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Neural Mechanisms of Visuo-Spatial Attention in School-Aged Children

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**NEURAL MECHANISMS OF VISUO-SPATIAL ATTENTION
IN SCHOOL-AGED CHILDREN**

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OF PRINCETON UNIVERSITY
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Abstract

Selective attention, the ability to focus on key information and filter out noise, is crucial for navigating the cluttered world. The neural basis of selective attention has been widely studied in the adult brain. However, much less is known about how selective attention operates and develops in children's brain. Using neuroimaging, this dissertation investigates visuo-spatial selective attention in school children (ages 6 to 12). It employs a framework that is grounded in biased competition theory in order to probe each part of the neural mechanisms underlying selective attention functions. The first study demonstrates sensory competition in children's visual cortex, providing a foundation for investigations of sensory-driven and goal-driven mechanisms that modulate the competition. The second study examines the extent to which children's visual system can use perceptual grouping principles, as one of the sensory-driven mechanisms. Evidence suggests that perceptual grouping in visual cortex continues to refine beyond age 6, which could serve as a bottleneck for efficient selective processing. The third study shows that the fronto-parietal attention network, a source of goal-driven attention control, matures by achieving a balance between the two hemispheres. Using a perceptual line bisection task, it demonstrates that children in early elementary grades (ages 6 to 8) show an attention bias towards the left-hand side of space, which gradually diminishes and becomes adult-like by middle school ages (ages 11 to 13). It also shows that the degree of spatial bias is linked to functional connectivity patterns within each child's attention network. Interestingly, such leftward biases in children are related to their reading fluency, suggesting an interaction between the attention network and the reading network across development. Together, this work demonstrates that the development of visuo-spatial selective attention in childhood is a dynamic process that is shaped by sensory processing and cognitive skills that continue to change throughout this age range. Interactions with perceptual functions and newly acquired cognitive skills should be addressed in order to better characterize the typical and atypical development of visuo-spatial selective attention.

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Table of Contents

Abstract.....	iii
Acknowledgements	iv
Introduction	1
Chapter 1. A theoretical overview: Biased competition model of visuo-spatial attention.....	8
Chapter 2. Sensory competition in the developing brain.....	22
Chapter 3. The effect of perceptual grouping on sensory competition in the developing brain ...	56
Chapter 4. Development of spatial biases and the fronto-parietal attention network in childhood	82
Part I. Development of spatial biases: A large-cohort behavioral study	86
Part II. Linking spatial bias to the fronto-parietal attention network	105
Part III. Interaction between visuo-spatial attention and reading development	128
General Discussion	146
References	152
Supplementary Information.....	165

Introduction

Imagine looking for a friend on a busy street in New York City. You cannot process every part of the scene, such as people, buildings, cars, and street signs, in much detail at a single brief glance. In order to find a friend, you need to pay attention to one object, say a person, at a time and shift your attention to another.

Our visual system is constantly bombarded with a large amount of information. However, the visual system has limited capacity and cannot fully represent all visual entities in a cluttered scene at once (Broadbent, 1958). Thus, the ability to select relevant information from our visual environments is essential for cognitive behavior. The cognitive and neural mechanisms underlying such selection processes, often referred to as selective attention, have been of great interest to the fields of cognitive psychology and neuroscience (Nobre & Kastner, 2014). Over the past few decades, a large body of research has led to several influential theories that aim to define selective attention functions and elucidating their neural mechanisms in adults and nonhuman primates.

Visuo-spatial attention refers to selective attention allocated at a specific location in visual space and is the most widely studied type of selective attention in the adult primate brain. It facilitates the processing of information from the attended location and filters out the input from unattended locations, which is unwanted and potentially distracting. These capacities are fundamental to a number of daily activities, from navigating new places to manipulating objects. They also play an important role when children learn and improve their cognitive skills. For example, novice readers learn to focus on a specific letter or word at a time and then to shift the

focus of attention in a coordinated manner throughout the space. Any impairment in this capacity could interfere with initial learning and lead to cascading effects on a wide range of behavior. Indeed, deficits in visuo-spatial attention have been observed in children with developmental disorders, such as attention deficit/hyperactivity disorder (ADHD; Bellgrove et al., 2008; Chan et al., 2009) and dyslexia (Gabrieli & Norton, 2012; Vidyasagar & Pammer, 2010; White, Boynton, & Yeatman, 2019).

This dissertation investigates selective attention functions in school children from a cognitive neuroscience perspective. Here I focus on visuo-spatial selective attention because its underlying neural mechanisms are extensively studied in the adult primate brain, providing a useful reference. A number of behavioral studies have primarily asked when each of different attention functions fully matures and stabilizes at an adult level (e.g., Rueda et al., 2004). By using neuroimaging to probe the neural mechanisms of children's visuo-spatial attention, this work examines *how* developmental changes occur (also see Amso & Casey, 2014; Karuza, Emberson, & Aslin, 2014). This work primarily focuses on typically developing children or the general population. However, it has a potential to generate a foundation for investigations of atypical attention functions in developmental disorders. Quantitative analyses of brain and behavioral development could provide insight into the biological underpinnings of atypical development, which will improve the strategies for diagnoses and interventions.

As visuo-spatial attention is one of the most fundamental cognitive capacities, the development of attention functions has received a great deal of interest (for comprehensive reviews, Amso & Scerif, 2015; Colombo, 2001; Plude, Enns, & Brodeur, 1994; Rueda, 2013). However, there is a critical gap between the current literature on attention development and the neural model of selective attention established in the adult brain. Here, I use the framework

derived from the biased competition theory of selective attention (Beck & Kastner, 2009; Desimone & Duncan, 1995), which will be described in more detail in Chapter 1. According to this theory, the interaction between “bottom-up” visuo-spatial processing (i.e., operating at the level of visual cortex) and “top-down” attention control (i.e., engaging the fronto-parietal attention network) is a key mechanism for visuo-spatial attention. Most of the existing developmental studies, however, have investigated attention capacities and perceptual skills as two distinct functions, and characterized their developmental trajectories independently from each other (e.g., Petersen & Posner, 2012). Attention functions in children have been examined often by using simplified visual stimuli in order to rule out any developmental differences in visuo-spatial processing. This has led to difficulties in designing a single paradigm that can test a wide age range, thereby generating mixed conclusions about when attention functions fully mature (but see Zelazo et al., 2013). Furthermore, when a child shows atypical behavior on attention tasks, it has been difficult to dissociate between deficits driven by low-level visuo-spatial functions and those from atypical higher-order control functions (Robertson & Baron-Cohen, 2017).

Recently, Amso and Scerif (2015) have proposed a model that emphasizes interactions among perceptual, attention, and higher-order control functions over the course of development. As the posterior and occipital parts of the brain appear to mature earlier than the frontal and parietal associative cortices (Gogtay et al., 2004; Sowell et al., 2003), functions that mature earlier (e.g., sensory functions) may shape or even trigger the maturation of later developing functions (e.g., control functions), which in turn will refine earlier functions via feedback circuits for the continued improvement in sensory functions. This model predicts that any disruption in

early developing functions could interfere with the subsequent developmental processes for higher-order cognitive functions.

However, what complicates the timeline of developmental milestones is that perceptual and cognitive functions do not mature in such a clear order that one function becomes fully mature before another function begins to develop. Instead, they undergo maturational processes at the same time. For example, although visuo-spatial capacities rapidly improve within the first postnatal year (e.g., Quinn & Bhatt, 1998), many of them continue to refine beyond the first year, and several continue to mature well into teenage years (Hadad, Maurer, & Lewis, 2010a; Hipp, Dickerson, Moser, & Gerhardstein, 2014; Kovács, Kozma, Fehér, & Benedek, 1999). Continued developmental changes in visual cortex have been found throughout childhood in terms of the functionality and distribution of neural modulators and receptors (Siu & Murphy, 2018) as well as cortical tissue composition and myelination (Gomez et al., 2017; Natu et al., 2019). Thus, children's attention functions do not solely develop based on fully mature visuo-spatial foundations; they develop by interacting with or further refining the outcome of still-maturing visuo-spatial functions. As visuo-spatial attention in the adult brain operates via interplay of sensory-driven processes and goal-driven attention control, children's visuo-spatial attention should operate via interactions among multiple component functions that are undergoing maturation. Thus, in order for a more complete understanding of attention functions in children, it is important to examine how each of the individual component processes involved in visuo-spatial attention changes through experience and/or interactions with environmental factors, which will then allow one to investigate how those functions interact to implement attention functions in typical or atypical development.

The goal of this dissertation is to characterize the dynamic developmental mechanisms of attention functions through interactions with perceptual and cognitive capacities. While Amso and Scerif's model (2015) emphasizes mutual impacts among these functions to account for their developmental trajectories across the lifespan, this work investigates visuo-spatial attention functions within a developmental period in which perceptual, attention, and cognitive skills develop together—roughly between ages 6 and 12 years. This age range is one of the crucial periods for cognitive development, as marked by the continued refinement of visuo-spatial skills and attention functions as well as the acquisition and rapid improvement of new cognitive skills, such as reading and mathematical reasoning, as children begin formal education. Given the remarkable changes that take place at these ages, it is not surprising that diagnoses of developmental disorders, such as ADHD and dyslexia, are most frequently made in this age range.

Overview of the dissertation

This dissertation investigates the neural basis of visuo-spatial selective attention functions in children by using fMRI and the framework of biased competition theory (Desimone & Duncan, 1995; Beck & Kastner, 2009).

Chapter 1 provides an overview of the theoretical framework with evidence from primate electrophysiology and human neuroimaging studies in the adult brain. I then discuss how this theoretical framework could offer a new perspective to the current literature and allow a hypothesis-driven approach to visuo-spatial attention functions in the developing brain. A version of this chapter was published as an article in *Current Opinion in Psychology* (Kim & Kastner, 2019).

Chapter 2 examines sensory competition in children's visual cortex, as a first step to examine the neural basis of biased competition in the developing brain. We found that, like in adults, multiple objects in the same display show competitive interactions in the visual cortex of children above age 8. The competitive interactions were also modulated by display size as a function of the receptive fields across visual hierarchy. A version of this chapter was published as an article in *Cerebral Cortex* (Kim, Pinsk, & Kastner, 2021)

Chapter 3 uses a variation of the paradigm established in Chapter 2 to investigate how sensory competition is modulated in a bottom-up manner via perceptual grouping in children's brain. This study has paused due to the COVID-19 shutdown, so this chapter presents preliminary results.

Chapter 4 examines the development of the dorsal fronto-parietal network, one of the main sources of top-down attentional control in the brain. This chapter combines a large-cohort behavioral study and a predictive modeling method to investigate when and how the network achieves a well-balanced attention control system across development. This chapter consists of three parts. In Part I, we found that children in early elementary grades (ages 6 to 8) show a preference in allocating attention to the left-hand side of space over the right-hand side. The leftward biases gradually diminished and became better balanced in middle school ages. The first part of this chapter was published as an article in *Developmental Science* (Hoyos, Kim, Cheng, Finkelston, & Kastner, 2020). In Part II, we show that individual children's spatial biases are predicted by functional connectivity strengths in their attention network, linking our behavioral findings to individual variability of functional interactions within the network. Part III further explores the relationship between children's spatial attention bias and reading development,

suggesting a potential interaction between the attention network and the reading network across development.

Overall, this work advances our understanding of how visuo-spatial attention develops in childhood. It also demonstrates that neuroimaging methods combined with hypotheses derived from the biased competition framework allow investigations of bottom-up functions in the visual cortex, top-down functions in the fronto-parietal attention network, and their interactions, all of which continue to mature to achieve an effective selective attention system. Finally, these studies together will ultimately provide a foundation for characterizing attention deficits in children with developmental challenges.

Chapter 1

A Theoretical Overview: Biased Competition Model of Visuo-spatial Attention

A version of this chapter was published as an article in Current Opinion in Psychology (Kim & Kastner, 2019).

Biased competition theory has provided a useful framework to systematically probe the *neural basis* of visuo-spatial attention (Beck & Kastner, 2009; Desimone & Duncan, 1995). Here, we suggest that the framework of this theory can offer a hypothesis-driven approach to investigating the development of visuo-spatial attention functions in children.

The first tenet of the biased competition theory is that multiple objects present in the visual field cannot be fully represented at the same time in the visual system and thereby mutually suppress each other's representation. As a consequence, the neural response evoked by an object embedded in a multi-object array is suppressed compared to the response when the same object is presented alone. These suppressive interactions occur automatically and reflect a competition for neural representation. As a second tenet, selective attention operates on these competitive interactions by facilitating processing of the target stimulus and filtering nearby distracter stimuli at the same time, thereby resolving neural competition. There is converging evidence for sensory competition and attentional modulation effects from electrophysiology

studies in non-human primates and fMRI studies in adult humans (Kastner & Ungerleider, 2000; Reynolds & Chelazzi, 2004). More recent studies have examined how these mechanisms are implemented at the network level, considering both local and large-scale interactions of neuronal populations (Buschman & Kastner, 2015; Fiebelkorn & Kastner, 2020; Halassa & Kastner, 2017). Thus, uniquely, biased competition theory has a firm grounding in a non-human primate brain model that has been translated to the human brain.

Competition as a fundamental principle of sensory processing

When two stimuli are present in a neuron's receptive field, the resulting response is a weighted average of the responses evoked by each stimulus individually (Reynolds, Chelazzi, & Desimone, 1999). The suppressed response to multiple stimuli, compared to the response to a single stimulus, indicates sensory competition among multiple stimuli. A neuron-level explanation of this sensory competition effect has been provided by a normalization model (Carandini & Heeger, 2012; Reynolds & Heeger, 2009). In this model, a response from an individual neuron in the event of a single stimulus is divided by the summed activity of a population of the surrounding neurons. This model provides multiple computational advantages by maintaining an optimal range of neural activity and maximizing sensitivity, as demonstrated in various sensory systems in a wide range of species (e.g., Heeger, 1992; Olsen, Bhandawat, & Wilson, 2010). That is, competitive sensory interactions that give rise to the normalization computation are a fundamental neural coding principle that is essential for efficient information processing in the visual system. Sensory competition can be measured at the population level; for example, visual areas exhibit weaker responses to simultaneously presented multiple stimuli (SIM in Figure 1.1A) than to the same stimuli presented in isolation (SEQ in Figure 1.1A)

(Kastner, De Weerd, Desimone, & Ungerleider, 1998). The strengths of the competition effects are scaled to the receptive field sizes of the visual system, suggesting that neural competition occurs at the level of the receptive field (Kastner et al., 2001).

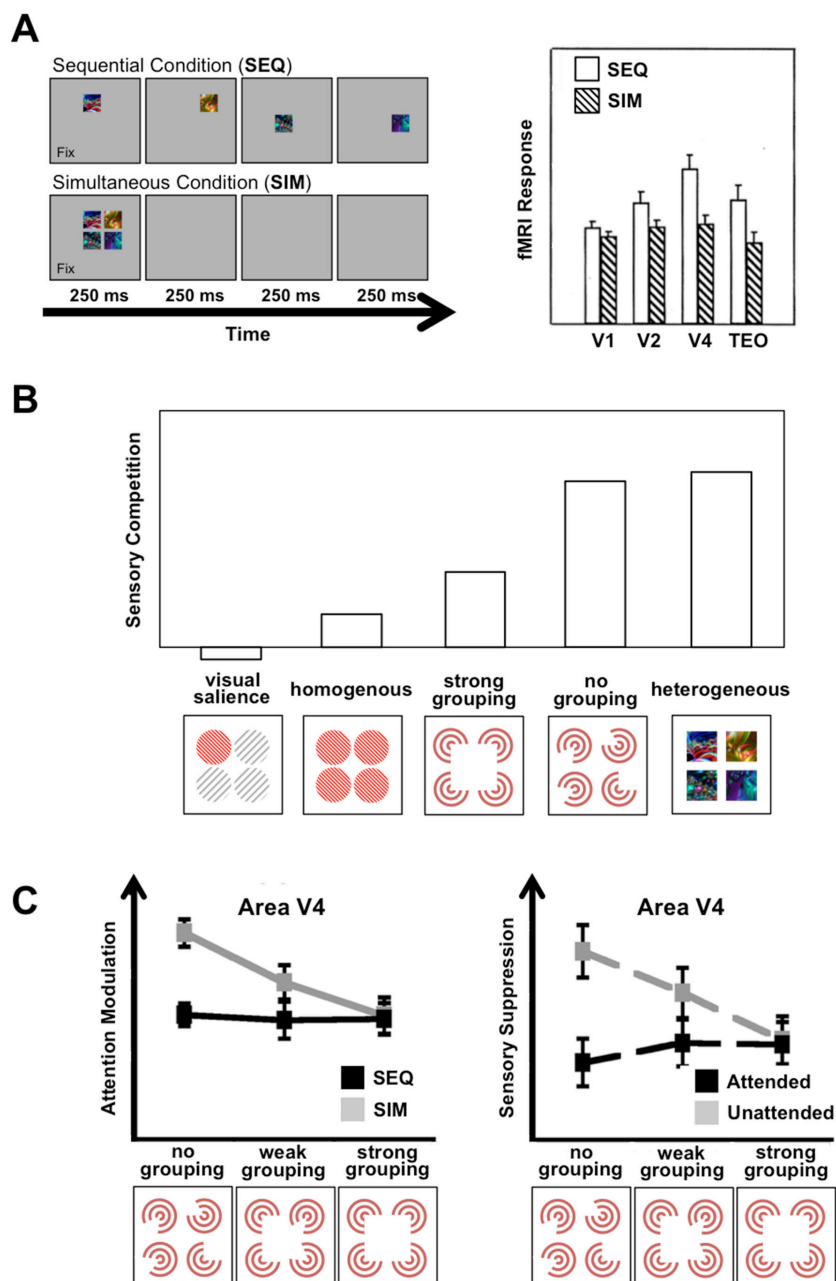


Figure 1.1. Key fMRI findings in adult humans supporting biased competition theory. (A) To probe sensory competition in visually evoked BOLD responses, four different stimuli were presented either sequentially (SEQ) or simultaneously (SIM). BOLD responses in the SIM

condition were suppressed as compared to the SEQ condition. Figures adapted from Kastner et al. (1998). (B) An illustration of sensory competition in different stimulus types, based on Beck & Kastner (2009) and McMains & Kastner (2010). Sensory competition (level of competition indicated by white bars) can be modulated by the physical properties of stimuli in a bottom-up manner. For example, displays consisting of a salient stimulus or grouped elements evoke less sensory competition than heterogeneous display. (C) Selective attention operates through interactions between bottom-up and top-down mechanisms to resolve sensory competition. In the strong grouping condition, competition is greatly resolved in a bottom-up manner, and thus the modulatory effects of attention are smaller than in the no grouping conditions (left panel). Indeed, sensory suppression is reduced in the attended condition across all three grouping conditions, indicating that the remaining competition in the no grouping condition was resolved by top-down mechanism (right panel). Figures adapted from McMains & Kastner (2011).

Particular features of visual stimuli can modulate such suppressive interactions in a pool of neurons and thus influence normalization computations (Figure 1.1B). For example, a salient object in a multiple-object array ‘pops out’ and evokes a greater neural response, effectively overcoming suppressive interactions from surrounding objects (Beck & Kastner, 2005). Another way to resolve sensory competition is by grouping multiple stimulus elements into one coherent object. For example, when multiple pac-man stimuli form an illusory shape, the pac-man stimuli are processed as one object and suppressive interactions among the constituting elements are greatly reduced (McMains & Kastner, 2010). As visual salience and perceptual grouping are represented early in the visual processing stream (as early as V1; e.g., Kok & De Lange, 2014), these functions resolve sensory competition in a ‘bottom-up’ manner by enhancing responses in a population of neurons (that respond to a salient object or to an illusory shape) to overcome the suppressive influences from surrounding neurons.

Visuo-spatial attention enhances neural responses evoked by an attended stimulus relative to an unattended one. This “top-down” mechanism modulates ongoing competition implemented by normalization computations in local populations of visual neurons. For instance, the neural responses to objects shown in the periphery of the visual field increase when an observer

covertly attends to a particular stimulus embedded in a multi-stimulus array, consistent with an attention-related increase of neural gain. This enhancement of neural responses by attention counteracts suppressive influences from nearby stimuli and, as a result, effectively filters out distracter information (Kastner et al., 1998; Reynolds et al., 1999).

