = 15

E. 10-12
N = 17

F. 13-17
N = 16
Figure 5.2 Caption

Bar graphs - IC difference amplitude (y axis) x hemiscalp (x axis) x extent (4° = blue, 7° = green, 10° = tan) x diagnosis, during N1 latency. Error bars = +/- 2 standard errors.

Figure 5.3 Caption

Scatterplot – IC difference amplitude (y axis) x age (x axis), during N1 latency for neurotypical (Blue) and ASD (green) participants.
Figure 5.2

Figure 5.3
Figure 5.4 Caption
Bar graph – Ratio of IC difference amplitude to P1 magnitude (y axis) x age (x axis)x diagnosis (TD = blue; ASD = Green)

Figure 5.5 Caption
Scatter plot – IC difference amplitude (y axis) x age (x axis), during Ncl latency, for TD (blue) and ASD (green) participants.
Figure 5.4

![Graph of N1-P1 Ratio x Age x Dx Group]

Error Bars = 2 SE

Figure 5.5

![Graph of IC Difference x Age]
Figure 5.6 Caption

Topographical Voltage Maps for difference between IC and No-IC conditions during N1 and Ncl latencies, for TD and ASD participants in 3 age groups (6-9, 10-12, 13-17).
Figure 5.6
Figure 5.7 Caption

Dipole Models for N1 and Ncl timeframes in TD and ASD participants of 3 age groups: 6-9 (red), 10-12 (blue), 13-17 (green) and their goodness of fit. Talairach coordinates are shown for only 1 hemisphere as models are symmetric.
Figure 5.7

Altschuler, T. S., Molholm, S., Butler, J. S., Mercier, M. R., Brandwein, A. B., & Foxe, J. J. (In submission). The effort to close the gap: Tracking the development of illusory contour processing from childhood to adulthood with high-density electrical mapping. *Neuroimage*.


Chapter Six
Discussion

The preceding pages have reported on four explorations of the dynamics of contour integration using Kanizsa illusory contour (IC) stimuli (Kanizsa, G., 1976). This is one of many processes by which the brain organizes the units of our visual world, grouping certain of those units together, while excluding others. Manipulations of extent parameters of ICs have led to variations in subjective reports of illusion strength (Petry, S. et al., 1983; Watanabe, T. & Oyama, T., 1988; Banton, T. & Levi, D.M., 1992; Shipley, T.F. & Kellman, P.J., 1992). We attempted to provoke a similar range of responses in the strength of electrophysiological indices of contour integration to help reveal underlying neural mechanisms. In addition, we detailed the developmental trajectory of this process over childhood and adolescence. Finally, given numerous accounts of altered integration of global and local processing in persons with autism spectrum disorders (ASDs) (Kanner, L., 1943; Frith, U., 1989), we applied our developmental analysis to elucidate possible mechanisms behind this aspect of the ASD phenotype.

Discussed here are three principle outcomes: 1) Neurotypical persons and those diagnosed with ASDs across the range of ages studied (6 years old to adulthood) were capable of perceiving the illusion and demonstrated a classic electrophysiological response to the presentation of an IC stimulus – the IC-effect. 2) The amplitude of this effect was invariant to manipulation of extent parameters. 3) The onset of this response was delayed in participants with ASD.

The analysis of the preceding data rests on two fundamental assumptions. One is, given that ambiguity and complexity are inherent to most sensory input, prior knowledge is necessary for perception (James, W., 1890; von Helmholz, H., 1910). The ideas of “priors” intended here are neural representations acquired through exposure of the usual occurrences of phenomena in nature, such as the direction from which light comes. Although most of us performed
summersaults as children, turning the usual pattern on its head, light sources were more frequently above us. Thus our exposure would produce a prior encoding this likelihood (Thomas, R. et al., 2010). Object perception using priors is envisioned as a process of inference. Because visual features could suggest a number of possible scenes, priors are applied to disambiguate those features on the basis of statistical likelihood (Pollen, D.A., 1999; Kersten, D. et al., 2004). In the case of light from above, the shadow cast by an object may help the visual system resolve ambiguity between potential representations of features.

Priors, as representations of configural or more abstract conceptual information, represent global dimensions of objects or scenes. Higher level cortex is associated with representing greater degrees of abstraction and lower areas with more concrete sensory-level data, so models in which internally generated global predictions shape the interpretation of sensory features generally implicate feedback pathways (Rao, R.P. & Ballard, D.H., 1999; Murray, S.O. et al., 2002; Lee, T.S. & Mumford, D., 2003). Adaptive resonance theory asserts that encodings of possible outcomes of sensory stimuli may precipitate synchronous resonance across a network of processing regions. For those representations failing to match the prediction, the resonance is suppressed via feedback activity (Mumford, D., 1992; Pollen, D.A., 1999).