What is the relation between the voluntary selection process and the automatically occurring competition? One possibility is that attention modulates neural gain regardless of the level of ongoing competition to boost information at the attended location. Alternatively, attentional gain control may interact or even depend on the degree of competitive interactions in the visual display. Evidence in support of the second hypothesis has been provided by a study that examined the effects of attention on the degree of grouping of object elements that was parametrically varied (McMains & Kastner, 2011). It was shown that modulatory attention effects on visually evoked responses were scaled to the amount of sensory competition in the display. When the display consisted of maximally competing items, attention effects were strongest, consistent with the notion that top-down mechanisms appear to resolve neural competition. When the display consisted of optimally grouped object elements, attention effects were small, consistent with the notion that bottom-up grouping had greatly resolved the competition and there was little left for a top-down mechanism to operate on (Figure 1.1C). Thus, there was no need for top-down modulation in the case where competition was resolved in a bottom-up manner through perceptual grouping. Attentional modulation of sensory processing operates through interplay between bottom-up and top-down factors, and the selection process appears to be constrained by the degree of ongoing competition resulting from normalization in sensory processing areas (Figure 1.2).

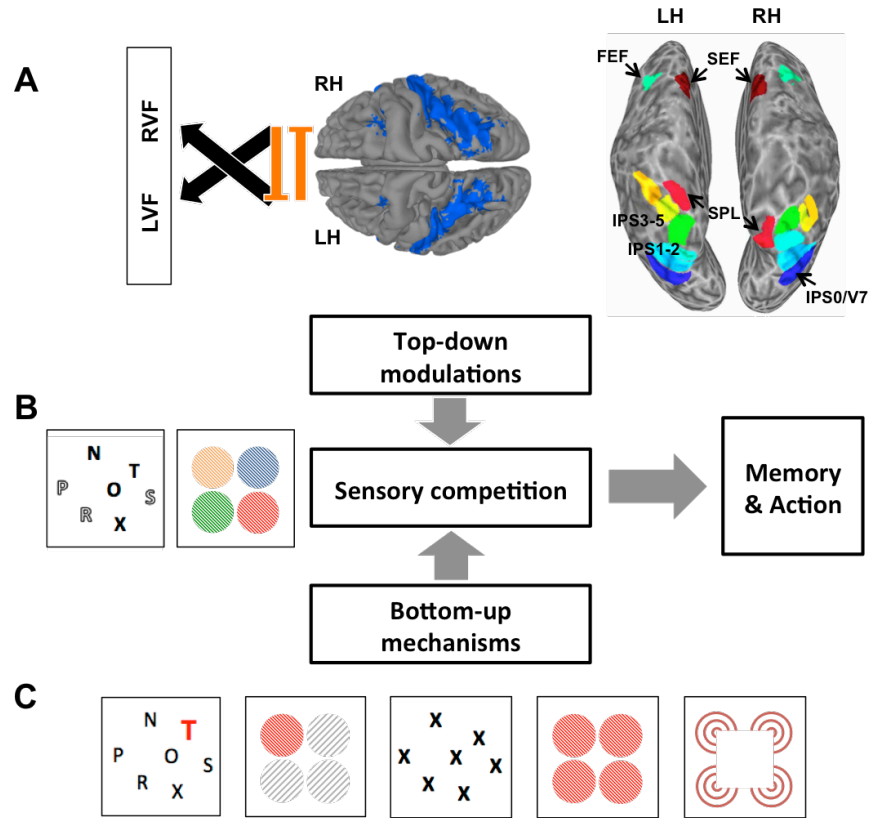


Figure 1.2. Our theoretical framework builds upon biased competition theory. (A-C) Objects in cluttered displays cannot be represented simultaneously in the visual system, thereby leading to sensory competition among the objects. Selective attention operates to resolve sensory competition through an interaction between top-down modulations and bottom-up sensory-driven mechanisms. (A) Top-down modulation engages regions in the frontal and parietal lobes (key areas indicated in the top right panel; adopted from Szczepanski et al., 2013). Fronto-parietal network is balanced through interhemispheric competition, as shown in black and orange arrows, in order to allocate attention across the left and right visual field (LVF and RVF, respectively). (C) Sensory competition can be resolved through bottom-up mechanisms, as shown in example displays. Sensory competition is greatly reduced when one object is salient and ‘pops out’ from the display or when objects are grouped together (also see Figure 1.1B). RH: right hemisphere, LH: left hemisphere, FEF: frontal eye fields, SEF: supplementary eye fields, SPL: superior parietal lobule, IPS: intraparietal sulcus.

Distributed control as a functional principle of cognitive processing

How is attentional selection controlled in the brain? Recent evidence suggests that several different control mechanisms are at play (Halassa & Kastner, 2017). One source for modulatory signals on visual processing originates from a network consisting of multiple brain areas in frontal and parietal cortex, located along the intraparietal sulcus (areas IPS1-5), in superior parietal lobule (areas SPL1-2) and including the frontal and supplementary eye fields (FEF, SEF) (Silver & Kastner, 2009). The role of the fronto-parietal network in attentional selection was first emphasized by studies in patients suffering from visuo-spatial hemineglect, an impairment in directing attention to contralesional visual space following unilateral lesions of a core area of the attention network, such as posterior parietal cortex (Corbetta & Shulman, 2011).

Later fMRI studies have systematically examined how the fronto-parietal network allocates attention to visual space in the healthy adult brain. Within the network, each hemisphere generates attentional weights towards the contralateral visual hemifield (Szczepanski, Konen, & Kastner, 2010). The attentional weights generated by the two hemispheres are in balance through reciprocal inhibition such that visuo-spatial attention can be allocated across the entire visual field (Figure 1.2A; interhemispheric competition theory; Kinsbourne, 1977). Perturbation in the balance within the fronto-parietal attention network can result in biases in spatial attention. In healthy adults, when the fronto-parietal areas in one hemisphere are perturbed by transcranial magnetic stimulation (TMS), spatial attention is temporarily biased toward the side ipsilateral to the TMS interference (Szczepanski & Kastner, 2013).

Interestingly, the balance in attentional weights generated from the two hemispheres is not perfect even in healthy adults as they often show a slight overall bias towards one hemifield

over the other. These individual differences can be related to a line bisection task (Reuter-Lorenz, Kinsbourne, & Moscovitch, 1990), where a subject simply indicates the midpoint of a horizontal line. Knowing a subject's individual distribution of attentional weights across the fronto-parietal network is a perfect predictor for the spatial offset from the veridical midpoint (Szczepanski & Kastner, 2013). Thus, the line bisection task is a good behavioral measure for general spatial attention control exerted in the adult brain. Consistent with these observations, a recent fMRI study in human adults has also found a rightward lateralization in the fronto-parietal network in individuals who show a leftward attentional bias measured in a line bisection task (Zago et al., 2017). Such spatial bias appears to influence the individuals' viewing behavior, such as the initial gaze direction (Afsari, Ossandón, & König, 2016).

To summarize, our theoretical framework accounts for the following components with respect to the neural mechanisms underlying visuo-spatial selective attention. First, competitive interactions among objects in a cluttered scene provide a basis for automatized sensory processing. Neural competition is implemented through normalization of local population activity in sensory cortex. Second, sensory competition can be modulated through the interplay of bottom-up (e.g. salience, grouping) and top-down factors. Third, a fronto-parietal network generates top-down control signals that are fed back to sensory cortex. Spatial attention control is implemented through interhemispheric competition and a balance of attentional weights generated by individual fronto-parietal areas.

Development of visual function and biased competition

Newborns have limited spatial vision, but their visual system undergoes dramatic changes with visual experience after birth (Wiesel, 1982). It is an open question when sensory

competition—the first tenet of the biased competition model—emerges in development. Given that competitive interactions utilized through normalization computations can be linked to the receptive field architecture of the visual system, their neural and structural correlates are likely local intra- and interareal network interactions. Intrinsic vertical connections within the primary visual areas V1 and V2 begin to develop prenatally, and are similar to the adult brain already at birth (Coogan & Van Essen, 1996). In contrast, horizontal and feedback connections mature more slowly and reach adult-level by 16 postnatal weeks in macaques and 16 postnatal months in human infants (Baldwin, Kaskan, Zhang, Chino, & Kaas, 2012; Burkhalter, Bernardo, & Charles, 1993). Local inhibitory interactions among orientation columns may not have quite matured in 5-month-old human infants (Candy, Skoczenski, & Norcia, 2001), but appear to be functional around 10 months of age (Li, Hagan, & Kiorpes, 2013). Similarly, the receptive field architecture of the visual system is present soon after birth. The center-surround interactions in areas V1 and V2 mature already at 2 weeks and 4 weeks of age, respectively, in monkeys (Baldwin et al., 2012; B. Zhang et al., 2013). Interestingly, a hierarchical, topographic organization of the visual cortex is already present in infant macaques at 10 postnatal days (Arcaro & Livingstone, 2017), providing a proto-organization for the development of extrastriate and ventral visual areas. It is not known whether human infants have a similar proto-organization. An fMRI study in 5-12 years old children have revealed that retinotopic organization, population receptive field sizes and visual coverage of areas V1 to VO in children between 5 and 12 years of age are similar to adults (Gomez, Natu, Jeska, Barnett, & Grill-Spector, 2018). Thus, the structural and physiological substrates that are necessary for normalization computations may already be fully developed after the first year, and one might hypothesize that basic neural competition induced by nearby objects emerges early in infancy and becomes adult-like by age 5 or earlier.

Even if the basic structural and functional substrates for sensory competition emerge early in life, bottom-up modulations of the competition are likely to continue maturing beyond the first few years of age. We provide some examples of bottom-up mechanisms based on salient features, contour perception, and perceptual grouping. For example, several studies suggest that the detection of a salient stimulus based on simple motion or luminance changes is observed as early as 3 months of age (Colombo, Ryther, Frick, & Gifford, 1995; Quinn & Bhatt, 1998; Rovee-Collier, Bhatt, & Chazin, 1996; Rovee-Collier, Hankins, & Bhatt, 1992), but the maturational pace varies depending on the type of stimuli and the development of perceptual skills. At 3 months of age, infants who perceived an occluded rod as a whole object (i.e., perceptual completion) were more likely to detect a slanted bar embedded among vertical bars than those who did not show such perceptual completion effects (Amso & Johnson, 2006; Johnson, Slemmer, & Amso, 2004). Orientation-based segmentation does not reach its adult capacity until after age 7 (Rieth & Sireteanu, 1994). The ability to detect a contour consisting of aligned, oriented Gabor patches embedded in different levels of visual noise continues to improve significantly between ages 5 and 14 (Hipp et al., 2014; Kovács et al., 1999). Similarly, in visual search tasks involving a perceptual group, age-related improvements in search performance continue to occur until age 10, especially when searching for a perceptual group comprising entities that are placed far apart from one another (Burack, Enns, Iarocci, & Randolph, 2000; Enns & Girgus, 1985). Indeed, converging evidence suggests that young children are more biased towards individual elements and gradually learn to perceive a global feature by integrating multiple entities into a meaningful object (Hadad & Kimchi, 2006; Hadad, Maurer, & Lewis, 2010b; Kimchi, Hadad, Behrmann, & Palmer, 2005; Nayar, Franchak, Adolph, & Kiorpes, 2015; Scherf, Behrmann, Kimchi, & Luna, 2009). Based on these findings, one

would predict that competitive interactions that are influenced and modulated by bottom-up factors such as visual salience or perceptual grouping would continue to mature well into older childhood.

Importantly, a protracted maturation of bottom-up modulations would affect the development of top-down attention mechanisms as a consequence, since these mechanisms operate on the degree of neural competition in sensory cortex. If competition of sensory information remains largely unresolved after bottom-up filtering, there will be a greater need for top-down modulation to resolve the remaining competition. In the Eriksen flanker paradigm (Eriksen & Eriksen, 1974), for instance, incongruent distractors (e.g., arrows pointing in the opposite direction) generate greater competition, compared to congruent distractors (e.g., arrows pointing in the same direction as the target), that is not resolved in a bottom-up manner. In order to overcome the suppressive influences from incongruent distractors, top-down filtering mechanism need to be recruited. This interaction appears to improve from early childhood to adolescence, as the flanker task performance improves between 3 and 15 years of age (Zelazo et al., 2013). The prolonged development of both bottom-up and top-down modulations could also explain children's vulnerability to nearby distractors in an object tracking task, which does not reach adult-level by age 11 (K. Wolf et al., 2018). Furthermore, sensory processing deficits in developmental disorders could affect the interplay between bottom-up and top-down mechanisms in processing cluttered visual environments (Robertson & Baron-Cohen, 2017).

Development of fronto-parietal control

There is evidence that the fronto-parietal network, which plays a crucial role in voluntary control of attentional selection, as discussed in the previous section, undergoes a significant

maturation in childhood and adolescence (Casey, Tottenham, Liston, & Durston, 2005; Mills et al., 2018). For example, in 4 to 7 year-old children, the development of attention control function has been studied by means of age-related changes in functional connectivity of the fronto-parietal network as a function of selective attention capacity (Rohr et al., 2017). There was an age-related increase in functional connectivity between areas along the IPS and FEF, which was also correlated with behavioral performance even after controlling for age. Interestingly, some have suggested that functional connectivity between areas IPS and FEF appears to increase steadily with a peak in childhood and then decreases until adulthood, as 7 to 12 year-old children show greater connectivity than adults (Farrant & Uddin, 2015; Vinette & Bray, 2015). However, how such connectivity changes are related to attention control behavior is not known.

Visuo-spatial attention control function is implemented by means of interhemispheric competition, as discussed above. How may the balancing of attentional weights across the fronto-parietal attention network develop? A recent study suggests age-related imbalances in visuo-spatial attention allocation across the visual field (Brennan, Bruderer, Liu-Ambrose, Handy, & Enns, 2017). When searching for a target object in a naturalistic setting (i.e., actual objects placed in a room), children (age 6) spent more time searching for a target object placed in left-hand space, compared to right-hand space, whereas older adults showed the opposite pattern. Although the experiment involved multiple confounding influences of motor functions like head and eye movements, it is possible that the results reflect the maturation of visuo-spatial attention function based on interhemispheric competition within the fronto-parietal network. A lab-based experiment provided consistent evidence that typically developing children (ages 8-14) experienced more interference by distractors when identifying a target placed in left-hand space (Chan et al., 2009). Interestingly, age-matched children with attention deficit disorder (ADD)

were more susceptible to distractors when the target was placed on the right-hand side. This opposite asymmetry in ADD suggests that the process of achieving symmetry in spatial attention allocation occurs slowly during development and may be vulnerable in developmental disorders.

Intriguingly, spatial attention biases can be measured using a simple line bisection task. However, developmental studies using such a task have derived mixed results. For example, Hausmann et al. found that all participants between ages 10 and 53 years showed a leftward bias when they indicated the midpoint with either the left or right hand, but only the youngest group (ages 10 to 12) showed a rightward bias when they used the right hand (Hausmann, Waldie, & Corballis, 2003). While some have reported age-related changes in the line bisection judgments (e.g., Bradshaw, Spataro, Harris, Nettleton, & Bradshaw, 1988), others could not confirm them (e.g., Pulsipher, Seidenberg, & Hermann, 2009). These mixed results are potentially due to the fact that the line bisection performance largely depends on the motor actions of the hand (Dobler et al., 2001). In order to test spatial attention biases related to the fronto-parietal control network, it would be essential to probe a perceptual version of the task that is not confounded with motor actions. In the light of these mixed results, it is an open question how the fronto-parietal network achieves a balance between the two hemispheres in childhood and early adolescence, in order to allocate visuo-spatial attention equally well across the visual field.

The review of the existing developmental literature relevant for our theoretical framework suggests that bottom-up and top-down modulations of sensory competition undergo significant modifications during development, which continue into adolescence. Sensory competition in the child brain may operate similarly to the adult brain as early as age 5. However, the ability to resolve sensory competition by effectively grouping multiple constituting elements continues to improve at least until age 14, which also implies that interactions between bottom-

up and top-down mechanisms will continue to mature until early adolescence. Indeed, the fronto-parietal network, which serves as a distributed source of top-down control, matures significantly until adolescence. There has been a growing effort to find more direct and specific associations between neural changes in the fronto-parietal network and cognitive development. We suggest that one aspect of the development of the fronto-parietal network is to find a better balance between right and left hemispheric regions of the network and be able to allocate spatial attention more effectively with age.

Chapter 2

Sensory Competition in the Developing Brain

A version of this chapter was published as an article in Cerebral Cortex (Kim, Pinsk, & Kastner, 2021).

Introduction

In this chapter, we investigated the first tenet of biased competition theory in the developing brain: multiple objects presented simultaneously in the visual field compete for neural representation in visual cortex. We examined sensory competition by adapting a paradigm used in previous studies conducted in adults (Kastner et al., 1998, 2001). Four visual stimuli were presented in the periphery of the visual field either simultaneously or sequentially while participants were engaged in a central fixation task. The degree of sensory competition was measured by the amount of reduction in BOLD responses to simultaneously presented stimuli. In the adult brain, those reductions of BOLD responses were scaled to the RF architecture across the visual processing hierarchy (Kastner et al., 2001). Visual areas with smaller RFs (e.g., early visual cortex) exhibited sensory competition for peripheral objects presented in small displays, while sensory competition effects were not present in these areas when objects were shown in larger displays and only seen in extrastriate areas with larger RFs. To test such display size-based modulation of sensory competition in children's brain, we also manipulated the spatial distance among the competing stimuli to examine how sensory competition was modulated by display

size in relation to the RF sizes across visual cortex. In doing so, we demonstrate and evaluate the application of a probabilistic atlas (Wang, Mruczek, Arcaro, & Kastner, 2015) in the developing brain as an alternative way of defining topographic visual areas without time-consuming and costly mapping sessions.

Based on the literature reviewed in Chapter 1, we probed the following alternative hypotheses. First, sensory competition may occur to a lesser degree in children's than in adults' visual cortex, as computational mechanisms for competitive interactions may still be developing. Second, sensory competition may be adult-like in this age range, but the modulation by display size may operate differently in children. Although the RFs and topographic maps are generally adult-like above age 5 to 6, some areas (e.g., MT) continue to adjust the size and range of the visual field that they represent between ages 5 and 12 (Gomez et al., 2019). Third, computations for sensory competition may develop early and become adult-like by age 8. Our findings will serve as a foundation for future research on how sensory competition is modulated in the developing visual system to process figure-ground segmentation and perceptual grouping in the visual scene.

Methods

Participants

A total of 11 adults (6 female, mean age 20.8 years, range 18.4–23.7 years, all right-handed) and 22 children (8 female, mean age 10.8 years, range 8.1–12.8 years, all right-handed) participated in the study, which was approved by the Institutional Review Board of Princeton University. All participants had normal or corrected-to-normal vision and no history of neurological or psychiatric illnesses. Adult participants gave written informed consent. A child

assent form was provided for children, and a full written informed consent form was obtained from their parents or guardians. Child participants were compensated with a gift card or toy. All children first participated in a mock scanner session (Psychology Software Tools' MR simulator) on a separate day. This procedure has been proven useful to improve the quality of data and avoid practical challenges associated with pediatric neuroimaging (Casey et al., 2018; Epstein et al., 2007; Raschle et al., 2009).

Visual displays and experimental design

Stimuli were presented using Psychophysics Toolbox (Brainard, 1997; Pelli, 1997) in MATLAB (Mathworks, Inc., Natick, MA, USA).

Sixteen colorful, complex pictures were used as visual stimuli (examples in Figure 2.1A). Four of these stimuli were randomly selected and presented in four nearby locations in the upper right quadrant at 7° eccentricity from a fixation point. A 2×3 factorial design was used, in which stimuli were shown in two different presentation conditions (sequential and simultaneous; Figure 2.1A) and three display sizes ($2 \times 2^\circ$, $4 \times 4^\circ$, and $8 \times 8^\circ$ of visual angle; Figure 2.1B). In the sequential condition (SEQ), one stimulus was presented in one of the four locations for 250 ms, followed by a second stimulus presented in a second location and so on, until all four stimuli had been presented in the four locations during a 1s period. In the simultaneous condition (SIM), the same four stimuli appeared together in the same locations as during the SEQ condition for the same time (250 ms) at a randomly selected time point (0/250/500/750 ms) within a 1s period. A given block consisted of 12 repetitions of SEQ or SIM presentations with randomly chosen visual stimuli. The order of the four stimuli per block and the presentation locations were kept identical between the SEQ and SIM conditions, so that the stimulation

conditions per location were exactly matched. For each run, SEQ and SIM conditions were presented in blocks of 12 s interleaved with 15 s blocks of blank period. The order of SEQ and SIM blocks was counterbalanced. During the blank periods, there was no peripheral stimulus. Blank periods (15 s) were also presented in the beginning and the end of each run. Thus, each run consisted of 8 visual stimulation blocks (4 SEQ blocks and 4 SIM blocks) and 9 blank blocks.

Figure 2.1B shows the three different sizes of visual displays ($2 \times 2^\circ$, $4 \times 4^\circ$, and $8 \times 8^\circ$ visual angle) used in our design. For the $2 \times 2^\circ$ display, each stimulus was $0.75 \times 0.75^\circ$ in size and 0.5° apart from the neighboring stimuli. For the $4 \times 4^\circ$ display, each stimulus was $1.75 \times 1.75^\circ$ in size and 0.5° apart from one another. For the $8 \times 8^\circ$ display, each stimulus was $2 \times 2^\circ$ in size and 4° apart from one another.

Participants performed a target detection task at a central fixation point throughout each run, both during visual stimulation and blank blocks (Figure 2.1). The task was designed to be engaging, to ensure proper fixation and prevent attentional capture by the peripheral stimuli. During the fixation task, participants indicated by button press the detection of a target Pokémon. Images of Pokémon characters (0.8° in size) were presented in a rapid serial visual presentation (RSVP) stream at the fixation point. Each Pokémon picture was presented for 250 ms for the adult participants. For children, the presentation time was adjusted (250–350 ms) based on their performance during practice trials outside the scanner. Targets occurred on average every 3.75–7.5 s. A feedback statement was displayed at the end of each run based on the hit rate. For each session, we obtained hit rates and reaction times.

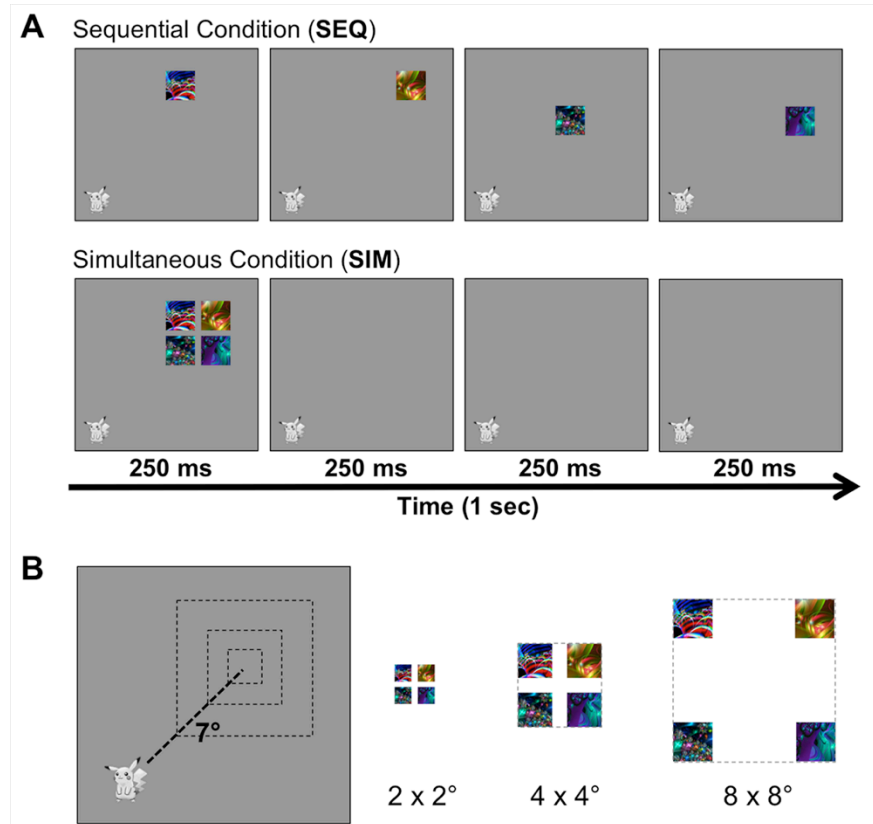


Figure 2.1. Experimental design. Four colorful images were presented in a 2×3 design, in two presentation conditions (sequential vs. simultaneous presentations; panel A) and three display sizes ($2 \times 2^\circ$, $4 \times 4^\circ$, $8 \times 8^\circ$; panel B). Each run consisted of 4 sequential and 4 simultaneous conditions in blocks of 12 s interleaved with blank presentations of 15 s in an ABBAABBA scheme. Display size conditions were blocked into separate runs. Participants performed a target detection task at a central fixation point throughout the run. Visual displays were centered at 7° eccentricity in the upper right quadrant.

Each run lasted for 4 min and 13 s including dummy scans in the beginning. Display size conditions were blocked into runs such that any given run consisted of one display size condition. The goal was to complete at least 3 runs for each display size condition for the pediatric scans. The order of runs was not randomized in order to acquire a sufficient amount of data for a given display size condition, even if a child was unable to complete an entire scan session. If excessive head motion was detected and participants were willing to continue, additional runs were acquired. As a result, seven children completed all three display size

conditions (three runs each), and 15 children completed two display size conditions (three to four runs each) in a single session. In order to avoid confounding effects of fatigue, the order of display size conditions was counter balanced across subjects. Nine adult participants completed nine runs; three runs for each display size condition. Two adult participants completed six runs; three runs for the $2 \times 2^\circ$ and $8 \times 8^\circ$ display conditions.

Data acquisition

MRI data were acquired for the whole brain on a Siemens 3T MAGNETOM Prisma using a 64-channel head/neck coil. Functional images were acquired using a multi-band accelerated echo planar imaging (EPI) sequence (release R014) provided by a C2P agreement with the University of Minnesota (references listed in <http://www.cmrr.umn.edu/multiband/>): TR = 1500 ms, TE = 30 ms, flip angle = 80° , FOV = 208×208 mm, matrix = 104×104 , 2.0 mm^3 resolution, 72 transverse slices, in-plane acceleration factor = 2, multiband acceleration factor = 3, bandwidth = 2090 Hz/Px. A whole-brain T1-weighted volume was collected (3D magnetized prepared rapid gradient echo (MPRAGE) sequence: 192 sagittal slices, 1.0 mm^3 resolution, FOV = 192×192 mm, matrix = 192×192 , TR/TE/TI = 2400/2.08/1000 ms, flip angle = 8° , in-plane acceleration factor = 2, bandwidth = 220Hz/Px, total time of acquisition (TA) = 5 min 11 s). To correct for susceptibility-induced distortions, three spin echo volume pairs were acquired in opposing phase encode directions (anterior to posterior and posterior to anterior) with slice prescription, FOV, matrix size, bandwidth, and echo spacing matching the BOLD EPI acquisition (TR/TE = 8000/66.60 ms; FA/RFA = 90/180 deg; TA = 32 s) (Andersson, Skare, & Ashburner, 2003).

An infrared eye tracking camera (SR-Research Eyelink, Ottawa, ON) was used to monitor wakefulness during the scan session.

Data analysis

fMRI data preprocessing

Image preprocessing was performed using FSL (<http://www.fmrib.ox.ac.uk/fsl>; Smith et al., 2004) and AFNI (<http://afni.nimh.nih.gov/afni>; Cox, 1996). The pipeline included slice timing correction, B0 distortion correction, motion correction, temporal filtering, and spatial smoothing.

The first four volumes (6 s) of each functional dataset were discarded. fMRI data were corrected for slice timing, head motion using the MCFLIRT linear realignment, and distortion correction using the spin echo volumes. Anatomical and functional volumes were skull-stripped using the brain extraction tool (BET). The data were co-registered to each subject's anatomical volume and normalized to the MNI152 template. Analyses were performed both in each subject's native space and in MNI standard space. Linear drift and a six-parameter motion model were regressed from functional volumes.

Further smoothing and artifact removal procedures were conducted separately for general linear model-based (GLM) analyses and for time course analyses. For GLM analyses, the data were spatially smoothed using a 4 mm Gaussian kernel (full-width at half-maximum). Volumes with movement >4 mm were corrected by adding a nuisance regressor in the model (see Whole-brain contrast maps below). For time course analyses, spatial smoothing was omitted, but temporal smoothing was performed to remove frequencies above 0.2 Hz. Volumes with

movement >2 mm were corrected via interpolation between the nearest non-affected volumes to reduce abrupt signal changes caused by head motion.

The anatomical volume was used for cortical surface reconstruction for each participant using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999).

Exclusion based on head motion

Motion-affected volumes were identified on the basis of frame-to-frame movement calculated from the 6 translation and rotation parameters. In order to identify motion outliers, we calculated the Euclidean norm of relative displacement at each time point, relative to the previous time point, and averaged the frame-wise displacements across all time points within the run and then across all runs for each display size condition in each participant (see Supplementary Figure 2.1). One pediatric data set from the $4 \times 4^\circ$ condition and two pediatric data sets from the $8 \times 8^\circ$ condition were identified as outliers and excluded from further analyses, based on the following criteria. One data set from the $8 \times 8^\circ$ condition exceeded more than 3 SDs from the mean (Supplementary Figure 2.1A). The other two data sets had a large amount of censored volumes beyond 3 SDs (Supplementary Figure 2.1B).

The amount of data collected was slightly different for each display size condition because a subset of participants completed two display size conditions out of three. After excluding motion outliers, participants included in the data analyses for each display size condition were as follows: the $2 \times 2^\circ$ condition comprised 11 adults (Age $M = 20.8$, $SD = 1.7$) and 17 children (Age $M = 10.7$, $SD = 1.3$, range = 8.1–12.8), the $4 \times 4^\circ$ comprised 9 adults (Age $M = 20.4$, $SD = 1.5$) and 13 children (Age $M = 11.3$, $SD = 0.9$, range = 10.0–12.8), and the $8 \times$

8° condition comprised 11 adults (Age M = 20.8, SD = 1.7) and 18 children (Age M = 10.8, SD = 1.1, range = 8.5–12.6).

Whole-brain contrast maps

Whole-brain voxel-wise GLM analyses were performed using FSL's FMRI Expert Analysis Tool (FEAT). Each condition within each preprocessed run was modeled with a square-wave function convolved with a gamma-variate hemodynamic response function. The model included explanatory variables (EVs) for the two presentation conditions: SEQ and SIM, as well as confound EVs, e.g., for the exclusion of time points affected by excessive head motion (greater than the size of two voxels; 4 mm). Two regressors were generated to contrast (1) peripheral visual stimulation (regardless of presentation condition) versus blank periods and (2) SEQ versus SIM conditions. Subject-level analyses combining multiple runs were performed using a mixed effects model, with the random effects component of variance estimated using FSL's FLAME 1 procedure. The FLAME procedures make more accurate estimates of the inter-run random-effects variance and degrees of freedom at each voxel than a fixed effects model. For each participant, runs for a given display size condition were combined to generate a statistical map for the condition. Statistical maps comparing visual stimulation blocks versus blank blocks were initially thresholded at $Z > 1.96$ ($p < 0.025$; upper-tailed test; uncorrected for multiple comparison). This comparison revealed voxels activated by the peripheral stimuli while subtracting out foveal voxels activated by the RSVP stream at fixation. Table 2.2 summarizes activated volumes in the contrast maps for each condition.

Statistical maps comparing SEQ blocks and SIM blocks were thresholded at $Z > 1.65$ ($p < 0.05$; upper-tailed test; uncorrected for multiple comparison). Since the SEQ > SIM contrast

revealed a more subtle difference than the visual stimulation > blank contrast, we examined the SEQ > SIM contrast maps for individual participants with a lenient threshold ($Z > 1.65$).

We identified visually responsive voxels from the visual stimulation > blank contrast maps for each display condition in each participant. For each display size condition, visually responsive voxels were assigned to each area of interest (V1-4, VO, V3A, MT), as determined based on the procedure described above.

For quantitative analyses of visually evoked responses, we performed time course analyses. Because there was individual variability in the amount of activated volumes at a particular threshold, we used a lenient threshold for each individual ($Z > 1.65$) and selected the voxels that were most responsive to the peripheral stimuli. For that purpose, we selected 20 voxels with the highest Z scores among the activated voxels that fell within each area of the probabilistic atlas. If fewer than 20 voxels were activated in the contrast map with a threshold of $Z > 1.65$, all voxels (< 20) were included.

For visualization of the contrast maps, volume-based data were projected to the surface by using AFNI's 3dVol2Surf function. All analyses were performed in the volume.

Probabilistic atlas and anatomical landmarks

Because retinotopic maps in children between ages 8 and 12 are adult-like (Conner, Sharma, Lemieux, & Mendola, 2004; Dekker, Schwarzkopf, de Haas, Nardini, & Sereno, 2019; Gomez et al., 2018), we identified topographic visual areas by using a probabilistic atlas (Wang et al., 2015) that was developed from a large cohort of adults. Areas of interest were obtained in the MNI152 standard space. The volume-based full probability map for each area was thresholded at $P > 5\%$ (the probability of a given coordinate being associated with a particular

functional region) such that the coverage of the atlas is broad enough to overcome individual variability while maintaining the borders between areas. The atlas was then registered into each subject's anatomical structure using FSL's nonlinear registration tool (FNIRT). Since visual stimuli were presented in the upper right quadrant, visually evoked responses were located in the ventral portion of areas V1, V2, and V3. In addition, areas of interest included hV4, VO, V3A and MT.

In order to confirm and refine the alignment of the probabilistic atlas with visually responsive voxels, we overlaid both each subject's whole-brain contrast maps (Peripheral stimulation > Blank) and the atlas registered into the subject's structural images. The activated voxels that fell within each area of the atlas were first assigned to that respective area. Next, we verified that those voxels were assigned correctly based on anatomical landmarks. The anatomical landmarks used to define each topographic area were as follows. In the human visual cortex, activated voxels found in the calcarine sulcus within BA17 were assigned to area V1 (Dougherty et al., 2003). Activity on the lingual gyrus (BA 18) was assigned to area V2. Activity on the lingual gyrus anterior to area V2 (BA19) was assigned to area V3. Activity on the fusiform gyrus within BA19 was assigned to area hV4. The boundary between hV4 and VO was found around the posterior transverse collateral sulcus (Witthoft et al., 2014). Activity in BA37, anterior to hV4 along the fusiform gyrus and collateral sulcus, was assigned to the VO cluster (Brewer, Liu, Wade, & Wandell, 2005). Activity in the dorsal stream was assigned to area V3A near the transverse occipital sulcus (Tootell et al., 1997). Activity in area MT+ was found near the inferior temporal gyrus (Tootell et al., 1995; Tootell & Taylor, 1995). We combined areas V3A and V3B as a V3A complex (labeled as V3A below) and areas MT and MST as an MT complex (labeled as MT below).

Retinotopic mapping

In order to evaluate the validity of using a probabilistic atlas based on adult data in children's brains, standard retinotopic mapping was performed with four of the children who also participated in the main experiment (2 females, age 10–12 years). Visual stimuli used to measure polar angle representations in visual cortex were identical to those used in the adult studies that provided the basis for the probabilistic atlas (Arcaro, McMains, Singer, & Kastner, 2009; Wang et al., 2015). Briefly, a wedge consisting of a flickering checkerboard stimulus that varied in color and luminance rotated clockwise or counterclockwise around a central fixation point. The wedge spanned 1 – 15° in eccentricity with an arc length of 45° and moved at a rate of 9°/s. Details of the retinotopic mapping paradigm are provided in Arcaro et al., (2009).

Subjects attended to and performed a change detection task at fixation. A circular ball was placed at the central fixation point and changed to a Pokémon character on average every 4.5 s. Subjects were instructed to indicate by button press when the change occurred. Each run consisted of five cycles (40 s each) of the rotating wedge and a 20 s blank period in the beginning (total length = 3 m 40 s). Runs alternated between clockwise and counterclockwise wedge rotation, with a total of four to six runs per scan session.

A total of 40 axial slices were acquired: TR = 2500 ms, TE = 29.6 ms, flip angle = 75°, FOV = 208 × 208 mm, matrix = 104 × 104, 2 × 2 × 3 mm³ resolution. A whole-brain T1-weighted volume was collected in the beginning of each session (MPRAGE sequence: 192 sagittal slices, 1.0 mm³ resolution, FOV = 192 × 192 mm, matrix = 192 × 192, TR/TE/TI = 2400/2.08/1000 ms, flip angle = 8°, in-plane acceleration factor = 2, bandwidth = 220Hz/Px, TA = 5 min 11 s).

fMRI data from retinotopic mapping sessions were slice-time corrected, motion corrected by aligning to the time point closest to acquiring the anatomical volume, detrended and smoothed with a 2–4 mm full-width half-max Gaussian kernel. The in-session anatomical volume was used for surface reconstruction with FreeSurfer, which was then aligned to fMRI data. Subsequent analyses were performed on the retinotopic data projected onto the surface. Polar angle representations were extracted from separate runs using standard phase encoding techniques (DeYoe et al., 1996; Engel, Glover, & Wandell, 1997; Sereno et al., 1995).

We investigated the validity of the probabilistic atlas by comparing the visually responsive voxels assigned by the probabilistic atlas and assigned by the retinotopic map to a given visual area, respectively, in the same subject. Since we reconstructed retinotopic maps on surface models and confirmed the atlas-based assignment of visual voxels in the volume space, we also compared the voxel assignments both on surface models and in the volume space. Contrast maps for visually responsive voxels, the probabilistic atlas, and retinotopic maps were converted from volume to surface or from surface to volume, using AFNI's 3dVol2Surf and 3dSurf2Vol functions.

Time course analysis

All time course analyses were performed on unsmoothed data. Each run's time course of signal changes was extracted from each area of interest (Supplementary Figure 2.2).

Time courses for each visual stimulation block were extracted from a time window based on the onset of each block. Time series were normalized to the first three time points preceding the stimulation block, which measured the level of baseline activity immediately preceding the evoked response. The first block of each run was excluded in order to avoid a potential

confounding effect of the first visual stimuli after a longer blank period that may have given rise to greater signal change (i.e., onset effect).

For each participant, each condition, and each area, mean signal changes were computed by averaging across the four peak time points within the time window of expected peak activity for each block (4.5–13.5 s after stimulus onset). The mean signal changes were then submitted to a mixed-effects model (using *lmer* function from R lmerTest package) for repeated measures ANOVAs.

In order to compare the degree of suppression across areas, display size conditions and between adults and children, we computed a sensory suppression index [$SSI = (R_{SEQ} - R_{SIM}) / (R_{SEQ} + R_{SIM})$; R is the average of peak signal changes of visually evoked responses as a function of stimulus presentation]. The SSIs provided a standardized measure of suppression, regardless of the overall degree of visually evoked responses. We performed post hoc comparisons from the mixed-effects model to examine age-related differences in SSIs for each visual area and for each display size condition (using R emmeans package; Lenth, 2016; Searle, Speed, & Milliken, 1980).

Results

The current study investigated sensory competition effects in the visual cortex of children aged 8–12 years. Four colorful, textured pictures were presented in the upper right quadrant in a 2 (presentation conditions: SEQ and SIM) $\times$ 3 (three display size conditions) design (Figure 2.1). Adults were recruited as a reference group. The degree of sensory competition was measured as the difference in responses evoked by peripheral stimuli, presented sequentially or

simultaneously. In order to ensure proper fixation and reduce attention to the peripheral stimuli, participants were engaged in a target detection task at fixation.