The second assumption is that contours are integrated over two successive phases. An early phase indexed by the IC-effect. During it, contours are automatically completed – an example of priors disambiguating visual features via feedback (Murray, M.M. et al., 2002; Shpaner, M. et al., 2013). We propose that the priors associated with this first phase are representations of perceptual level parameters, such as the distance between features. The LOC is proposed to be the source of the feedback to lower visual cortex. The later phase - the N_{cl} - is seen in situations of increased perceptual burden such as the processing of complex objects, or processing
compromised by pathology (Doniger, G.M. et al., 2002; Murray, M.M. et al., 2006). It is believed to index a gradual filling-in process employing conceptual-level priors, facilitated by recurrent processing among a distributed network of regions, meaning the LOC is not only a source of information, but also a recipient of feedback from prefrontal cortex (Sehatpour, P. et al., 2008) (Fig 1.9).

The IC-Effect From Six Years of Age to Adulthood

In Chapters 2 and 3, we offered evidence of the elicitation of the IC-effect in neurotypical persons 6 to 31 years-of-age. We consistently measured effects associated with IC processing during the latency of the highly stable N1 component no matter the age of the participant. This suggests that the early automatic phase of contour integration arises out of consistent overall visual processing across ages. However, we also measured a significant period of IC processing during the later Nc1 timeframe in children that was not present in adults. Topographical voltage mapping during this timeframe showed greater activity over fronto-central scalp (Figure 3.8). We propose that this may reflect the activity of frontal areas that are implicated in later, conceptual-level processing of objects (Sehatpour, P. et al., 2008) and that children may require a longer time to resolve the ambiguity of whether to integrate contour fragments. Given that the second phase is believed to involve processing across a more widely dispersed network which includes frontal areas, we believe that less mature visual systems cannot rely solely on the perceptually based statistical estimates that underlie the IC-effect. Higher level processes likely compensate for the relative immaturity of automatic processing in the same way that later processing phases appear to compensate for other challenges to contour completion such as increased stimulus complexity (Doniger, G.M. et al., 2000), or processing compromised by pathology (Doniger, G.M. et al., 2002; Foxe, J.J. et al., 2005).
The LOC serves a prominent role in representing object identity (Grill-Spector, K. et al., 2001). In an inferential processing model it is proposed to represent predictions regarding the configuration of elements encoded at lower levels (Kersten, D. et al., 2004). Indeed, our own dipole models suggest LOC involvement in the generation of the IC-effect (Figures 2.7, 3.9, and 5.7). It is possible that the LOC is a repository for the encoding of these predictions, or alternatively that they are conveyed there from dorsal stream inputs which have arrived by this latency (Murray, M.M. et al., 2002; Bar, M. et al., 2006; Snyder, A.C. et al., 2012). Integrating with feedforward sensory input from the ventral stream, an inference is made regarding whether the inducers represents 4 objects or 1. It is clear that this process has its limits since the filling-in of the gap between inducers is a mistake. There are 4 inducers present. Humans are unlikely to have encountered enough Kanizsa ICs over the millennia to tune statistical thresholds which more accurately predict their specific parameters – that, or the efficiency has served us better than accuracy. There is evidence to suggest that reliance on priors in general (Adams, W.J. et al., 2004; Thomas, R. et al., 2010) and processing of ICs specifically (Bertenthal, B.I. et al., 1980; Csibra, G. et al., 2000; Putzar, L. et al., 2007) are exposure dependent.

Chapter 1 (pp 65-70) offered a contradictory array of conclusions regarding development of grouping and completion processes. We assayed children 6 to 18 years of age based on reports of development in grouping of visual features during infancy (e.g., Bertenthal, B.I. et al., 1980), childhood (e.g., Dukette, D. & Stiles, J., 1996), and adolescence (e.g., Scherf, K.S. et al., 2009). It had been widely accepted that 10 is the approximate age of change from local to a global bias (Carey, S. & Diamond, R., 1977). In addition, given that IC processing likely involves the integration of information from the two cerebral hemispheres (Pillow, J. & Rubin, N., 2002), evidence for anatomical development of the corpus callosum from 4 to 18 years-of-age (Giedd,
J.N. et al., 1996) led us to begin our developmental exploration around this age. So why didn’t we see evidence for such development in the amplitude of the *IC-effect* across our age groups?

In a comparison of early and late processing phases of contour integration, the accuracy of shape discriminations made of illusory objects was correlated only with effects during the *N*<sub>cl</sub> and *not* during the N1 latency (Murray, M.M. et al., 2006). The binding processes occurring during *IC-effect* latency can occur without awareness, as studies with hemi-neglect patients has shown (Vuilleumier, P. et al., 2001). Much of the developmental literature exploits behavior and fMRI as metrics. These are valuable tools, but neither offers the temporal resolution of visually evoked potentials (VEPs). In the case of IC processing, this could conflate processes occurring during early and late phases. Task-dependent paradigms rely on awareness of stimuli in order to elicit measurable behaviors. This leads us to believe that the behaviors measured in previous studies likely reflected processing during the *N*<sub>cl</sub> timeframe. This is indeed the timeframe during which we observed change in amplitude across age (Figure 3.4).

With regard to the automatic contour completion processes indexed by the *IC-effect*, we propose that children older than 5 years-of-age have acquired sufficient exposure to signal the binding of contours based on statistical prediction in this initial phase, but insufficient exposure to rely on this inference completely in resolving the ambiguity of the sensory input. Therefore, the later recurrent processing, which involves matching to more conceptual level representations of objects, while slower, yields more reliable outcomes.

However, a post-hoc analysis of the earlier phase response as a ratio of overall visual response revealed changes in *IC-effect* amplitude across age for typically developing participants but not for those with an ASD (Figure 5.4). When adjusting for the amplitude of the overall visual response, younger brains produce electrophysiological signals which differentiate less
between illusion-inducing and non-inducing conditions of ICs. This may mean that the predictive output is less reliable than that produced by more mature brains, justifying the additional phase of activity seen in younger participants. At this point, we do not know which analysis yields a “truer” picture of IC processing.

Future Studies
The results covered in the previous chapters suggest three future studies.

1) The absence of an electrophysiological difference between age groups in the context of so much behavioral evidence prompts our interest in widening the age range of the present exploration to include younger participants. A VEP study measured the IC-effect in typically developing boys 3 to 6 years-old, but it was significant only at 1 of the 6 electrodes measured (Stroganova, T.A. et al., 2007). This suggests a less robust effect in younger children, but these investigators assayed medial rather than lateral electrodes and their baselining was less than optimal.

2) We would like to explicitly assay the development of processing during the Ncl timeframe with stimuli that elicited such a response in adults. This could be accomplished using either the degraded pictures paradigm described on page 72 (Doniger, G.M. et al., 2000; Doniger, G.M. et al., 2001) or the fat/thin task described on page 74 (Murray, M.M. et al., 2006).

3) A less fully developed, but intriguing question raised by these results is, if the initial predictive phase in children produced a less reliable outcome which necessitates compensatory processing – what did that outcome look like? One possibility is that less reliable predictions would produce some sort of error. Measuring an error with IC stimuli could be challenging. There are no extraneous elements to be bound. Feature Integration Theory (FIT) (Treisman, A.M. & Gelade, G., 1980) asserts that errors in binding can be
made. In executing a visual search for a target among multiple features, under conditions such as reduced time or attention, features not belonging to the same object can be combined. For example, in searching among a field of green-horizontal and red-vertical elements, a red-horizontal element might be reported – a so-called illusory conjunction. Developmental analyses of such errors in binding have thus far produced confusing results. Fewer illusory conjunctions of color and shape have been measured in children 5 to 8 years old than in adults, and children failed to produce them altogether in a task involving parts of triangles. It is possible that binding errors may not be a metric of early stage contour integration; they may reflect later stages of processing (Kolinsky, R., 1989). A number of studies have employed a search paradigm among a field of 15 or 20 Kanizsa IC inducers in two conditions, one where no ICs are formed and the other where a single IC is induced among the many inducers (e.g., Bulf, H. et al., 2009). VEPs have been recorded in adults participating differentiating processing during N1 and N2 timeframes to this type of stimulus (Senkowski, D. et al., 2005). Similar stimuli could be developed, including a second feature such as color or orientation. This experiment would combine IC integration metrics with the possibility of making illusory conjunctions. It would be useful to know if binding errors are more frequent in children. Knowing during what timeframe they are made would help us better understand the neural mechanisms beneath contour integration.

An alternative picture of a less reliable outcome of the early phase in children would be that it simply results in further processing. We proposed in Chapter 2 that the process underlying the IC-effect is one with a binary outcome – either disambiguation of the visual elements is accomplished or it is not. If neurons spoke in the language of a computer from a 1960s science fiction film, they might say: ‘disambiguation achieved, no further processing
Continued processing might exact some costs in situations where there is competition for cognitive resources, but it wouldn’t necessarily produce binding errors. In this alternative scenario, we might expect delayed processing when the visual system is challenged by the process of contour integration. This is what occurred relative to manipulations of support ratio in adults, and when comparing neurotypical and ASD groups.