Behavioral results

We measured accuracy and reaction times (RT) to evaluate performance on the target detection task. The overall accuracy was 85% in children (SEM = 2.5%) and 95% in adults (SEM = 1.8%). Children's accuracy was significantly lower than adults' [$F(1, 29) = 6.7, p = 0.01$]. Similarly, children had slower RTs ($M = 741$ ms, SEM = 23 ms) than adults ($M = 624$ ms, SEM = 23 ms) [$F(1, 29) = 12.1, p = 0.002$]. We compared accuracy and RTs by splitting children by the median age (younger children: mean age = 9.8, range = 8.1–10.9; older children: mean age = 11.8, range = 11.0–12.8). There was no difference in accuracy ($p = 0.66$) or RTs ($p = 0.32$) between younger and older children.

Table 2.1 summarizes accuracy and RTs for blank blocks, and the two visual presentation conditions (SEQ and SIM) for each display size condition. We first examined the possibility that the peripheral stimuli distracted participants by comparing performance in the detection task during blank blocks and peripheral stimulation blocks. For accuracy, there was no main effect of visual stimulation ($p = 0.41$) nor an interaction effect between visual stimulation and age group ($p = 0.65$), indicating that accuracy did not differ between visual stimulation and blank periods either in adults (visual: $M = 95\%$, SEM = 2%; blank: $M = 95\%$; SEM = 1.5%), or in children (visual: $M = 86\%$, SEM = 2.6%; blank: $M = 85\%$; SEM = 2.5%). There was a main effect of age [$F(1, 29) = 6.7, p = 0.01$], consistent with the analysis of overall accuracy. We found similar results for RTs: no main effect of visual stimulation ($p = 0.44$) or an interaction effect ($p = 0.91$), but a main effect of age [$F(1, 29) = 12.1, p = 0.002$].

We further examined accuracy and RTs for blank, SEQ, and SIM blocks for each display size condition, in order to examine whether participants were more distracted in any particular condition in our experimental design. For example, it is possible that visual stimuli in the SEQ condition were more attention capturing than in the SIM condition due to the greater amount of stimulus onsets. However, we found no differences in accuracies ($p = 0.48$) or RTs ($p = 0.66$) for the three different presentation conditions. There was no difference among the three different display size conditions both for accuracy ($p = 0.24$) and RTs ($p = 0.34$). Although there was a main effect of age group indicating that children achieved lower accuracies [$F(1, 29) = 6.3, p = 0.02$] and had slower RTs [$F(1, 29) = 12.0, p = 0.002$]. Such age-related differences were consistent across display size and presentation type conditions. In summary, there was no indication that any difference in visually evoked responses in our design was attributable to differences in distractibility by the visual presentations relative to blank periods, nor for any specific condition, such as presentation or display size.

Table 2.1. Accuracy and reaction time (RT) for behavioral task

		Accuracy (%)		RT (msec)	
Display size	Block type	Children	Adults	Children	Adults
$2 \times 2^\circ$	Blank	84.1 (9.7)	95.6 (4.0)	748 (120)	618 (87)
	SEQ	86.0 (9.4)	96.3 (4.3)	752 (127)	619 (82)
	SIM	83.0 (13.4)	97.1 (3.3)	766 (125)	606 (82)
$4 \times 4^\circ$	Blank	83.5 (14.9)	93.4 (7.2)	728 (86)	641 (67)
	SEQ	86.0 (15.8)	94.1 (8.2)	717 (97)	633 (69)
	SIM	86.3 (16.1)	90.9 (10.7)	722 (87)	635 (80)
$8 \times 8^\circ$	Blank	86.0 (11.2)	95.2 (3.8)	750 (115)	621 (81)
	SEQ	86.6 (11.6)	95.4 (6.6)	736 (119)	621 (92)
	SIM	86.5 (12.3)	95.8 (7.1)	721 (108)	619 (83)

Shown are the mean and standard deviation of the participants' performance on the central fixation task for each condition.

Topography of visually-evoked responses

Peripheral visual stimuli evoked greater activity as compared to blocks without presentations in early visual, ventral and dorsal extrastriate cortex including in areas V1, V2, V3, hV4, VO, V3A and MT of the left hemisphere, which were defined using a probabilistic atlas (Wang et al., 2015) and anatomical landmarks as described in Methods.

For each participant, GLM contrast maps (visual stimulation > blank) were obtained separately for each display condition: $2 \times 2^\circ$, $4 \times 4^\circ$, and $8 \times 8^\circ$. Figure 2.2 illustrates example contrast maps from one adult participant and one child participant. For the purpose of visualization, contrast maps were thresholded at $Z > 1.96$ ($p < 0.025$; upper-tailed test). Early visual areas V1, V2, and V3, ventral extrastriate areas hV4 and VO, and dorsal extrastriate areas

V3A and MT exhibited responses to visual stimuli presented in the SEQ and SIM blocks as compared to blank intervals (activated volumes summarized in Table 2.2).

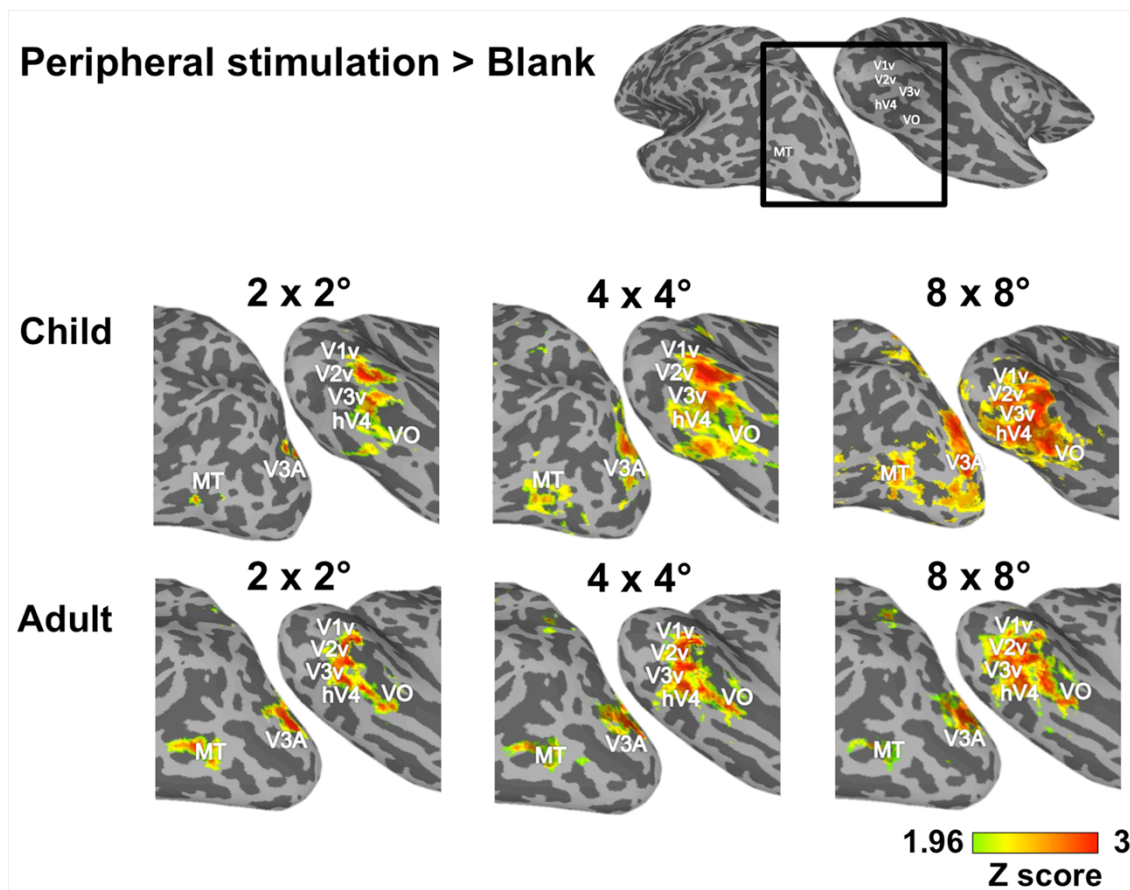


Figure 2.2. Visually evoked responses (peripheral stimulation > blank) for three different display size conditions. The lateral and occipital parts of the brain (black outlines in top panel) were enlarged for visualization. As expected, visually evoked responses were observed in visual areas of the left hemisphere for visual stimuli presented in the upper right quadrant. Contrast maps from one child participant (upper panel) and one adult participant (lower panel) show visually responsive voxels for each display size condition. Visually responsive voxels were assigned to each topographic area based on a probabilistic atlas (Wang et al., 2015).

Table 2.2. Volume analysis of activated areas by display and presentation conditions

Age	Condition	Area	Activated volume (mm ³) Mean $\pm$ SE		Ratio (%)	n
			Visual > Blank	SEQ > SIM		
Children	$2 \times 2^\circ$	V1	273 $\pm$ 40	5 $\pm$ 3.5	1.8	17
		V2	533 $\pm$ 97	93 $\pm$ 43	14	17
		V3	504 $\pm$ 58	77 $\pm$ 26	17	17
		V4	566 $\pm$ 79	103 $\pm$ 37	19	17
		VO	369 $\pm$ 61	64 $\pm$ 27	16	17
		V3A	473 $\pm$ 80	96 $\pm$ 46	20	16
		MT	335 $\pm$ 100	117 $\pm$ 57	35	14
	$4 \times 4^\circ$	V1	606 $\pm$ 97	4.3 $\pm$ 3.0	0.7	13
		V2	790 $\pm$ 104	42 $\pm$ 24	5.4	13
		V3	841 $\pm$ 91	82 $\pm$ 27	9.8	13
		V4	1206 $\pm$ 141	156 $\pm$ 55	13	13
		VO	929 $\pm$ 140	63 $\pm$ 29	6.8	13
		V3A	929 $\pm$ 227	130 $\pm$ 64	14	12
		MT	439 $\pm$ 146	135 $\pm$ 52	31	11
	$8 \times 8^\circ$	V1	807 $\pm$ 111	0.9 $\pm$ 0.9	0.1	18
		V2	1425 $\pm$ 154	24 $\pm$ 23	1.8	18
		V3	1293 $\pm$ 141	38 $\pm$ 18	2.8	18
		V4	1860 $\pm$ 223	128 $\pm$ 49	6.8	18
		VO	1576 $\pm$ 259	98 $\pm$ 30	6.2	18
		V3A	1704 $\pm$ 260	320 $\pm$ 138	19	17
		MT	813 $\pm$ 205	235 $\pm$ 110	29	15
Adults	$2 \times 2^\circ$	V1	234 $\pm$ 55	12 $\pm$ 9	5.0	11
		V2	406 $\pm$ 62	49 $\pm$ 37	12	11
		V3	407 $\pm$ 60	45 $\pm$ 26	11	11
		V4	508 $\pm$ 126	57 $\pm$ 27	11	11
		VO	282 $\pm$ 94	14 $\pm$ 9	5.1	10
		V3A	429 $\pm$ 135	44 $\pm$ 38	10	11
		MT	168 $\pm$ 66	35 $\pm$ 23	21	10
	$4 \times 4^\circ$	V1	487 $\pm$ 91	0	0	9
		V2	756 $\pm$ 123	8 $\pm$ 6	1.1	9
		V3	619 $\pm$ 111	40 $\pm$ 15	6.5	9
		V4	775 $\pm$ 156	77 $\pm$ 34	10	9
		VO	406 $\pm$ 143	15 $\pm$ 12	3.7	8
		V3A	641 $\pm$ 185	36 $\pm$ 19	5.7	9
		MT	257 $\pm$ 103	82 $\pm$ 45	32	8
	$8 \times 8^\circ$	V1	809 $\pm$ 124	4 $\pm$ 4	0.4	11
		V2	1551 $\pm$ 160	9 $\pm$ 7	0.6	11
		V3	1249 $\pm$ 124	3 $\pm$ 3	0.2	11
		V4	1591 $\pm$ 238	49 $\pm$ 23	3.1	11
		VO	988 $\pm$ 191	45 $\pm$ 25	4.6	11
		V3A	1642 $\pm$ 161	213 $\pm$ 73	13	10
		MT	370 $\pm$ 76	140 $\pm$ 51	38	10

Probabilistic atlas versus retinotopic maps in children

Visually responsive voxels were assigned to topographic visual areas of interest (V1–4, VO, V3A, MT). We compared the assignment of visually responsive voxels to regions-of-interest (ROIs) according to the probabilistic atlas and based on retinotopic mapping in individual children. Figure 2.3 displays the alignment in one example participant (age 11.4). The subject's visual stimulation > blank contrast map for the $4 \times 4^\circ$ display (middle panel) was aligned with the area boundaries in visual cortex that were determined as a result of retinotopic mapping (top panel). The same voxels were assigned to visual areas according to the probabilistic atlas (bottom panel). Because our analyses focused on voxels that were most responsive to visual stimuli, we compared how consistently those voxels were assigned to each ROI based on the atlas-based procedures or based on individual retinotopic mapping, respectively. We found that more than 90% of the most significantly activated voxels were assigned to the same ROI regardless of atlas- or retinotopy-based assignment, except for area hV4 (Table 2.3, Supplementary Table 2.1). For area V4, about 80% of the voxels were assigned consistently regardless of procedure. Overall, both retinotopic map-based and atlas-based assignments of visual voxels were consistent with each other, thereby confirming that the probabilistic atlas developed from adult data can be useful in defining topographic visual areas in pediatric populations (also see Rohr et al., 2017).

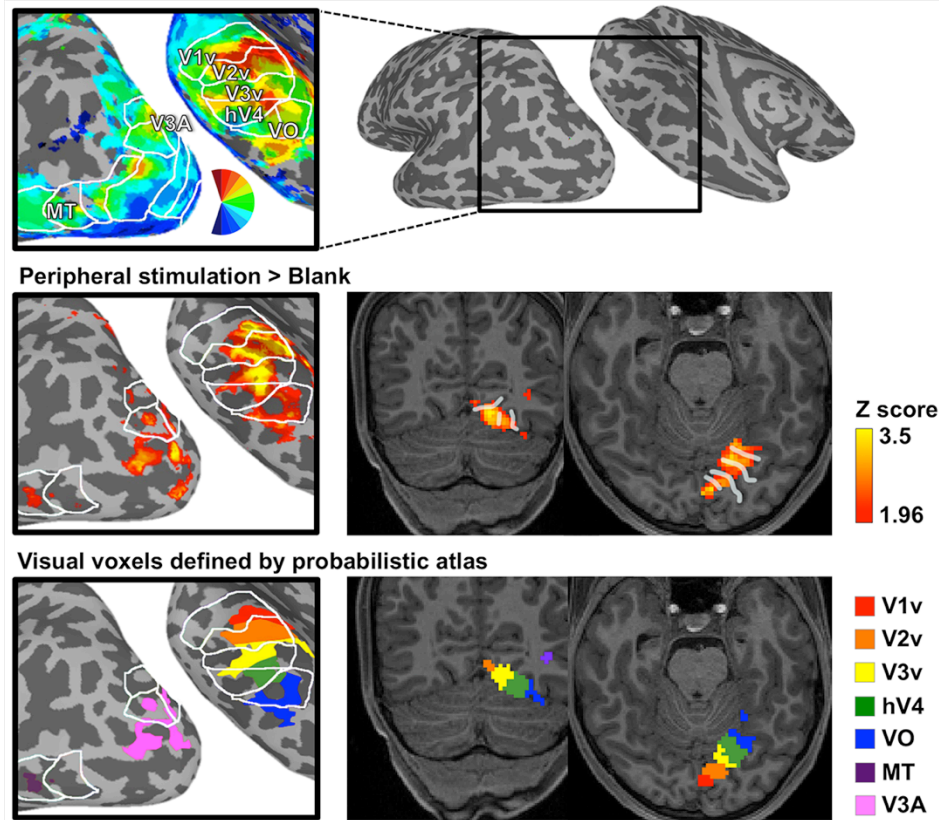


Figure 2.3. Comparison of voxel assignments based on a probabilistic atlas relative to individual retinotopic mapping. In order to evaluate the validity of using a probabilistic atlas in children’s brains, we collected retinotopic mapping data in four children. In an example child subject (age 11.4) polar angle representations (color) and visual topographic areas (outlined in white) were displayed on the reconstructed surface (top panel). Visually responsive voxels evoked by the $4 \times 4^\circ$ display from the same participant were overlaid together with retinotopy-defined area boundaries (outlined in white) both on a surface reconstruction and in volume space (middle panel). Lastly, the bottom panel displays our procedure for assigning the visually responsive voxels from the middle panel to each topographic area based on the probabilistic atlas and anatomical landmarks (see Methods). For comparison, the area boundaries based on this participant’s retinotopic maps are also overlaid (outlined in white) on the surface reconstruction. Because the subsequent time course analyses were performed on 20 voxels that are most responsive to peripheral visual stimuli based on the Z score, we examined how consistently those voxels would be assigned to the same area if we defined the topographic areas based on each participant’s retinotopic map (Table 2.3). Supplementary Table 2.1 provides a comparison of all voxels assigned to each topographic area based on the retinotopic map, probabilistic atlas, and their overlap in each participant.

Table 2.3. Number of voxels assigned to the same retinotopic area (among the 20 voxels that were most responsive to peripheral visual stimuli) by the probabilistic atlas.

Area	Subject 1		Subject 2		Subject 3		Subject 4		Mean	SD
	2 × 2	4 × 4	2 × 2	4 × 4	4 × 4	8 × 8	2 × 2	8 × 8		
V1	10	20	20	20	20	20	20	19	18.6	3.5
V2	20	18	20	20	18	14	18	18	18.3	2.0
V3	18	20	18	20	20	19	17	16	18.5	1.5
V4	19	14	16	17	14	14	17	16	15.9	1.8
VO	20	18	20	19	18	14	18	19	18.3	1.9
V3A	20	20	20	20	20	20	20	20	20.0	0.0
MT	20	20	20	20	.	.	20	20	20.0	0.0

Sensory suppression effects across the visual system

Next, we investigated sensory suppression effects across the visual system by comparing sequential (SEQ) versus simultaneous (SIM) presentation conditions. The SEQ > SIM contrast maps looked qualitatively similar in adult and pediatric populations. Figure 2.4 shows z-scored maps from the SEQ > SIM contrast (single voxel threshold $Z > 1.65$, $p < 0.05$; upper-tailed test) for one representative adult and child participant, respectively. In this example, the contrast maps differed between display size conditions for both participants such that the SEQ > SIM contrast for the $2 \times 2^\circ$ display revealed activations in early visual areas (e.g., V2 and V3), but the contrast map for the $8 \times 8^\circ$ display did not show those activations. Visually evoked voxels in areas V3A and MT appeared in the SEQ > SIM contrast maps for all three display size conditions (activated volumes summarized in Table 2.2).