**Parametric manipulations**

We manipulated three extent parameters to tax integration processes and reveal their vulnerability in the context of typical and atypical development. Amplitude of the *IC-effect* was invariant to all manipulations in adults *(Chapter 2)*. One manipulation, varying contour extent and inducer volume while holding support ratio constant (Figure 2.3), resulted in no VEP differences in amplitude, latency, or in the dipole source model. For this reason, we chose this manipulation to explore developmentally, since any elicited variation could likely be attributed to age. Four age groups of neurotypical children were assayed *(Chapter 3 and 4)*, resulting in no significant variation in amplitude or latency. Within the range of our manipulations, the *IC-effect* appears remarkably robust developmentally, and this is not because the visual system was insensitive to our manipulation. A variation in P1 amplitude was measured in neurotypical children.

Manipulation of configural parameters has been shown to impact the subjective experience of illusion strength in multiple studies *(Petry, S. et al., 1983; Watanabe, T. et al., 1988; Banton, T. et al., 1992; Shipley, T.F. et al., 1992)*, so we conjectured that there would likely be an electrophysiological antecedent to this experiential change. Most of this work relied on participants’ awareness of stimuli to elicit measures. As such, they likely measure processing
indexed by the N_{el}. We asserted in Chapter 2 that this is because during N1 latency no shape has yet been induced for the viewer to assess. It might be more accurate to say that whether or not binding has produced the boundaries of the illusory square, that it is not accessible to awareness. The process indexed by the IC-effect classifies stimulus elements as belonging to the same object but it remains for recurrent loops of processing between higher and lower areas to make that object a representation accessible to awareness (Pollen, D.A., 1999).

The results of our dipole modeling of the IC-effect implicate LOC anatomically (Figures 2.7, 3.9, and 5.7), but cue invariance adds support for LOC involvement. There are those who pose that contour integration occurs exclusively via feedforward processes in lower level visual areas (e.g., Grosof, D.H. et al., 1993) and others who implicate initial activity in higher visual regions such as the LOC, which feedback to lower visual cortices (Murray, M.M. et al., 2002; Shpaner, M. et al., 2013). As reviewed in Chapter 1, while V1 and V2 are sensitive to featural dimensions of objects such as orientation, there is abundant evidence that LOC responses are cue-invariant (Grill-Spector, K. et al., 2001). We not only measured LOC activity prior to latencies when V1 or V2 activation have typically been measured (Seghier, M.L. & Vuilleumier, P., 2006; Shpaner, M. et al., 2013), we also measured cue-invariance to the parametric manipulation of IC inducers. This invariance, as a response property of LOC, but not of V1 or V2 neurons, adds support to early involvement of the LOC.

We did measure sensitivity to the parametric manipulation during P1 latency, but not 60 ms later during the IC-effect. One could argue that the failure to measure the effect of the extent manipulation results because the IC-effect is a subtraction of two conditions in which extent are the same, but no effect is measured in the overall N1 either, which is an average of the two conditions. If you recall from Chapter 1 (p 65) Lee and Mumford (2003) believed that feedback
facilitated disambiguation by reducing irrelevant representations at the feature-level, an idea evoking the Gestaltist conception of Prägnantz (Koffka, K., 1935), which posits that grouping stimulus elements facilitates the pithiest representation of sensory information. This subsuming of feature level information under the broader object category might represent Lee and Mumford’s “explaining away” in action.

Our comparison of neurotypical participants with those with ASDs also measured no amplitude variation of the IC-effect in response to the manipulation of extent. Despite multiple accounts of impaired global processing in ASDs (e.g., Shah, A. & Frith, U., 1993; Pellicano, E. et al., 2005), the processes tested here, which we propose to facilitate Gestalt grouping of visual elements into objects, are not impaired. What is notable is that individuals with ASDs show variation of the overall N1 amplitude relative to manipulation of contour extent, suggesting that their visual processing does differ from that of typical persons, as it maintains representation of this lower-level stimulus dimension. Apparently, this has not impeded the ability of persons with ASDs, by their own report, to perceive ICs. Persons with ASDs generate an IC-effect, suggesting that the binding of contour elements has been anticipated, if not achieved via some means. In Chapter 5 we proposed that the visual system may have adapted the statistical threshold for this process to accommodate a signal dominated by a greater representation of feature-level information and, hence, one less influenced by prior knowledge.

If extent has not been entirely “explained away,” if its neural representation exists beyond the point where it appears relevant to neurotypical object processing – how does that affect a person with ASD? Chapter 1 is filled with examples of individual perceptual experiences that differ from that of many typical persons. Accounts of senses overwhelmed by details abound (e.g., Akari, 2010; Listic, A., 2012). Perhaps this arose in visual systems that have not eliminated
representations of irrelevant stimulus dimensions. Even if these fall beneath the level of awareness, their encoding could burden the sensory processing system in cases where information load exceeds processing capacity. A possible example of this may be seen in an ERP assay of TD and ASD individuals 9 to 20 years-of-age (Baruth, J.M. et al., 2010). They performed a detection task of targets among different IC shapes. The P100 (which they called P50), N100, and N200 components were measured. Generally, P50 responses are of greater amplitude to target versus non-target stimuli, but the reverse was true for ASD participants. Strong responses to non-target stimuli over parietal-occipital and frontal sites and later (P200) responses that failed to discriminate between target and distractor stimuli, and an increased error rate, all suggested to these investigators that early sensory discrimination processes fail to filter out what is irrelevant.

*Future Studies*

We had hoped to reveal the limits of the automatic binding process which underlies the IC-*effect* and instead revealed no amplitude effects within the range of our manipulation. But a predictive process with a parametric basis *must* have limits, or else our world would be one big mass of bound fragments

1) We would like to extend the range of the parametric manipulations to discover the extent or support ratio that does not elicit a response. Lamb and Robertson’s (1990) investigation of hierarchical stimuli found that the processing advantage progressed from a global to a local as the size of stimulus increased. However, when they compared two sets of stimuli, one ranging from 1.5° to 6° and the other from 3° to 12°, the transition occurred at a larger size for the larger set. This suggests that parametric effects are not merely tuned via exposure during a developmental window, but are updatable. This could be tested with a blocked
design that started at the lowest support ratio and worked up to approximately 21%, the lower limit of the present investigation. After a break or activity to interfere with contextual effects of the first range, the manipulation would be presented in the opposite direction. We expect that any limits to parametric manipulation will vary relative to the range of that manipulation.

2) We have interpreted our results based upon intracranial work implicating a coherent network including the LOC, prefrontal cortex, and hippocampal in the generation of the N_{cl}. Two assays of the neural generators of the N_{cl} (Sehatpour, P. et al., 2006; Sehatpour, P. et al., 2008) offer model paradigms to confirm the sources and add support to our contention that immature early phase processes are being compensated for by later ones. These could make use of the thin/fat stimuli (Murray, M.M. et al., 2006) or degraded pictures stimuli (Doniger, G.M. et al., 2001) described in Chapter 1. The first approach would integrate the temporal precision of ERP and the spatial resolution of MRI by co-registering their data. Given the large percentage of persons with ASD who have a co-morbid epilepsy diagnosis, a small number of persons could be recruited for intracranial recordings directly from these hypothesis-defined regions of interest and these data submitted to an analysis of coherence in the beta bandwidth, a metric of oscillatory activity that could provide evidence of a coherent network among these regions, as is seen in adult processing during the N_{cl} timeframe. We hypothesize that this coherence may be reduced in ASD compared to TD groups, given reports of reduced long-range connectivity (Barttfeld, P. et al., 2011).

**Temporal Processing Differences and ASDs**

In addition to understanding contour integration development, our initial inquiry concerned atypical balances of global/local processing in ASDs. A recent model posits that this commonly observed aspect of the phenotype may arise from the fact that prior knowledge shapes incoming
sensory information less – the hypo-priors account (Pellicano, E. & Burr, D., 2012). We measured a delay in the onset of the IC-effect in ASD relative to typical children and adolescents. If the IC-effect is a feedback-dominated process, an assumption supported in Chapter 1 (pp 60 – 66), a delay in its onset, with no delay in the onset of the feedforward visual signal, offers a credible mechanism for this hypo-priors model.

Why would a feedback-specific dysfunction offer a credible mechanism of this ASD phenotype? Feedback and feedforward circuitry arise from different populations of neurons and target anatomically different synaptic targets. While feedforward axons reach their targets around four months of age, feedback axons do not do so until later (Burkhalter, A., 1993). This makes their development potentially vulnerable to assaults (Berezovskii, V.K. et al., 2011) and the maturity of their predictive processes vulnerable, as they are initially tuned by exposure to feedforward inputs (Rao, R.P. et al., 1999). Behavioral signs of autism are often reported as absent in early infancy, emerging over time (Ozonoff, S. et al., 2010). The later development of feedback circuitry could offer a biological explanation for delayed symptom onset. In addition, it is hypothesized that feedback fibers ability to reach their targets may be facilitated by the pruning back of cell density (Burkhalter, A., 1993). Brain overgrowth in the first 3 years is much replicated finding in ASDs (e.g., Hutsler, J.J. & Zhang, H., 2010), so one possibility is that fewer feedback fibers reach their targets in individuals with ASD due to insufficient pruning.