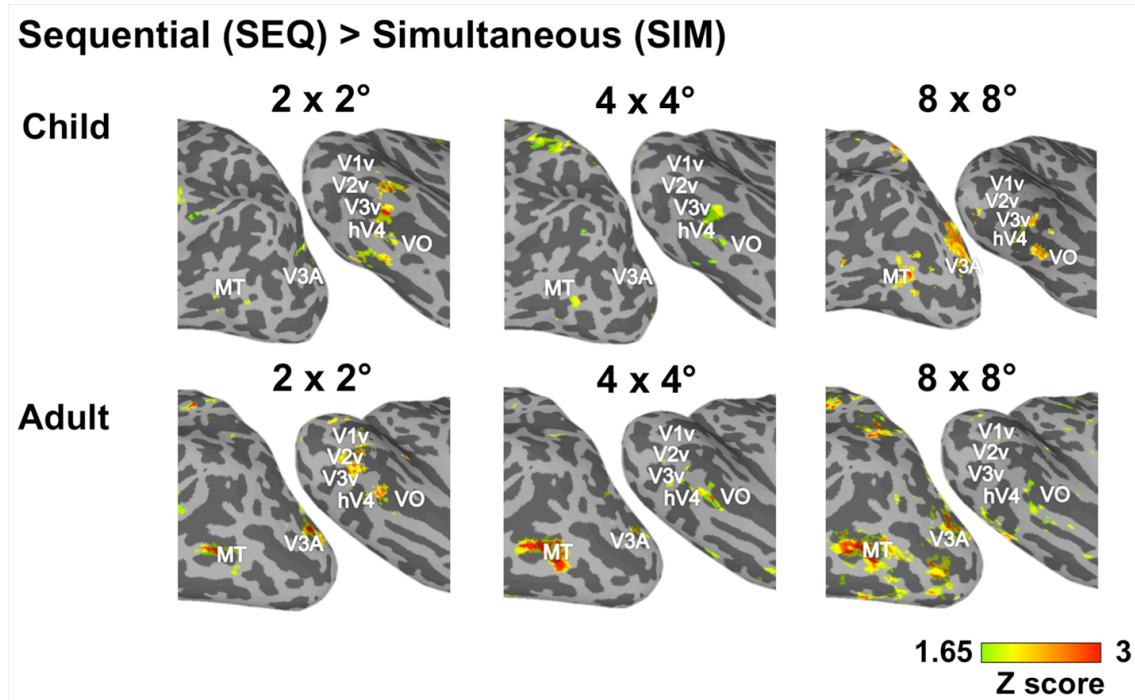


Figure 2.4. Regions that showed stronger activation for sequential (SEQ) as compared to simultaneous (SIM) presentations. The lateral and occipital parts of the brain were enlarged for visualization (same format and participants as in Figure 2.2). Both in the child and adult participants, earlier areas (e.g. V2) exhibited greater activation for SEQ blocks compared to SIM blocks for the $2 \times 2^\circ$ display. For the $4 \times 4^\circ$ display, SEQ blocks evoked greater activity in V3, hV4, VO, V3A and MT than SIM blocks. Such pattern was prominent in VO, V3A, and MT for the $8 \times 8^\circ$ display. Therefore, both in the exemplar adult and child participants, visually-evoked responses to SIM blocks were smaller compared to SEQ blocks. Areas that exhibited such suppression varied for different display sizes.

In order to quantify sensory suppression effects in visually evoked responses across participants as a function of visual area and display size, we conducted time course analyses. First, we compared percent signal changes for sequential and simultaneous presentations of visual stimuli across all participants (Figure 2.5 and Table 2.4). Sensory competition was indicated by the difference in signal change between sequential (SEQ; blue) and simultaneous (SIM; red) conditions.

A mixed-effects model demonstrated that there was a main effect of presentation condition [SEQ > SIM; $F(1, 12289) = 126.1, p < .0001$]. Importantly, there was an interaction between presentation condition and visual area [$F(6, 12289) = 4.88, p < .0001$]. Visually evoked responses in SEQ blocks were greater than those in SIM blocks, and different visual areas had different patterns of suppression in SIM blocks. There was no main effect of age group ($p = 0.90$), no two-way interaction of presentation and age group ($p = 0.22$) and no three-way interaction of presentation, area, and age group ($p = 0.61$). Thus, children exhibited suppression in visual responses evoked by SIM relative to SEQ presentations similarly to adults. Specifically, in adults, all areas but V1 showed suppression effects with the $2 \times 2^\circ$ display. For the $4 \times 4^\circ$ display, area V3 and later visual areas exhibited suppression effects (statistics are summarized in Table 2.4). For the $8 \times 8^\circ$ display, suppression was observed only in areas VO, V3A, and MT, and earlier areas showed similar responses to visual stimuli evoked during SEQ and SIM blocks. Our results from adult participants thus replicated previous findings (Kastner et al., 2001), suggesting that sensory suppression effects were scaled to the increasing RF sizes of the visual processing hierarchy. As there was no main effect of age group, children showed a similar pattern of results. However, children showed suppression effects in area V1 for the $2 \times 2^\circ$ display and in area V2 for the $4 \times 4^\circ$ display while adults did not show suppression effects in these areas for these display sizes. However, an additional ANOVA on those regions demonstrated that there was no interaction between presentation condition (SEQ > SIM) and age group (all $p > .1$).

Sensory suppression effects between children and adults were further examined and compared with the help of an index (Figure 2.6). Sensory suppression indices [$SSI = (R_{SEQ} - R_{SIM}) / (R_{SEQ} + R_{SIM})$] served as a normalized measure of sensory suppression across areas and

display size conditions, thereby controlling for differences in the overall amount of activation across areas and conditions. First, we confirmed that there was a main effect of display size [$F(2,493.8) = 12.67, p < .0001$] and a main effect of area [$F(6,474.7) = 18.76, p < .0001$]. Importantly and consistent with our analyses of mean signal changes, there was an interaction between display size and area [$F(12,474.5) = 1.94, p = 0.028$], further suggesting that sensory suppression occurs at the level of RF in each area. There was no main effect of age group ($p = 0.34$), no interaction of age group and display size ($p = 0.23$), and no interaction of age group, area, and display size ($p = 0.98$). In addition, there was an interaction between area and age group [$F(6,474.7) = 2.82, p = .01$]. Post-hoc comparisons revealed that it was driven by differences in SSIs between adults and children in area MT. Children showed suppression in area MT to a lesser degree than adults, for the $2 \times 2^\circ$ display [adults > children contrast; t ratio = 2.67; $p = 0.0081$, FDR adjusted] and for the $8 \times 8^\circ$ display [adults > children contrast; t ratio = 2.74; $p = 0.0064$, FDR adjusted]. This difference was not observed for the $4 \times 4^\circ$ display [adjusted $p = 0.24$] possibly because the final sample of children included in the $4 \times 4^\circ$ display had a slightly older age range (10.0–12.8 years) than the other two display size conditions ($2 \times 2^\circ$ display: 8.1 – 12.8 years; $8 \times 8^\circ$ display: 8.5–12.6 years).

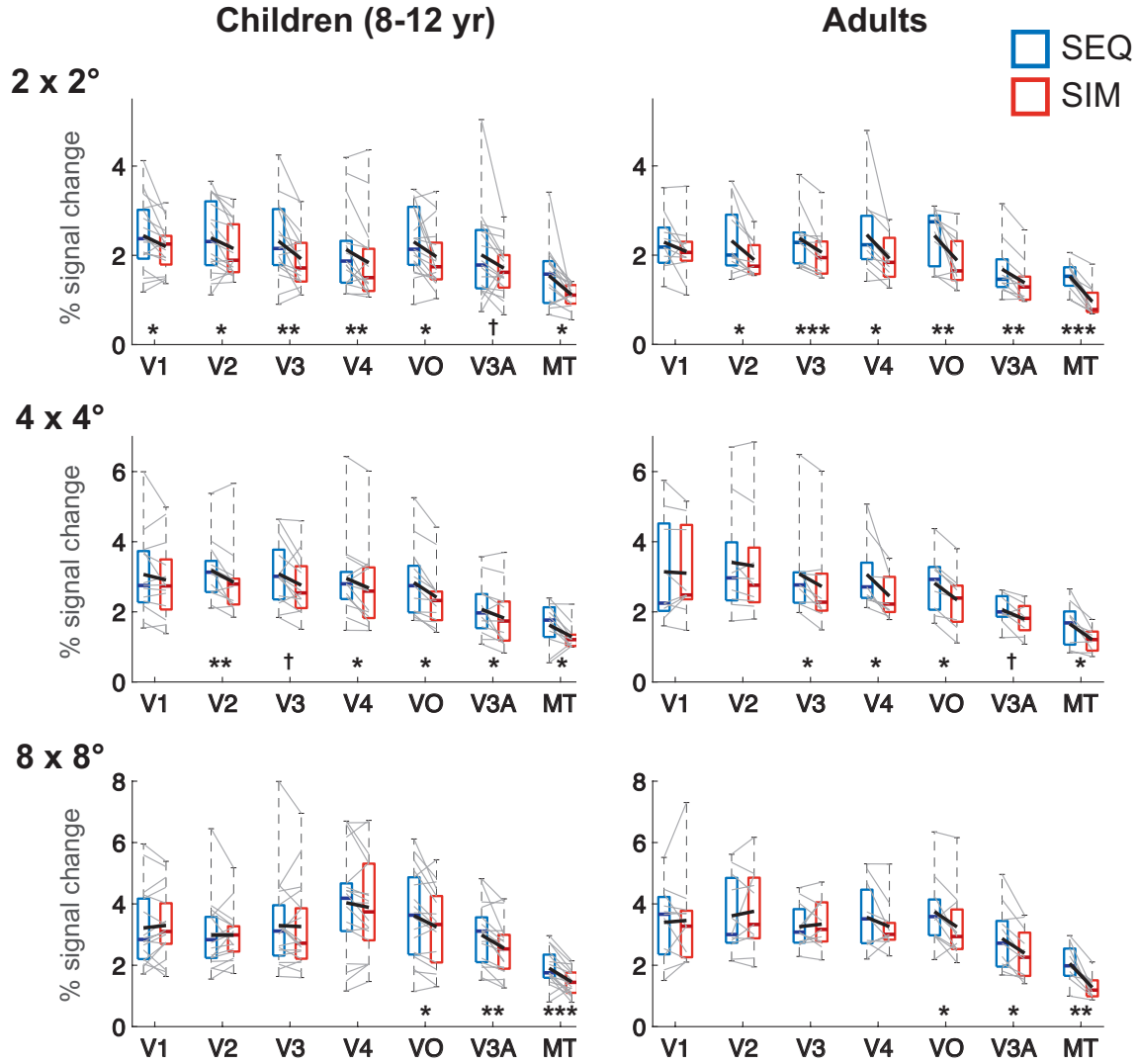


Figure 2.5. Average signal changes in children and adults. Four peak values from each block (SEQ or SIM) were averaged to obtain mean signal changes. Box plots: bold line indicating median; box indicating 25th and 75th percentiles; whiskers indicating range. Individual participants' data are displayed in gray lines. The negative slope of the gray lines indicate smaller responses evoked by SIM presentations compared to SEQ presentations in the same participant. Black bold lines indicate group-level estimations (i.e., estimated linear functions to probe differences between the SEQ and SIM conditions, as summarized in Table 2.4). There was a main effect of presentation condition (SEQ > SIM) and an interaction between presentation condition and visual area, confirming significant response differences between presentation conditions as a function of visual area. Age group (adults vs. children) did not have a main effect or modulate the interaction between presentation condition and area. The difference between SEQ and SIM blocks for each area and each condition is indicated: † $p < 0.1$; * $p < .05$; ** $p < .01$; *** $p < .001$.

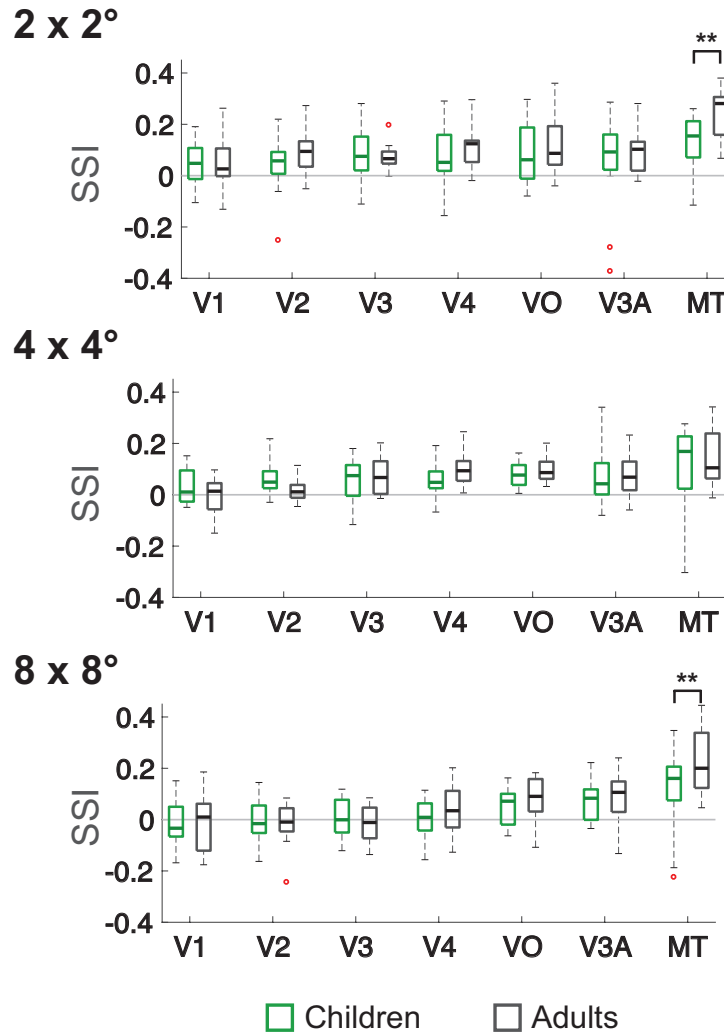


Figure 2.6. Sensory Suppression Indices (SSIs) in children and adults. Sensory suppression indices provided a normalized measure of suppression effects across different display size conditions and age groups. Box plots: bold line indicating median; box indicating 25th and 75th percentiles; whiskers indicating range; red circles indicating outliers (exceeding $2 \times$ box height). Consistent with the results from mean signal changes (Figure 2.5), there was an interaction between display size and area, indicating that sensory suppression in visual cortex occurs as a function of RF size and thus such suppression effects were modulated by display size. A similar overall pattern of results was observed in children, except that, in area MT, suppression effects occurred to a smaller degree in children than in adults.

Table 2.4. Linear mixed model functions for comparison of visually evoked responses between SEQ and SIM presentation blocks.

Condition	Area	Children				Adults			
		Slope	<i>t</i>	<i>p</i>		Slope	<i>t</i>	<i>p</i>	
$2 \times 2^\circ$	V1	-0.25	-2.18	.04	*	-0.21	-1.64	.13	
	V2	-0.24	-2.44	.02	*	-0.43	-2.81	.02	*
	V3	-0.40	-3.53	.003	**	-0.32	-3.51	< .001	***
	hV4	-0.30	-2.85	.008	**	-0.53	-3.05	.01	*
	VO	-0.33	-2.60	.01	*	-0.56	-3.33	.008	**
	V3A	-0.30	-2.07	.05	+	-0.30	-3.19	.003	**
	MT	-0.43	-2.87	.01	*	-0.57	-5.79	< .001	***
$4 \times 4^\circ$	V1	-0.16	-1.19	.23		-0.04	-0.26	.80	
	V2	-0.34	-2.83	.006	**	-0.10	-0.64	.52	
	V3	-0.32	-2.16	.05	+	-0.36	-2.40	.02	*
	hV4	-0.28	-2.34	.02	*	-0.62	-2.95	.01	*
	VO	-0.42	-2.55	.01	*	-0.47	-2.39	.02	*
	V3A	-0.25	-2.09	.04	*	-0.27	-1.83	.07	+
	MT	-0.34	-2.22	.04	*	-0.45	-2.82	.02	*
$8 \times 8^\circ$	V1	0.08	0.68	.50		0.06	0.24	.81	
	V2	0.01	0.05	.96		0.15	0.71	.50	
	V3	-0.04	-0.25	.81		0.08	0.52	.60	
	hV4	-0.15	-1.01	.32		-0.30	-1.53	.14	
	VO	-0.37	-2.37	.02	*	-0.50	-2.56	.01	*
	V3A	-0.43	-3.49	.002	**	-0.48	-2.71	.01	*
	MT	-0.45	-4.32	< .001	***	-0.78	-4.75	.001	**

Slope refers to the slope (i.e. beta estimate) of an estimated linear mixed model function from SEQ to SIM; A negative slope indicates reduced signal change in SIM blocks (i.e. sensory suppression). *t* statistics and *p* values are obtained from the estimated linear function: + $p < 0.1$; * $p < .05$; ** $p < .01$; *** $p < .001$.

Discussion

The current study examined sensory competition among simultaneously presented stimuli in the visual cortex of children between 8 and 12 years of age. We found that, similar to adults (Kastner et al., 1998, 2001), visual topographic areas in children exhibited smaller responses to multiple stimuli when they were presented simultaneously (SIM), as opposed to sequentially (SEQ), indicating competitive interactions among the simultaneously presented stimuli for neural representation. As in adults, sensory competition in children's visual cortex occurred at the level of the RF and was modulated by display size according to the estimated RF size of each visual area. Children showed competition effects in areas V1, V2, V3, V4, VO, V3A, and MT for the $2 \times 2^\circ$ display, in areas V2, V3, V4, VO, V3A, and MT for the $4 \times 4^\circ$ display, and in areas VO, V3A, and MT for the $8 \times 8^\circ$ display. The overall pattern of results was similar to adults with subtle differences observed in early visual areas V1 and V2 as well as in area MT. This study establishes a paradigm in a pediatric population that may prove useful for systematically examining the typical and atypical development of visual perceptual functions by utilizing the theoretical framework of biased competition.

Sensory competition is a fundamental neural coding principle that utilizes divisive normalization computations in the visual system (Carandini & Heeger, 2012; Reynolds & Heeger, 2009). According the normalization model, a neuron's response is divided by the summed activity of a population of the surrounding neurons. This model provides multiple computational advantages by maintaining an optimal range of neural activity and maximizing sensitivity, as demonstrated in various sensory systems in a wide range of species (Heeger, 1992; Olsen et al., 2010). That is, competitive sensory interactions that give rise to the normalization computation are essential for efficient information processing in the visual system.

Prior research has suggested that the RF architecture—a basic principle of organizing visuo-spatial input in the cortex—emerges soon after birth (Conner et al., 2004; Dekker et al., 2019; Gomez et al., 2018). However, substantial development has been observed in visuo-spatial functions beyond age 8 (Jeon, Hamid, Maurer, & Lewis, 2010; Kovács et al., 1999). Because those slowly developing visuo-spatial functions appear to rely on neural interactions in the visual cortex (e.g., Gilbert et al., 1996), we hypothesized that sensory interactions among visual stimuli within and across the RFs may continue to mature beyond age 8. As a first step, we investigated sensory competition effects in children’s visual cortex—the most basic form of functional interactions in the visual system. We found that the visual cortex of 8 to 12-year-old children, particularly extrastriate areas, showed adult-like competition effects when four different stimuli were simultaneously displayed in nearby locations. Thus, as the topographic organization and spatial tuning properties of extrastriate visual areas become adult-like by age 8, competitive interactions among stimuli within their RFs also operate similarly to the adult brain.

To probe competition effects, the current experimental paradigm used a set of stimuli whose colorful patterns were independent and distinct from one another. What remains unanswered is the capacity of the developing visual system to modulate competitive interactions effectively, when elements of the display are perceptually related to each other. In the adult brain, competitive interactions among visual stimuli depend on the relations between the physical properties of the stimuli. For example, competition is greatly reduced when simultaneously presented objects have the same color or orientation, or when one object is salient and easily distinguishable from the surrounding objects (Beck & Kastner, 2005, 2007). Competition effects decrease when multiple elements can be grouped together as one coherent object, as in a display consisting of multiple pac-man stimuli that form an illusory shape

(McMains & Kastner, 2010). Some of those factors that modulate the degree of sensory competition appear to rely on perceptual learning through experience or feedback mechanisms from higher-order areas (Hipp et al., 2014; Li et al., 2013). Even if basic sensory competition in visual cortex emerges early in development, the ability to utilize relations among visual elements to resolve the competitive interactions may mature late and not fully develop until early teenage years. Future research using variations of the current study's paradigm will be needed to examine such stimulus-driven modulations of sensory competition in the developing brain.