Delayed integration of global/local stimulus dimensions during the N1 latency (Kemner, C. et al., 2009) in the context of typical amplitude (Foxe, J.J. et al., 2005), as we measured here, has been reported as a mechanism of dysfunctional sensory processing in another clinical population - schizophrenic persons. Connective dysfunction is widely reported in ASDs Chapter 1 (pp 31-35). This includes numerous accounts of impaired connections between frontal and parietal,
temporal, or occipital areas (e.g., Just, M.A. et al., 2007; Kana, R.K. et al., 2009; Barttfeld, P. et al., 2011), as well as between the hemispheres (Alexander, A.L. et al., 2007), all of which could impact feedback in perceptual processing generally, and processing of ICs specifically. Of specific interest to the present work includes reduced fractional anisotropy, a measure of white matter integrity, specific to occipital-temporal areas (Barnea-Goraly, N. et al., 2004). This measure is correlated with processing speed (Tuch, D.S. et al., 2005) and is therefore presumed to reflect axonal density or myelination (Travers, B.G. et al., 2012), suggesting these structural alterations of feedback connections are a possible cause for delayed transmission of signals.

Two investigation in ASDs have implicated horizontal connective fibers specifically. These contour integration studies used texture stimuli (see p47). Bertone et al (2005) argues that enhanced lateral inhibition is implicated in stronger performance in a visual discrimination task for luminance-defined stimuli and weaker performance for texture-defined stimuli. Vandenbroucke et al (2008) using VEP argues the opposite, that weaker contour detection of texture-defined stimuli during N1 latency, is attributable to diminished lateral inhibition. Based on her stimulus processing model, reviewed in Chapter 1 (p 64, 71), she adds that this atypical outcome is specifically not attributable to feedback (Lamme, V.A. et al., 1998).

Bertone and Vandenbroucke implicate horizontal circuitry, and certainly a good deal of evidence supports contour integration being facilitated by horizontal connections in lower visual cortex (e.g., Grossberg, S. & Williamson, J.R., 2001; Stettler, D.D. et al., 2002), but we believe that the preponderance of evidence, especially when considering latency of that activity (e.g., Shpaner, M. et al., 2013), points to feedback processes implicating the LOC. One possibility is that visual integration in texture-defined stimuli occurs differently than in ICs. Li and Gilbert’s paradigm using masked fields of contour fragments suggests that human adults detect integrated
contour composed of collinear fragments at a rate above chance so long as the space between
fragments is below $2^\circ$ (Li, W. & Gilbert, C.D., 2002), as would be the case with texture stimuli,
they suggest that V1 is the neural substrate of such interactions. However, Angelucci et al’s
work (2002) suggests that the spatial scale of feedback connections is explicitly necessary for
processes integrating global and local stimulus dimensions, such as contour filling-in.

Bertone’s model convincingly argues that strong lateral inhibition within a single functional
region would likely produce enhanced detection of his “simple” stimulus condition, defined by
luminance. He acknowledges that diminished detection of his “complex” condition requires
integrated processing of multiple regions, and is typically thought to involve feedback. Yet he
seems to balk at implicating feedback as a mechanism. He prefers enhanced lateral inhibition
because it offers one mechanism for their results rather than two, but the connection he draws to
diminished performance of texture-defined stimuli is unconvincing. In fact, Vandenbroucke’s
study showed the same behavioral results, but attributed them to weakened lateral inhibition, a
more convincing explanation. Delayed feedback would account for both of their findings. To
understand why, let us examine the model of object processing upon which it is based (Pollen,
D.A., 1999).

Information moves up and down the visual system as discussed in Chapters 1 and 3. Several
criteria interact in this model of the system grappling with representing an IC. This is depicted in
cartoon form in Figure 6.1. The criteria include: the anatomical structure involved (labeled
above the grey squares), the size of its receptive fields (represented by the grid and approximated
below the grey squares), the properties to which its neurons are sensitive, and the direction of
information flow (green arrows are feedforward and red are feedback). Initial input to area V1
can be detected around 55 ms after stimulus presentation (Foxe, J.J. & Simpson, G.V., 2002;
Kelly, S.P. et al., 2008). So if we measure then and there, we will have a picture largely of feedforward information, and, because of the receptive field properties of V1 neurons, low-level featural information such as orientation is encoded, not a representation of the entire IC form. The earliest portion of the C1 component (50-62 ms) is presumed to reflect the initial feedforward volley of activity from V1, so it would be unlikely to differentiate between IC-inducing and non-inducing conditions (Shpaner, M. et al., 2013). In contrast, a measurement taken around 100 ms later, would include much more influence of feedback that at VEP onset, and many processes occurring around this latency have been convincingly shown to depend on feedback circuitry (Lamme, V.A. et al., 1998; Hupe, J.M. et al., 2001; Angelucci, A. et al., 2002). The idea of functional brain activity described throughout the literature as ‘feedforward’ or ‘feedback’ is really an oversimplification. Processing following the presentation of a visual stimulus is ongoing and multi-directional. Any measurement is a picture of a specific region (or an average across multiple regions depending on spatial resolution of the instrument) at a specific time (or an average across a range of time points, depending on temporal resolution of the instrument). As such, this measurement will depict ongoing activity reflecting some percentage of contributions from feedforward and feedback activity.

The initial pass of information feeding forward from V1 reaches dorsolateral frontal cortex in approximately 30 ms (Foxe, J.J. et al., 2002). Feedback influences of dorsal area MT on V1 and V3 in macaque monkeys have been measured to occur in as little as 10 ms poststimulus (Hupe, J.M. et al., 2001). From these data, it is not hard to see how quickly the influence of feedback may permeate every level of the visual hierarchy. At 160 ms poststimulus, we propose that the visual signal underlying the IC-effect contains enough representation of feedback to facilitate the
integration of prior knowledge of similarly spaced inducers to disambiguate two possible interpretations of the sensory stimulus.

Delayed feedback would explain both Bertone and Vandenbroucke’s results. Bertone’s enhanced performance of luminance defined stimuli could occur because lower visual areas have access to information more heavily weighted by lower-level influences. Both their diminished detection of texture-defined contours would result because feedback influences the same processors less. This too is a scenario for an instantiation of hypopriors. Behavioral outcomes of neural processes are less shaped by priors because the information arrives later. It would depend on the particular process whether “less interpreted” output is so ill-equipped for the cognitive task at hand that it appears disordered – this is certainly one outcome we see in ASD – or whether it is compensated for by either subsequent processing, or because neurons adapt themselves to perform tasks using output more heavily weighted by feedforward information – as might be the case with IC processing.

A delayed feedback thesis would account for both strengths and weaknesses associated with ASDs. For example, persons with ASDs excel at copying geometrically impossible figures. If signals are more heavily weighted toward feedforward content, the signal would likely convey lower-level sensory content that is less shaped by our prior knowledge of what kind of objects are “possible.” This would become the output signal of visual processing which feeds into the motor requirements of copying.

Feedback allows for a dynamic range of responsivity in the neurons of lower cortical receptive fields. Higher order processors interpret multiple dimensions of a stimulus bundled into one information stream and instruct lower-level neurons to perform calculations, based on
the cognitive requirements of a task. This effectively broadens response properties toward which they were initially tuned (Gilbert, C.D. & Li, W., 2013). The delay of feedback could allow less adaptability. A behavioral outcome of such reduced range of responsivity may be demonstrated in the comparisons of TD and ASD individuals performing categorization tasks in Chapter 1 (pp 93-4). Rather than spontaneously apply generalized prototypes flexibly in response to the needs of a situation, persons with ASDs used lower-level criteria or applied fixed rules whether or not it was advantageous (Minshew, N.J. et al., 2002; Vladusich, T. et al., 2010). To the eyes of neurotypical individuals this behavior might appear inflexible and, therefore, disordered. Indeed, rigidity across functional domains is a hallmark of the ASD phenotype. What the results of the present studies begin to suggest is that this may not be a behavioral preference. With information more heavily weighted toward low-level criteria, over time it is adaptive to perform categorization tasks as well as possible with the information available to the nervous system. Amanda may not have been so far off in telling us as she did in Chapter 1:

*Medical and mainstream culture descriptions of autism are... very superficial descriptions of things autistic people do, with the implication that autistic people do these things simply because they like them, or for no reason at all. People with ASD have real problems...*

If priors allow a dynamic range of response that is outside the tuned purview of neuron’s receptive field, it is not far-fetched to extrapolate that delayed feedback could relate to inflexibility in other domains in ASDs such as restricted interests, inflexible adherence to routines, or insistence on sameness (American Psychiatric Association, 2013), but these conjectures will have to hold up the scrutiny of empirical testing.
Future studies

As with neurotypical persons, we would like to broaden the age range of participants. Dipole modeling outcomes for the Ncl were more variant for the ASD group. So we would like to follow up this experiment with a specific exploration of Ncl spatio-temporal dynamics using the thin/fat stimuli (Murray, M.M. et al., 2006) or degraded pictures stimuli (Doniger, G.M. et al., 2001) described in Chapter 1. Co-registered ERP and MRI data would be collected and analyzed across age groups to more precisely measure anatomical sources of the effects.