The degree of sensory competition was measured by comparing visually evoked activity between the SEQ and SIM presentation conditions. As in previous studies using similar experimental designs (e.g. Kastner et al, 1998, 2001; Beck & Kastner, 2005, 2009; McMains & Kastner, 2011), stimuli in the SEQ condition were presented with four onsets over a 1 s trial length, while in the SIM condition they were presented with only one onset, though the overall stimulation time for each location was identical across the two presentation conditions. One may argue that stimuli in the SEQ condition could induce apparent motion that may have led to greater responses in the SEQ condition. We argue that such difference in temporal onsets does not account for the suppression effects in visual responses. For example, areas V3 and V4 in children exhibited suppression in response to the $2 \times 2^\circ$ and $4 \times 4^\circ$ displays, while no suppression effects were observed for the $8 \times 8^\circ$ display. This rules out the possibility of apparent motion perception, which involves feedback mechanisms from areas MT and V3A that give rise to activity in primary visual areas even for long-range motion (Liu, Slotnick, & Yantis, 2004; Muckli, Kohler, Kriegeskorte, & Singer, 2005; Sterzer, Haynes, & Rees, 2006). If differences in stimulus onsets—or the percept of apparent motion—had led to differential responses evoked by SEQ and SIM conditions, these effects would have occurred regardless of

the spatial distance among the visual stimuli. In addition, prior work using similar experimental designs in adults have demonstrated that the suppression effects were greatly reduced in the presence of a salient stimulus (Beck & Kastner, 2005) or when multiple stimuli grouped to form a coherent object (McMains & Kastner, 2010). Thus, the suppression effects measured in children appeared to reflect sensory competition among the stimuli rather than an artifact of temporal onset differences between SEQ and SIM conditions.

Another factor that could potentially affect the amount of visually evoked activity is covert attention involuntarily directed to the peripheral stimuli. Indeed, the allocation of attention to one of the objects is another factor that modulates sensory competition; covert attention can counteract suppressive influence from surrounding objects and thereby “bias” neural representation toward the attended object (e.g., Kastner et al., 1998). We ruled out this possibility by examining the participants’ performance on a target detection task performed at fixation. The accuracy and reaction times did not differ across different presentation conditions (i.e., blank, SIM and SEQ conditions) or across different display size conditions in children. Thus, any difference in visually evoked responses primarily reflects the degree of sensory competition, as opposed to top-down influences due to attentional capture by the peripheral stimuli.

Prior research has demonstrated that children above age 5 show adult-like retinotopic maps and RF architecture in early visual cortex and extrastriate areas up to VO1 (Dekker et al., 2019; Gomez et al., 2018). The RF architecture appears closely linked to sensory competition effects given that it provides the scaffold for competitive interactions on which selective attention functions operate. In the current study, we further demonstrate that competitive interactions are modulated by the size of stimulus displays in children. As in adults, sensory competition appeared to occur at the level of the RF. The overall pattern was similar as

compared to adults with several notable differences. First, we noted that children showed sensory competition to a lesser degree in area MT compared to adults in the $2 \times 2^\circ$ display and in the $8 \times 8^\circ$ display conditions. This may be related to an incomplete maturation of the RF architecture within area MT in our age group, as the population RF of area MT in children of age 8 to 12 has been estimated to yield smaller RF sizes that are less peripheral than in adult MT (Gomez et al., 2019). Second, we observed that areas V1 (for the $2 \times 2^\circ$ display) and V2 (for the $4 \times 4^\circ$ display) appeared to show greater suppression in children than adults. It has been suggested that surround suppression contributes to competition among multiple stimuli, particularly in areas V1 and V2 where RF sizes are small (Kastner et al., 2001; Knierim & Van Essen, 1992; Nothdurft, Gallant, & Van Essen, 1999). Our results may indicate that lateral inhibition from the RF surround may have a stronger impact in the developing visual cortex. However, those differences were subtle and need to be confirmed and further explored in future studies.

In addition, we evaluated the use of a probabilistic atlas of the adult visual system (Wang et al., 2015) in developmental populations. Ideally, conventional retinotopic mapping procedures in individual participants would be used to delineate topographic visual areas. However, it is not always feasible to obtain retinotopic maps from individual participants, especially for young children or for clinical populations. We obtained retinotopic maps from a subset of children and examined how consistently visually responsive voxels were assigned to each topographic area. Among the voxels that were most significantly responsive to peripheral stimuli, more than 80% were assigned to the identical area for all regions of interest. Among all of the visually responsive voxels that were assigned to each retinotopic area, 60-100% were consistently assigned to the same area by the probabilistic atlas, which supports the validity of utilizing this atlas in school-aged children. We did not use age-specific brain templates because all our child

participants were above age 8. Indeed, age-specific brain templates are publicly available for pediatric fMRI studies (e.g., Fonov et al., 2011), and it has been suggested that using the age-appropriate templates is particularly beneficial for young ages (4 to 7 years). Thus, additional anatomical alignment using age-specific brain templates might be necessary when probabilistic atlases are applied to younger ages.

Because the main scope of the current study was to examine sensory competition in children of ages 8–12 in light of previous behavioral findings on visuo-spatial development, we aimed to have a comparable sample size between the child and adult groups. Previous studies in adult participants (Kastner et al., 1998, 2001) demonstrated compelling sensory competition effects in a relatively small sample (e.g., six to eight subjects). Thus, we replicated these findings from a comparable sample size for the adult group (9–11 subjects for each display size condition) and for the child group (13–18 subjects for each display size condition). However, the sample size in our study was not sufficient to examine potential individual variability within each of the age groups. Expanding our findings, future work should include a bigger sample size and a battery of visuo-spatial tasks to address the individual variability in the neural measures and the relation to visuo-spatial skills in children.

Chapter 3

The Effect of Perceptual Grouping on Sensory Competition in the Developing Brain

Introduction

The visual system organizes the retinal input in an early, pre-attentive stage of information processing in an automatic and effortless manner (Davis & Driver, 1998; Driver, Davis, Russell, Turatto, & Freeman, 2001; Wertheimer, 1923). Consider the Kanizsa illusion (Kanizsa, 1976), where multiple pac-man inducers generate the percept of one coherent shape in the middle. According to the biased competition theory, perceptual organization facilitates selective attention functions by defining a meaningful “unit”; competitive interactions are present only among those units, but not among the individual features within each unit (Figure 1.2).

This chapter examines how perceptual grouping occurs in children’s brain as a bottom-up, sensory-driven mechanism that modulates sensory competition, by employing a variation of the paradigm we introduced in Chapter 2. We presented four pac-man stimuli in the peripheral locations. The pac-man stimuli were rotated differently based on the grouping condition; in one condition, the stimuli faced inward to form an illusory shape, and in the control condition, they faced outward such that they were independently processed. As in Chapter 2, these stimuli were presented simultaneously or sequentially. Sensory competition among these stimuli was

measured by a reduction in responses evoked by the simultaneous presentation of the stimuli. In the adult brain, such competition effects would be reduced when the display consisted of a perceptual group (McMains & Kastner, 2010).

Converging evidence suggests that perceptual organization skills continue to improve until early teenage years (Hadad et al., 2010a; Hipp et al., 2014; Kimchi et al., 2005; Kovács et al., 1999; Scherf, Luna, Kimchi, Minshew, & Behrmann, 2008). Interestingly, when responding to Kanizsa shapes, children between ages 4 and 7 predominantly looked at and touched individual pac-man stimuli, whereas older children and adults looked at and touched the middle of the illusory shape (Nayar et al., 2015). These gaze fixations and touch responses indicated a gradual shift in the perceptual strategy from local (i.e., individual inducers preferred) to global processing (i.e., global shape preferred).

However, these behavioral findings could not dissociate the effect of attention engagement and thus could not test whether perceptual grouping occurred in an automatic and effortless manner at the level of visual cortex in children's brain. Indeed, studies using scalp electroencephalogram (EEG) have found that children below age 9 showed stronger activity in the frontal lobe in response to perception of Kanizsa shapes, whereas adults did not engage the frontal lobe (Altschuler et al., 2014; Csibra, Davis, Spratling, & Johnson, 2000). These findings suggest that even when children exhibit adult-like behavioral responses to Kanizsa shapes, they may require greater cognitive effort to process illusory shapes than adults. It is possible that the underlying mechanisms for perceptual grouping in the visual cortex continue to mature through extensive perceptual learning until ages 7 to 9 or later.

The goal of this study is twofold. First, it extends Chapter 2 by probing sensory competition in younger ages (ages 6–7) and replicates the findings in older children (ages

11–12). Second, it examines the effect of perceptual grouping on sensory competition in younger and older children. Adults are recruited as a reference group. If perceptual grouping in the visual cortex matures by age 6, children in both age groups will show the same effects of perceptual grouping as adults. However, if the grouping mechanisms in the visual cortex are still developing, one or both age groups will show a weaker effect of grouping and show a greater amount of competition unresolved even in the presence of perceptual groups, compared to adults. Based on previous behavioral studies, we hypothesize that the effect of grouping will be weaker in 6 to 7-year-olds while older children (ages 11–12) might show a grouping effect similar to adults.

This chapter presents preliminary results as the data collection has paused due to the COVID-19 shutdown.

Methods

Participants

A total of 8 adults, 6 older children, and 6 younger children participated in the study, which was approved by the Institutional Review Board of Princeton University. All participants had normal or corrected-to-normal vision and no history of neurological or psychiatric illnesses. Adult participants gave written informed consent. A child assent form was provided for children, and a full written informed consent form was obtained from their parents or guardians. Child participants were compensated with a gift card or toy.

Two of the younger children did not complete the session, and another was excluded due to excessive head motion (see below for exclusion criteria). One of the older children was excluded due to poor performance ($< 70\%$ hit rate) on the fixation task. The final sample

consisted of 8 adults (4 female, mean age 21.1 years, range 18–30 years, all right-handed), 5 older children (4 female, mean age 12.0 years, range 11.4–12.6 years, 1 left-handed), and 3 younger children (all females, mean age 7.2 years, range 6.7–7.6 years, all right-handed).

Visual displays and experimental design

Stimuli were generated and presented using Psychophysics Toolbox (Brainard, 1997; Pelli, 1997) in MATLAB (Mathworks, Inc., Natick, MA, USA).

The visual stimuli consisted of four pac-man inducers (width of 1.75°) presented in four nearby locations (separated by 0.5°) in the upper right quadrant of the visual field (Figure 3.1). The entire stimulus display encompassed $4 \times 4^\circ$ and was centered at 8° eccentricity from a fixation point in the upper right or left quadrant. In order to probe the effect of illusory shape-based grouping, each of the four inducers differed in color and luminance (colors used: red, green, yellow, purple, cyan). The angle of the four inducers was the same for a given display (angle: 50° , 70° , 90° , 110° , or 130°). A 2×2 factorial design was used, in which stimuli were shown in two different presentation conditions (sequential and simultaneous; Figure 3.1A) and two grouping conditions (NoGroup and StrongGroup; Figure 3.1B).

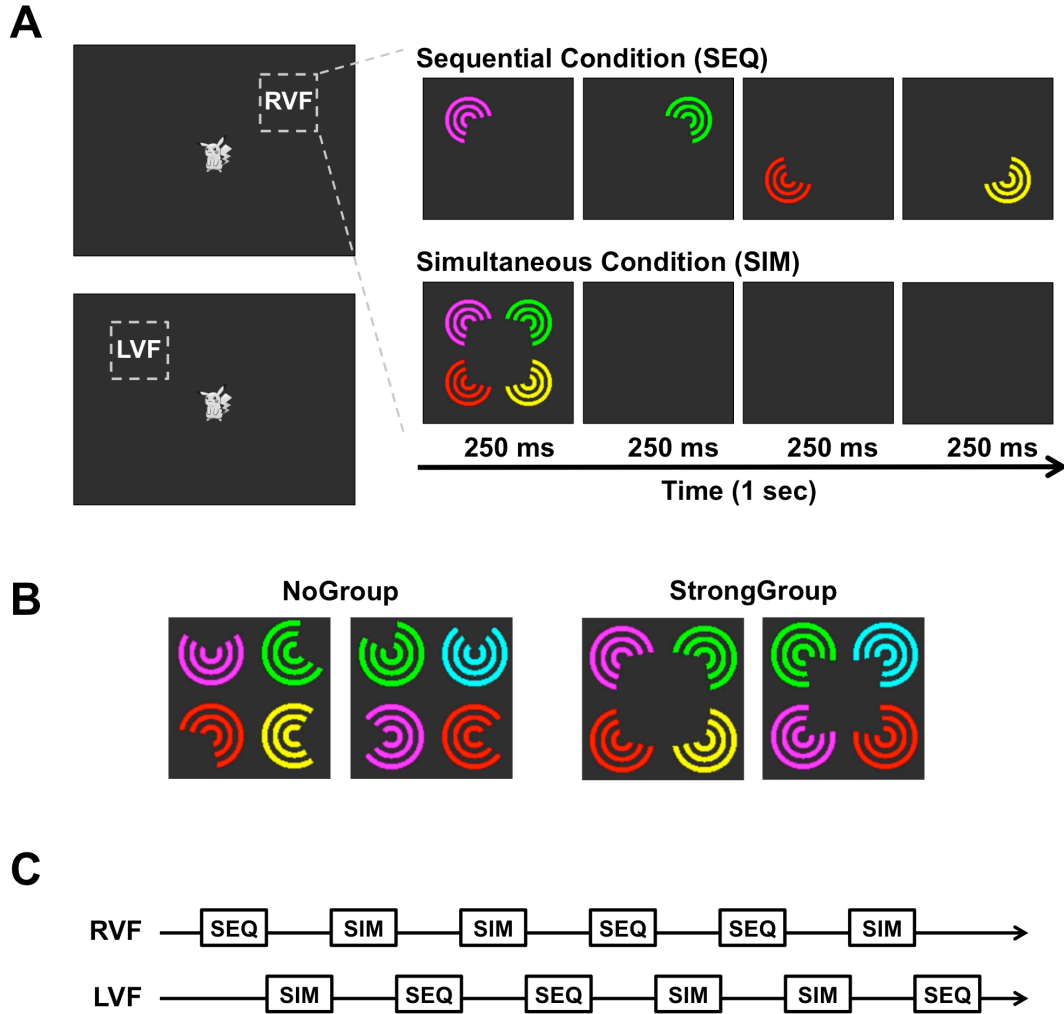


Figure 3.1. Experimental design. Four pac-man inducers were presented in a 2×2 design, in two presentation conditions (sequential (SEQ) versus simultaneous (SIM) presentations; panel A) and two grouping conditions (NoGroup versus StrongGroup; panel B). Visual displays were centered at 8° eccentricity from a central fixation point. In each run, a total of 3 SEQ and 3 SIM conditions were presented in blocks of 16 s interleaved with blank presentations in an ABBAAB scheme in each visual field (upper right and upper left quadrants). Stimulus presentations alternated between the right visual field (RVF) and the left visual field (LVF) such that stimuli presented on one hemifield during the blank periods of the other hemifield (panel C). Across the two hemifields, each run consisted of 6 SEQ and 6 SIM presentation blocks. The grouping conditions were blocked into separate runs. Participants performed a target detection task at the fixation point throughout the run.

In the sequential condition (SEQ), one stimulus was presented in one of the four locations for 250 ms, followed by a second stimulus presented in a second location and so on, until all four stimuli had been presented in the four locations during a 1 s period. In the simultaneous condition (SIM), the same four stimuli appeared together in the same locations as during the SEQ condition for the same time (250 ms) at a randomly selected time point (0/250/500/750 ms) within a 1 s period. A given block consisted of 12 repetitions of SEQ or SIM presentations. The presentation order, locations, colors, and angles of the four inducers were kept identical between the SEQ and SIM conditions and between the NoGroup and StrongGroup conditions, so that the stimulation conditions were exactly matched. For each run, SEQ and SIM conditions were presented in blocks of 16 s (12 s of stimulus presentation followed by a 4 s blank period) interleaved with 16 s blocks of blank period on each hemifield. In order to double the number of presentation blocks in a given run, we alternated stimulus presentations between the right and left upper quadrants, by presenting a stimulus block on one hemifield during the blank block on the other hemifield (Figure 3.1C). The order of SEQ and SIM blocks was counterbalanced on each quadrant; the blocks on the right upper quadrant were presented in the SEQ-SIM-SIM-SEQ-SEQ-SIM order while they were presented in the SIM-SEQ-SEQ-SIM-SIM-SEQ order on the left upper quadrant. No peripheral stimulus was presented during the blank periods. Blank periods (16 s) were also presented in the beginning and the end of each run. Thus, each run consisted of 6 visual stimulation blocks (3 SEQ blocks and 3 SIM blocks) and 7 blank blocks on each hemifield. Across both hemifields, each run yielded a total of 12 visual stimulation blocks (6 SEQ blocks and 6 SIM blocks).

Participants performed a target detection task at a central fixation point throughout each run, regardless of the presence of stimuli. The task was designed to be engaging, to ensure proper

fixation and prevent attentional capture by the peripheral stimuli. In this task, participants detected and made a button response to the target Pokémon character. As a default, an image of Pokéball (0.8° in size) was presented at the fixation point. The image was replaced by an image of a Pokémon character (0.8° in size) every 0.5-1 s. Each Pokémon picture was presented for 150 ms for the adult participants. For children, the presentation time was adjusted (150-350 ms) based on their performance during practice trials outside the scanner. Targets occurred on average every 10-20 characters. In order to make the task more engaging, we provided a brief feedback image immediately after every button response. A smiley face was presented when a button response was made at a target character. A surprise face was presented at false alarms. Both feedback images were presented in the same size as the Pokéball and Pokémon characters. A feedback statement was displayed at the end of each run based on the hit rate. For each session, we obtained hit rates and reaction times.

Each run lasted for 3 min and 54 s including dummy scans in the beginning. Grouping conditions were blocked into runs such that any given run consisted of either the NoGroup or the StrongGroup condition only. The goal was to complete at least 3 runs for each display size condition. If excessive head motion was detected and participants were willing to continue, additional runs were acquired.

Data acquisition

MRI data were acquired for the whole brain on a Siemens 3T MAGNETOM Prisma using a 64-channel head/neck coil. Functional images were acquired using a multi-band accelerated echo planar imaging (EPI) sequence (release R014) provided by a C2P agreement with the University of Minnesota (references listed in <http://www.cmrr.umn.edu/multiband/>): TR

= 2 s, TE = 30 ms, flip angle = 76° , FOV = 210×210 mm, matrix = 84×84 , 2.5 mm^3 resolution, 56 transverse slices, in-plane acceleration factor = 2, multiband acceleration factor = 2, bandwidth = 1985 Hz/Px. A whole-brain T1-weighted volume was collected (3D magnetized prepared rapid gradient echo (MPRAGE) sequence: 192 sagittal slices, 1.0 mm^3 resolution, FOV = 192×192 mm, matrix = 192×192 , TR/TE/TI = 2400/2.08/1000 ms, flip angle = 8° , in-plane acceleration factor = 2, bandwidth = 220Hz/Px, total time of acquisition (TA) = 5m 11s).

To correct for susceptibility-induced distortions, three spin echo volume pairs were acquired in opposing phase encode directions (anterior to posterior and posterior to anterior) with slice prescription, FOV, matrix size, bandwidth, and echo spacing matching the BOLD EPI acquisition (TR/TE = 8000/66.60 ms; FA/RFA = 90/180 deg; TA = 32 s) (Andersson, Skare, & Ashburner, 2003).

An infrared eye-tracking camera (SR-Research Eyelink, Ottawa, ON) was used to monitor fixation during the task.

Data analysis

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 1.2.3 (Esteban et al., 2019; RRID:SCR_016216), which is based on *Nipype* 1.1.6-dev (Gorgolewski et al., 2011; RRID:SCR_002502).

Anatomical data preprocessing

The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) using N4BiasFieldCorrection (Tustison et al., 2010, ANTs 2.2.0), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped

using `antsBrainExtraction.sh` (ANTs 2.2.0), using OASIS as target template. Brain surfaces were reconstructed using `recon-all` (FreeSurfer 6.0.1, RRID:SCR_001847, Dale et al., 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al., 2017). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov et al., 2009; RRID:SCR_008796) was performed through nonlinear registration with `antsRegistration` (ANTs 2.2.0, RRID:SCR_004757, Avants et al., 2008), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL 5.0.9, RRID:SCR_002823, (Zhang, Brady, & Smith, 2001).

Functional data preprocessing

For each of the 6 BOLD runs found per subject, the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A deformation field to correct for susceptibility distortions was estimated based on two echo-planar imaging (EPI) references with opposing phase-encoding directions, using `3dQwarp` (AFNI 20160207). Based on the estimated susceptibility distortion, an unwarped BOLD reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation

matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as preprocessed BOLD in native space. The BOLD time-series were resampled to MNI152NLin2009cAsym standard space, generating a preprocessed BOLD run in MNI152 standard space. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., 2014).