We’ve interpreted the delayed latency of the IC-effect to constitute a metric of delayed feedback-influenced processing and put forward this delayed feedback as a neural mechanism of global-local processing differences in ASD. This suggests three follow-up studies:

1) To associate the time difference with global and local processing. A straightforward correlation of individual subject IC-effect onset latencies with metrics of individual subject global local biases would be the approach. Choosing a valid assessment which disentangles global from local processing is not a simple task. In our design of the present studies, we included the Child Embedded Figures Test (Witkin, H.A. et al., 1971), a standard among investigations of global-local processing in ASDs. However, we found adherence to the administration guidelines clearly did not reflect the same constructs across children, as they employed different strategies to achieve the best performance they could. We agree with White and Saldana (2011) that this test may not be valid across participants and we discontinued its administration. An alternative would be to develop a composite measure combining outcomes of Hierarchical Figure processing indicating global/local biases, Shah and Frith’s alternative administration of the Wechsler Block Design subtest (Shah, A. et al., 1993), and answers to questions from the ADI-R assessing circumscribed interests and interest in parts of objects.
2) To correlate the time difference with measures of clinical severity. Our initial attempt to correlate the IC-effect with normed Clinical Severity Scores of the ADOS (Gotham, K. et al., 2009) as well as with normed scores from the Restricted Interests and Repetitive Behaviors subdomain (Hus, V. et al., 2012) post hoc did not yield a statistically significant result (Fig 6.2). Unfortunately, normed severity scores exclude all participants administered a Module 4, diminishing statistical power of the analysis. Future exploration will require an increase in number of participants to use these metrics. It would be useful to analyze clinical severity and sensory processing metrics together to understand how these two factors interact.

3) To directly associate the ASD diagnosis with developmental differences in cell morphometry of feedback circuitry. Connection of dorsal stream structures with the LOC and the LOC with V1 and V2 would be particularly pertinent to the thesis advanced here. Techniques exist to analyze activity specific to cortical laminae. We may begin to directly relate differences specific to feedback fiber to ASD severity or aspects of its phenotype because feedforward and feedback fibers terminate in different layers of cortex (Rockland, K.S. & Pandya, D.N., 1979). One technique couples high-definition DTI with histology on post-mortem tissue (Huang, H. et al., 2012). This has the advantage of permitting direct scrutiny of tissue and the disadvantage that one is dependent on limited samples from deceased persons. The second technique uses high-definition T1 MRI images to estimate cortical depth and then DTI to measured diffusion of fiber tracts (Govindan, R.M. et al., 2013). This technique is of particular interest since it could be conducted on living human participants and related to differences in age or diagnosis.

**Conclusion**

Our developmental assay suggests that perceptual level priors are sufficient to cue automatic contour completion in a single early phase neurotypical adults, but that children and adolescents require a second phase involving conceptual level priors. We propose that the first phase, by
virtue of its timing, involves a signal weighted toward feedback contributions. Our data implicates the LOC as a prominent source. It electrophysiological index, the \textit{IC-effect}, is robust in children as young as five years of age, and its amplitude is invariant the manipulation of contour extent. However, additional processing is recruited during a second more extended phase of contour completion in children and adolescents. Previous experimental evidence supports this phase as involving recurrent processing between the LOC, prefrontal and hippocampal areas, facilitating a matching process between incoming sensory data and conceptual level priors. Our data suggests that need for this second phase decreases as the visual system matures. Despite the presence of both phases across ages and identical developmental trajectory of the second phase in children with ASD, the onset of the \textit{IC-effect} is delayed. This suggests that contour completion, although accomplished successfully in children with ASD, involves processing less strongly shaped by configural priors and therefore more heavily weighted toward sensory-level data.

Kanner’s initial observations suggested to him that persons with ASD do not generalize past experiences to help process new ones. “\textit{A situation, a performance, a sentence is not regarded as complete if it is not made up of exactly the same elements that were present at the time the child was first confronted with it. If the slightest ingredient is altered or removed, the total situation is no longer the same and therefore is not accepted as such}” (Kanner, L., 1943). This is a description of behavior, not of brain processes. Such study is clearly valuable, however, it has led to descriptions of pathological processes that presume knowledge of individuals internal experiences and motivations. The weak central coherence model was, for years, referred to as a processing \textit{“style.”} If Kanner’s description were true about the brains of people with ASD, then the mechanisms that drive priors might never develop. Groups of features would have to be
assembled from the bottom up *ad infinitum*. What we have measured here suggests that there is something fundamental to observed differences in sensory processing. That the bit-by-bit assembly of the perceptions of persons with ASDs may arise from different brain processes with antecedents in brain structures. It is not a behavioral preference. These results demand both replication and expansion. It is stimulating to wonder whether IC processing generalizes to all mechanisms of priors; whether using metrics of structural differences in feedback fibers, we could predict development of inflexibility, or potential success in social interaction; or whether a developmental window of feedback connections exists which is vulnerable to intervention.
Grey squares represent anatomical level of visual processing hierarchy. Grids approximate receptive field size (Gallant, J.L. et al., 1996; Smith, A.T. et al., 2001; Yoshor, D. et al., 2007). Green arrows represent information conveyed by feedforward fibers and red by feedback.
Figure 6.1
Figure 6.2 Caption

Correlation of IC-effect onset latency with Calibrated Severity Scores (upper panels) and with Restricted Interests and Repetitive Behaviors (lower panels).
Figure 6.2
Bibliography