Nuisance regression and smoothing

Subsequent preprocessing and analyses were performed using FSL (<http://www.fmrib.ox.ac.uk/fsl>; Smith et al., 2004) and AFNI (<http://afni.nimh.nih.gov/afni>; Cox, 1996).

Further smoothing and artifact removal procedures were conducted separately for general linear model-based (GLM) analyses and for time course analyses. For GLM analyses, the data were spatially smoothed using a 4 mm Gaussian kernel (full-width at half-maximum). Volumes with movement > 2.5 mm were corrected by adding a nuisance regressor in the model (see Whole-brain contrast maps below). For time course analyses, spatial smoothing was omitted, but temporal smoothing was performed to remove frequencies above 0.2 Hz. Volumes with

movement > 2.5 mm were corrected via interpolation between the nearest non-affected volumes to reduce abrupt signal changes caused by head motion.

The anatomical volume was used for cortical surface reconstruction for each participant using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999).

Exclusion based on head motion

Motion-affected volumes were identified on the basis of framewise displacements (FDs) calculated from the six translation and rotation parameters. In order to identify motion outliers, we calculated the Euclidean norm of relative displacement at each time point, relative to the previous time point, and averaged the FDs across all time points within the run and then across all runs for each grouping condition in each participant. One of the younger children was excluded because the average FD was outside the range of three standard deviations from the mean of all participants.

Whole-brain contrast maps

Whole-brain voxel-wise GLM analyses were performed using FSL's FMRI Expert Analysis Tool (FEAT). Each condition within each preprocessed run was modeled with a square-wave function convolved with a gamma-variate hemodynamic response function. The model included explanatory variables (EVs) for the two presentation conditions: SEQ and SIM, as well as confound EVs, e.g., for the exclusion of time points affected by excessive head motion (greater than the size of two voxels; 5 mm). Four regressors were generated: (1) SEQ blocks on the right visual field, (2) SIM blocks on the right visual field, (3) SEQ blocks on the left visual

field, and (4) SIM blocks on the left visual field. Using these regressors, four contrast maps were generated: (1) peripheral visual stimulation (regardless of the presentation conditions) versus blank periods on the right visual field (coefficients: 1, 1, -1, -1), (2) peripheral visual stimulation (regardless of the presentation conditions) versus blank periods on the left visual field (coefficients: -1, -1, 1, 1), (3) SEQ > SIM across the entire visual field (coefficients: 1, -1, 1, -1), and (4) SIM > SEQ across the entire visual field (coefficients: -1, 1, -1, 1). While we visually inspected statistical maps comparing the SEQ and SIM conditions (Contrasts 3 and 4), quantitative comparisons of the SEQ and SIM conditions were performed in the *time course analysis* section below.

For each participant, all runs from both grouping conditions were combined to generate a statistical map for each contrast. We did not examine the contrast maps separately for each grouping condition because the same areas were activated in response to peripheral stimuli regardless of the grouping conditions. Subject-level analyses combining multiple runs were performed using a mixed effects model, with the random effects component of variance estimated using FSL's FLAME 1 procedure. The FLAME procedures make more accurate estimates of the inter-run random-effects variance and degrees of freedom at each voxel than a fixed effects model. Statistical maps comparing visual stimulation blocks versus blank blocks on each hemifield (Contrasts 1 and 2) were thresholded at $Z > 3.5$ ($p < 0.0005$; upper-tailed test; cluster correction $P < 0.05$). This comparison revealed voxels activated by the peripheral stimuli on the contralateral visual field while subtracting out foveal voxels activated by the central fixation task.

We identified visually responsive voxels from the visual stimulation > blank contrast maps for each hemifield in each participant. For each hemisphere, visually responsive voxels

were assigned to each area of interest in the contralateral hemisphere, as determined by a probabilistic atlas (Wang et al., 2015) using the same procedures described in Chapter 2.

For quantitative analyses of visually evoked responses, we performed time course analyses. Because there was individual variability in the amount of activated volumes at a particular threshold, we used a relatively lenient threshold for each individual ($Z > 2.3$; uncorrected) and selected voxels that were most responsive to the peripheral stimuli. For that purpose, we selected 50 voxels with the highest Z scores among the activated voxels that fell within each area of the probabilistic atlas.

For visualization of the contrast maps, volume-based data were projected to the surface by using AFNI's 3dVol2Surf function. All analyses were performed in the volume.

Time course analysis

All time course analyses were performed on unsmoothed data. Each run's time course of signal changes was extracted from each area of interest.

Time courses for each visual stimulation block were extracted from a time window based on the onset of each block. Time series were normalized to the first 3 time points preceding the stimulation block, which measured the level of baseline activity immediately preceding the evoked response. The first block of each run was excluded in order to avoid a potential confounding effect of the first visual stimuli after a longer blank period that may have given rise to greater signal change (i.e. onset effect).

For each participant, each condition, and each area, mean signal changes were computed by averaging across the four peak time points within the time window of expected peak activity for each block (4.5-13.5 s after stimulus onset). The mean signal changes were then submitted to

a mixed-effects model (using *lmer* function from R lmerTest package) for repeated measures ANOVAs.

In order to compare the degree of suppression across areas, grouping conditions and across the three age groups, we computed a sensory suppression index [$SSI = (R_{SEQ} - R_{SIM}) / (R_{SEQ} + R_{SIM})$; R is the average of peak signal changes of visually evoked responses as a function of stimulus presentation]. The SSIs provided a standardized measure of suppression, regardless of the overall degree of visually evoked responses. We performed post-hoc comparisons from the mixed-effects model to examine age-related differences in SSIs for each visual area and for each grouping condition (using R emmeans package; Lenth, 2016; Searle, Speed, & Milliken, 1980).

Preliminary Results

The current study investigated the effect of perceptual grouping on sensory competition in the visual cortex of children in two age groups (6–7 years vs. 11–12 years) and adults (18–30 years). We first quantified sensory competition effects by measuring the reduction in visually evoked responses in the simultaneous (SIM) presentation condition, relative to the sequential (SEQ) presentation condition. In Chapter 2, we observed similar competition effects between children ages 8 to 12 and adults. Here, we aimed to extend to a younger age range (ages 6–7) by comparing the degree of competition effects across the three age groups.

Secondly, we examined how the grouping-based modulation of competition effects might vary across the age groups. In the “strong perceptual grouping” (StrongGroup) condition, four pac-man inducers were facing inward such that they formed an illusory figure (e.g., square) in the SIM condition. In the “no perceptual grouping” (NoGroup) condition, four pac-man inducers were facing outward and not aligned to form an illusory shapes. The four inducers in a given

display were displayed in four different colors. The colors, arc angles, and presented locations of the stimuli were matched between the StrongGroup and NoGroup conditions. The only difference between the two grouping conditions was the direction in which the inducers were rotated. We measured the effect of perceptual grouping by assessing the decrease of competition effects in the StrongGroup condition compared to the NoGroup condition.

Behavioral results

The current study was designed to examine the effect of perceptual grouping on competition effects outside the focus of attention. It has been suggested that perceptual groups tend to capture attention more strongly than non-grouped elements (Arrington, Carr, Mayer, & Rao, 2000; Kimchi, Yeshurun, & Cohen-Savransky, 2007; Yeshurun, Kimchi, Sha'shoua, & Carmel, 2009). To rule out the potential confounding effects of attention allocation, we ensured that participants' performance on the target detection task was consistent for the SIM conditions across the NoGroup and StrongGroup conditions. Behavioral measures were averaged across the left and right visual field presentation blocks.

We obtained accuracy and response times (RT) for each of the age groups, presentation conditions, and grouping conditions (Table 3.1). A repeated-measure ANOVA confirmed that accuracy during SIM presentation blocks did not differ across the three age groups ($p = 0.25$) or between the grouping conditions ($p = 0.50$). There was no interaction between age group and grouping ($p = 0.20$). Similarly, RTs did not differ between the grouping conditions ($p = 0.14$), and there was no interaction effect between age group and grouping ($p = 0.19$).

Table 3.1. Accuracy and response time (RT) for behavioral task

Grouping	Block type	Accuracy (%)			RT (msec)		
		Younger Children	Older Children	Adults	Younger Children	Older Children	Adults
NoGroup	SEQ	93.4 (6.4)	91.4 (6.8)	95.0 (4.1)	902 (86)	643 (81)	599 (50)
	SIM	93.1 (1.0)	95.5 (5.0)	95.8 (5.1)	847 (44)	685 (114)	600 (28)
StrongGroup	SEQ	92.6 (5.0)	93.7 (3.8)	98.2 (3.7)	881 (63)	668 (101)	617 (60)
	SIM	95.8 (3.8)	92.8 (3.3)	98.1 (2.4)	911 (85)	674 (63)	626 (67)

Shown are the mean and standard deviation of the participants' performance on the central fixation task for each condition.

Topography of visually evoked responses

Because the presentation of peripheral visual stimuli alternated between the upper left and upper right quadrants (Figure 3.1C), visual stimulation > contrast maps were obtained separately for stimuli presented in each quadrant (Figure 3.2). As expected, visual stimuli evoked robust activity in early visual, ventral and dorsal extrastriate cortex of the hemisphere that is contralateral to the stimulus presentation. Topographic areas (white dotted lines in Figure 3.2) were defined using a probabilistic atlas (Wang et al., 2015). For the following analysis, we combined areas VO1 and VO2 (labeled as area VO), TO1 and TO2 (labeled as area MT), and V3A and V3B (labeled as area V3A).

Figure 3.2 illustrates visually evoked activation maps from a representative participant of each age group. For the purpose of visualization, contrast maps were thresholded at $Z > 3.5$ ($p < 0.0005$; upper-tailed test). Stimuli presented in the upper right quadrant evoked greater activity as compared to blank periods exclusively in areas of the left hemisphere (LH; left panels), and stimuli presented in the upper left quadrant evoked activity exclusively in areas of the right hemisphere (RH; right panels), demonstrating no or minimal interfering effects between the two

hemifields. Across the three age groups, early visual areas V1, V2, V3, ventral extrastriate areas hV4 and VO, and dorsal extrastriate areas V3A, MT, IPS0 (area V7) exhibited responses to visual stimuli across the presentation and grouping conditions. In the example participants from the older (age 12) and younger (age 7) children groups, a small area in LO1-2 was also activated (see RH for the 12-year-old participant and LH for the 7-year-old participant).

Peripheral stimulation > Blank

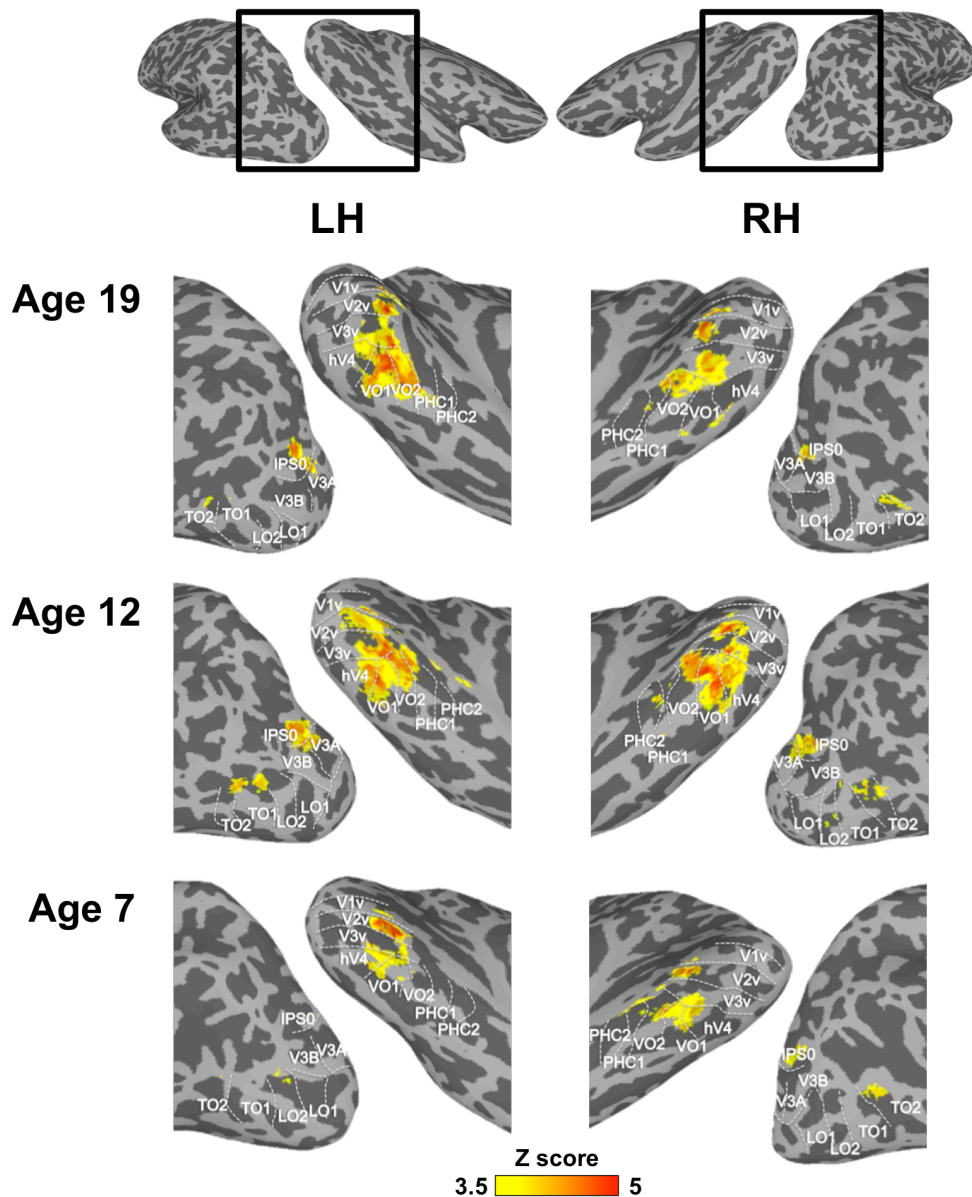


Figure 3.2. Visually evoked responses (peripheral stimulation > blank) to stimulus presentation in the contralateral hemifield. The lateral and occipital parts of the brain (outlined in black in top panel) were enlarged for visualization. As expected, visually evoked responses were observed in visual areas of the left hemisphere (LH; left panels) for visual stimuli presented in the upper right quadrant, and in areas of the right hemisphere (RH; right panels) for the stimuli presented in the upper left quadrant. Contrast maps from representative participants of the three age groups are displayed. Visually responsive voxels were assigned to each topographic area based on a probabilistic atlas, as shown in white dotted lines (Wang et al. 2015).

Comparison of competition effects across age groups

In order to quantify competition effects in visually evoked responses, we conducted time course analyses. First, we analyzed evoked responses in the NoGroup condition alone, in order to assess the basic form of competition effects when there is no perceptual group. As in Chapter 2, we compared percent signal changes for SEQ and SIM presentations of visual stimuli for each age group. Competition effects were indicated by the difference in signal change between the SEQ and SIM conditions. To compare competition effects across the three age groups, we used a sensory suppression index [$SSI = (R_{SEQ} - R_{SIM}) / (R_{SEQ} + R_{SIM})$]. SSI served as a normalized measure of competition effects by controlling for difference in the overall amount of activation across areas and participants.

Time courses of the NoGroup condition were extracted from the following topographic areas averaged across the two hemispheres: V1-V4, VO, V3A, and MT. As expected and consistent with our findings in Chapter 2, stimuli in the SIM condition gave rise to competition effects, indicated by a smaller response than the same stimuli in the SEQ condition. We found an area $\times$ presentation interaction [$F(6, 4145) = 5.1, p = 0.023$], indicating that all but area V1 showed competition effects across all of the three age groups. Both adults and older children showed competition effects in all areas (all $t > 3.2, p < 0.01$) except V1. Younger children also showed a similar pattern; they exhibited significant competition effects in areas V3, V4, and MT (all $t > 2.2, p < 0.05$) and a trend in areas V2 ($t = 1.6, p = 0.12$), VO ($t = 1.5, p = 0.13$), and V3A ($t = 1.4, p = 0.17$), but no competition effect in area V1. As in Chapter 2, area V1 did not show competition effects due to the small RF size of the area relative to the size of our stimulus display.

We compared the competition effects across the three age groups based on the SSIs obtained from the NoGroup condition. There was no effect of age group ($p = 0.69$) or area $\times$ age group interaction ($p = 0.63$). Although this should be revisited with more data points and equal number of participants across the age groups, the current results did not reveal any age-related differences in competition effects.

Comparing grouping effects across age groups

Next, we examined percent signal changes and SSIs in both the NoGroup and StrongGroup conditions. We focused this analysis on areas V3, V4, and VO because these areas showed the most reliable competition effects across age groups based on the analysis of the NoGroup condition described above.

Figure 3.3 illustrates a comparison of percent signal changes within each age group. Sensory competition was indicated by reduced responses in the SIM condition than in the SEQ condition. The grouping-induced release of competition was reflected as an interaction between the grouping (NoGroup vs. StrongGroup) and the presentation (SEQ vs. SIM) conditions.

In adults, activity evoked by the stimuli in the SIM condition was smaller than that evoked by the SEQ condition across both grouping conditions [main effect of presentation: $F(1, 1853) = 92, p < 0.001$], indicating competition effects across the grouping conditions. This was expected because individual stimuli in a given display varied in color and luminance regardless of the grouping condition. Importantly, there was a grouping $\times$ presentation interaction [$F(1, 1853) = 5.1, p = 0.023$]. Post hoc analyses confirmed that responses evoked by the SEQ blocks did not differ between the NoGroup and StrongGroup conditions ($t = 0.7, p = 0.90$) while responses evoked by the SIM blocks were greater in the StrongGroup condition than in the

NoGroup condition ($t = -2.5, p = 0.06$). Thus, the observed difference was driven by the grouping-based release of competition in the SIM condition, rather than low-level perceptual differences between the two grouping conditions.

In older children (ages 11–12), there was a main effect of presentation [$F(1, 1064) = 67.3, p < 0.001$], reflecting competition effects in the SIM condition of both grouping conditions. Similarly to adults, we found a grouping $\times$ presentation interaction [$F(1, 1064) = 8.7, p = 0.0033$], which was driven by the increase of responses evoked by the StrongGroup SIM blocks relative to the NoGroup SIM blocks ($t = -2.7, p = 0.04$). There was no difference in the responses during the SEQ blocks between the two grouping conditions ($t = 1.5, p = 0.45$).

In the youngest group (ages 6–7), we also found a main effect of presentation [$F(1, 634) = 17.0, p < 0.001$], demonstrating that the youngest age group also presented competition effects during the SIM presentation blocks across the grouping conditions. The grouping $\times$ presentation interaction was not significant [$F(1, 634) = 1.12, p = 0.29$], as the amount of evoked responses did not differ between the NoGroup and StrongGroup conditions both for the SEQ blocks ($t = 0.51, p = 0.96$) and for the SIM blocks ($t = -1.0, p = 0.76$).

The grouping-based modulation of sensory competition effects was compared across age groups with the help of SSIs, in order to control for difference in the overall amount of activation across areas and grouping conditions. Figure 3.4 summarizes the results from the comparison of SSIs between the grouping conditions across the three age groups. We confirmed that there was a main effect of grouping [$F(1, 65) = 38.2, p < 0.001$], consistent with the grouping $\times$ presentation interaction in the analysis of percent signal changes. Post hoc analyses demonstrated that a reduction of competition effects in the StrongGroup condition was observed in areas V4 and VO in adults [V4: $t = 2.8, p = 0.006$; VO: $t = 3.4, p = 0.0013$] and in older children [V4: $t = 2.9, p =$

0.005; VO: $t = 4.0$, $p = 0.0001$], and a trend was observed in area V3 both in adults ($t = 1.5$, $p = 0.15$) and in older children ($t = 1.7$, $p = 0.10$). In younger children, however, such reduction in competition effects was not statistically significant in all three areas [V3: $t = 1.3$, $p = 0.21$; V4: $t = 1.6$, $p = 0.13$; VO: $t = 0.9$, $p = 0.40$], although area V4 exhibited a trend. Across the three areas, adults' and older children's visual areas showed a release of sensory competition in the StrongGroup condition (adults: $t = 4.4$, $p < 0.001$; older children: $t = 5.0$, $p < 0.001$), but such pattern was not as clearly presented in younger children's visual areas ($t = 2.1$, $p = 0.29$). Although the overall grouping $\times$ age group interaction effect was not significant [$F(2, 65) = 1.1$, $p = 0.34$], the numerical differences suggested a smaller effect of grouping on sensory competition in younger children, compared to older children and adults. These results need to be confirmed with a larger sample.

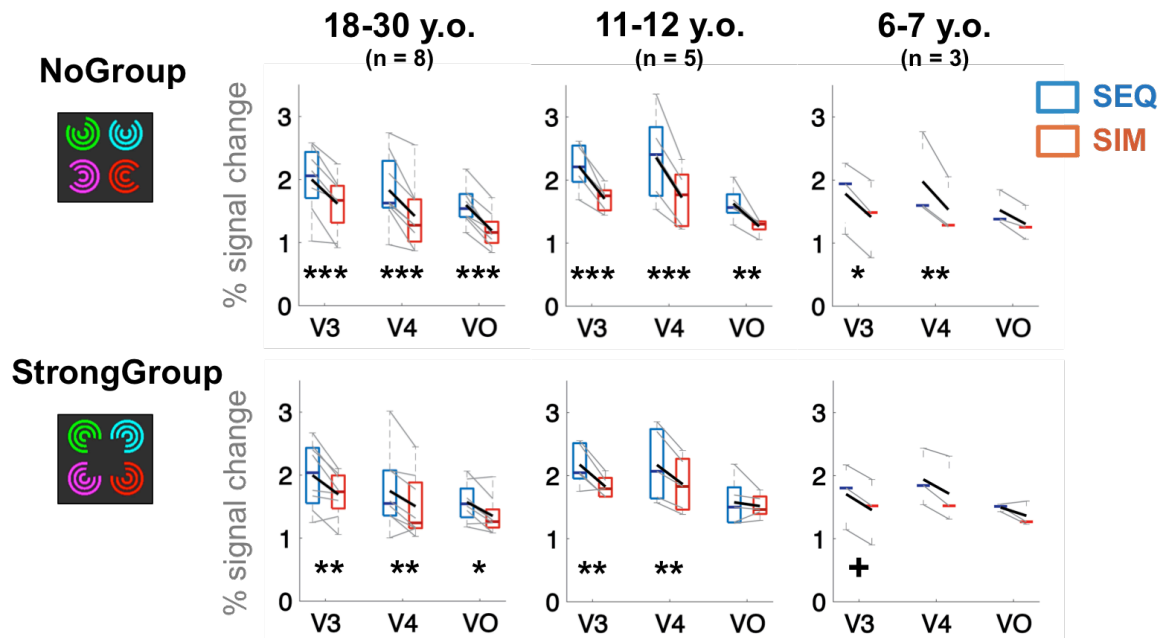


Figure 3.3. Comparison of signal changes between the SEQ and SIM presentation conditions for each grouping condition in each age group. Four peak values from each block (SEQ or SIM) were averaged to obtain mean signal changes. Box plots: bold line indicating

median; box indicating 25th and 75th percentiles; whiskers indicating range. Individual participants' data are displayed in gray lines. The negative slopes of the gray lines indicate competition effects (i.e., smaller responses evoked by SIM presentations compared to SEQ presentations). Black bold lines indicate group-level estimations based on the linear functions to probe the competition effects for each area and each grouping condition: *** $p < .001$; ** $p < .01$; * $p < .05$; + $p < 0.1$. The effect of grouping was reflected as an interaction between presentation and grouping conditions in each age group. The preliminary results suggest that all three age groups show competition effects in extrastriate visual areas and that the youngest group appears to show a weaker grouping effect compared to adults and older children.

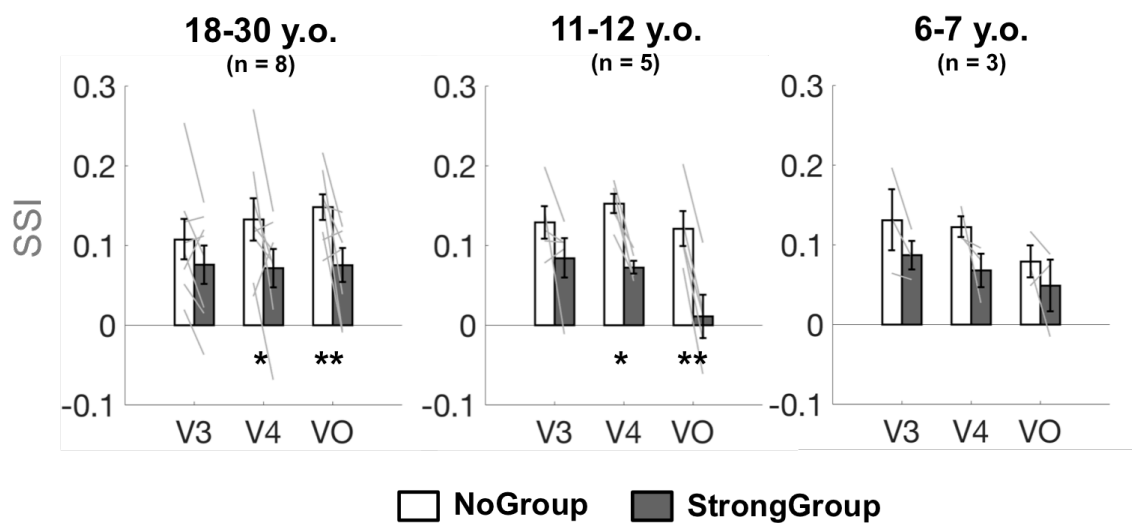


Figure 3.4. Comparison of sensory suppression indices (SSIs) between the two grouping conditions across three age groups. SSIs provided a normalized measure of competition effects across the grouping conditions and age groups [$SSI = (R_{SEQ} - R_{SIM}) / (R_{SEQ} + R_{SIM})$]. The analysis of SSIs yielded results that were consistent with our findings based on signal changes (Figure 3.3). Competition effects in the NoGroup condition, which was similar to the paradigm in Chapter 2, did not differ across the three age groups. Although the grouping $\times$ age group interaction was not significant in the current dataset, the effect of grouping (indicated as a decrease in the SSIs) was smaller in the youngest group than adults and older children. These results should be further examined when data collection is complete.

Discussion

This chapter investigated how sensory competition in the developing visual cortex (ages 6–7 vs. ages 11–12) is modulated by perceptual organization. In the adult brain, competitive interactions among the stimuli are reduced when the stimuli generate perceptual groups following perceptual organization principles (e.g., Gestalt principles) (McMains & Kastner, 2010). Based on behavioral findings on the prolonged development of visuo-spatial integration (e.g., Kovács et al., 1999), we hypothesized that the visual system's capacity to utilize perceptual groups continues to refine between ages 6 and 12. That is, younger children (ages 6–7) will show a weaker effect of grouping on sensory competition, compared to older children (ages 11–12) and adults. Our preliminary results were consistent with the hypothesis. If these results hold, the current study will have implications for characterizing visuo-spatial attention functions in the developing brain.

In order to investigate the effect of perceptual grouping, we compared the degree of sensory competition between the two grouping conditions (StrongGroup vs. NoGroup). The two conditions consisted of the same pac-man stimuli, which were matched in color, shape, and location of each stimulus. The only difference between the two conditions was the direction in which the stimuli were rotated (inward vs. outward). Because all other low-level features except the presence of an illusory shape were matched, we argue that the reduction in sensory competition in the StrongGroup condition is indeed driven by the presence of a perceptual group. This can be further supported by the observation that such differences appeared only when the stimuli were presented simultaneously (SIM). The amount of signal changes in the sequential (SEQ) presentation did not differ between the two grouping conditions, which further supports that no low-level differences were observed between the two conditions.

One may ask whether the reduction in sensory competition in the StrongGroup condition reflects the effect of attentional capture. Indeed, as emphasized in Chapter 2, attention involuntarily directed to the peripheral stimuli also modulates the degree of sensory competition (e.g., Kastner et al., 1998). To rule out the possible confounding effect of attention allocation, we ensured that each participant's performance on the fixation task was consistent both across the presentation conditions (SEQ versus SIM) and across the grouping conditions (StrongGroup versus NoGroup). We also monitored participants' gaze fixations throughout the session, but the target detection accuracy and reaction times for the fixation task provided more compelling evidence because these measures were able to reflect any covert attention allocated to the stimuli. In future data collection, it would be crucial to continue to monitor participants' performance on the central fixation task during the entire session based on these two measures.

In the adult brain, perceptual grouping facilitates selective attention, by meaningfully organizing visual entities such that it reduces the amount of competition in the display and thus reduces the demand for top-down attention (McMains & Kastner, 2011). If our preliminary results hold and younger children indeed show a weaker effect of perceptual grouping, it suggests that younger children's visual system experiences greater sensory competition for displays consisting of perceptual groups, compared to older children and adults. That is, visuo-spatial functions like perceptual grouping are automatic and effortless in older children and adults, but they may require younger children to engage attentional resources to a greater extent and thereby prevent them from efficiently process target information in complex visual scenes. Such interaction between developing visuo-spatial functions and top-down selection could be systematically examined in future research.

Finally, results from this study may provide insight into the neural basis of integrative perceptual functions that continue to develop until early adolescence, such as the Kanizsa shape perception and contour integration. Although converging evidence suggests the prolonged development of those perceptual functions (Hadad et al., 2010a; Kimchi et al., 2005; Kovács et al., 1999; Nayar et al., 2015; Scherf et al., 2009, 2008), these studies left unanswered whether these age-related improvements in behavioral performance are driven by developmental changes in neural circuits of visual cortex. Since the current experimental paradigm measures the effect of grouping outside the focus of attention, it avoids any top-down factors and probes the mechanisms within the visual cortex. If younger children exhibit a weaker effect of grouping as we hypothesized, this indicates that the visual system is undergoing maturation beyond age 7 to gain better capacities to organize visual input based on perceptual regularities. Although our data would not be able to pinpoint the underlying circuits, prior studies in infant macaques suggest that the slow development of feedback mechanisms from higher-order areas might be responsible (Li et al., 2013). Indeed, the fine-grained representation of Kanizsa illusory shapes in early visual cortex appears to reflect predictive signals from higher-order areas that are sensitive to shape information (Kok & De Lange, 2014). By testing perceptual grouping in the context of biased competition, the current study will further our understanding of the neural underpinnings for the prolonged development of integrative visuo-spatial functions.

Chapter 4

Development of Spatial Biases and the Fronto-parietal Attention

Network in Childhood

A version of the Part I of this chapter was published as an article in Developmental Science (Hoyos, Kim*, Cheng, Finkelston, & Kastner, 2020 * co-first authorship).*

Introduction

The selection of information from cluttered visual environments is one of the most fundamental cognitive operations and the foundation for functional higher cognition. In the adult brain, visuo-spatial attention is controlled by a large-scale network that comprised multiple areas in frontal and parietal cortex (Buschman & Kastner, 2015; Corbetta & Shulman, 2002; Fiebelkorn & Kastner, 2020; Kastner & Ungerleider, 2000). Within the dorsal fronto-parietal network, each hemisphere generates attentional weights towards the contralateral visual hemifield (Szczepanski et al., 2010). The attentional weights generated by the two hemispheres are in balance through reciprocal inhibition such that visuo-spatial attention can be allocated across the entire visual field (Kinsbourne, 1977; Szczepanski et al., 2010).

Perturbation in the balance within the fronto-parietal network can result in biases in spatial attention. In the most extreme case of visuo-spatial hemineglect following lesions of right parietal cortex (or other network parts in the right hemisphere), patients display a spatial bias

towards the ipsilesional (right) hemi-field that is so strong that the contralesional (left) hemi-field is entirely neglected. As a consequence, a neglect patient may eat only from one half of his/her plate or apply make-up to only one half of the face. In healthy adults, when the fronto-parietal areas in one hemisphere are perturbed by transcranial magnetic stimulation (TMS), spatial attention is temporarily shifted toward the side ipsilateral to the TMS interference (Szczepanski & Kastner, 2013), providing further evidence for the role of interhemispheric balance in the control of spatial attention.

Spatial biases as observed in visuo-spatial hemineglect or TMS perturbation can be measured using a line bisection task. In the bedside version of this task, the subject is presented with horizontal lines and asked to bisect the lines in two equal parts. Patients suffering from visuo-spatial hemineglect underestimate the length of the left side of the line and bisect the line far to the right of the veridical center (e.g., Ishiai, Furukawa, & Tsukagoshi, 1989). Alterations of spatial biases have also been observed in pediatric populations. For example, children with ADHD who were not medicated had a visuo-spatial bias significantly rightward compared to controls and children with ADHD who were medicated (Sheppard, Bradshaw, Mattingley, & Lee, 1999). Children with dyslexia showed less of a leftward bias than age-matched controls (Sireteanu, Goertz, Bachert, & Wandert, 2005). However, many of the previous studies in pediatric populations either lacked a neurotypical control group or had small sample sizes that were not robust enough to characterize the neurotypical development of visuo-spatial attention biases. Thus, it remains unclear whether such visuo-spatial attention bias in ADHD or dyslexia populations is part of neurotypical development, or alternatively associated with the disorder.

Despite the extensive literature on the fronto-parietal attention network in the adult brain, it remains unclear how the network develops across children to acquire adult-level visuo-spatial

attention function (Kim & Kastner, 2019). Converging evidence supports that the fronto-parietal network undergoes significant maturation in childhood and adolescence (e.g., Casey, Tottenham, Liston, & Durston, 2005). However, when and how the fronto-parietal network achieves an equilibrium in spatial attention control between left and right hemispheres across development is largely unknown.

In this study, we used a perceptual, computerized version of the line bisection task similar to the task used in Szczepanski and Kastner (2013) and often referred to as a landmark task. The perceptual version of the line bisection task has been shown to provide a robust measure of spatial attention bias (Bisiach, Ricci, Lualdi, & Colombo, 1998; Bjoertomt, Cowey, & Walsh, 2002; Milner, Brechmann, & Pagliarini, 1992). In our version, participants were presented with pre-bisected horizontal lines and asked to judge which side was shorter or longer by pressing buttons corresponding to the left or right. An important advantage of this version of the task is that, unlike manual line bisection tasks used in previous studies (Bowers & Heilman, 1980; Bradshaw, Nettleton, Wilson, & Bradshaw, 1987; Chokron & De Agostini, 1995; Dellatolas, Coutin, & De Agostini, 1996; Hausmann et al., 2003; Van Vugt, Fransen, Creten, & Paquier, 2000), it does not require hand-eye coordination. This avoids any confounds driven by manual actions, which are even more critical for children who are still developing their motor skills through adolescence (Cole, Mostofsky, Gidley Larson, Denckla, & Mahone, 2008; Gidley Larson et al., 2007), and for clinical populations such as ADHD and dyslexia, who have a high rate of motor difficulties as co-morbidities (Kaplan, Wilson, Dewey, & Crawford, 1998). The developmental trajectory of spatial biases using a perceptual version of the line bisection task has not yet been explored.

This chapter consists of three parts. In Part I, we examined the developmental trajectory of spatial attention biases in a large cohort of school children by using a perceptual version of the line bisection task. We found that school children (grades 1 to 8, equivalent to ages 6 to 14) exhibited a leftward distribution of spatial biases. The leftward biases were most expressed in lower grades (grades 1 to 3), diminished with advancing grades, and became similar to adults in higher grades (grades 6 to 8). In Part II, we linked spatial attention biases in children (age 6 to 12) to functional connectivity within the dorsal fronto-parietal network. Behavioral spatial biases in individual children were predicted by the functional connectivity patterns, specifically within the dorsal fronto-parietal network. In Part III, we demonstrated functional connectivity patterns within the same network also predicted reading fluency in children. With a behavioral finding that first to third graders with leftward biases tend to have better reading fluency, this suggests that spatial biases in young children may be related to reading development. Based on these results, we discuss how the dorsal fronto-parietal network develops in childhood, which may be shaped by children's acquisition of reading skills.

Part I. Development of spatial biases:

A large-cohort behavioral study in school-aged children

We investigated the development of spatial attention bias in school-aged children from grades 1 through 8 (equivalent to ages 6 to 14) in comparison to young adults. In Part I, we examined the developmental trajectory based on grade level because it reflects the child's educational background. We also conducted the analyses based on age, which yielded consistent results. Patricia Hoyos and Abigail Finkelston have contributed to this part.

Methods

Participants

A total of 397 subjects (336 children in grades 1 to 8 and 61 college freshmen) gave informed consent (Table 4.1) to participate, which was approved by the Institutional Review Board (IRB) of Princeton University. Children were recruited from two venues: a local summer camp ($n = 208$) and a local school ($n = 128$). Adults ($n = 61$) were undergraduate freshmen at Princeton University. Each participant's handedness, gender, and age were obtained.

Table 4.1. Demographics

Grade	Number of subjects	Mean Age; Range	Handedness			Gender	
			Right	Left	Ambi	Male	Female
Children							
1	38	6.11; 5-7	34	4		12	26
2	44	6.93; 6-8	38	6		29	15
3	42	8.02; 7-9	40	2		19	23
4	30	9.03; 8-10	28	2		13	17
5	34	9.91; 9-11	33	1		20	14
6	56	10.84; 10-12	46	10		34	22
7	53	12.08; 11-13	47	5	1	20	33
8	39	13.08; 12-14	36	3		18	21
Total	336	9.65; 5-14	302	33	1	165	171
Adults							
College Freshmen	61	18.38; 17-21	46	15		20	41

Task design

To assess spatial attention bias in individual participants, we used a perceptual version of a line bisection task, also known as the landmark task (Milner et al., 1992; Bjoertomt et al., 2002; Bisiach et al, 1998), that was modified for use in pediatric populations (Szczepanski & Kastner, 2013). In adults, this perceptual task is a robust measure for the hemispheric balance of spatial attention control signals produced by the fronto-parietal attention network (Szczepanski & Kastner, 2010). The task was administered on a laptop using MATLAB software (MathWorks) and Psychophysics Toolbox functions (Brainard, 1997).

Participants were seated 30 to 40 centimeters away from the laptop screen. On each trial, a bisected line was presented in the center of the display (see Figure 4.1). Each stimulus

consisted of a horizontal line bisected by a short vertical line (roughly 2° visual angle in length). The horizontal line was presented in four different lengths (20, 21, 22, 23° visual angle) in random order. Each participant made a judgment based on the stimulus, as to whether one side of the bisected line was shorter or longer. Specifically, each participant was assigned to answer one of the following two questions based on each stimulus: “Which side is longer, right or left?” or “Which side is shorter, right or left?”. Participants were instructed to make a response by pressing one of two buttons on the keyboard. They pressed the ‘A’ button on the keyboard with their left index finger to answer “left” and pressed the ‘L’ button with their right index finger to answer “right.” We placed colored stickers on the ‘A’ and ‘L’ buttons and used color names to refer to the buttons (e.g., the blue button for “left” and the yellow button for “right”) so that children could find the buttons easily on the keyboard. The use of hands for the two buttons was kept consistent across all participants in order to avoid confusion in using the right hand to answer “left” and the left hand to answer “right.” Practice trials were provided at the start of testing. In order to avoid confusion, particularly with the pediatric population, the type of question remained the same throughout the entire session including practice trials. The type of question was counterbalanced across participants.

As shown in Figure 4.1, each trial started with a 1.5 s preparation period, in which participants maintained fixation at a smiley face in the middle of the screen. A pre-bisected line stimulus was then presented for 200 ms, followed by the presentation of a visual mask for 2 s. The stimulus duration was chosen to minimize the confounding effects of eye movements during display presentation. However, the stimulus duration was extended to 225-700 ms for 40 children, who were unable to perform the task with the short presentation time. We ruled out the possibility that the spatial bias measures in those children were systematically influenced by the

extended stimulus duration by assessing the correlation between the stimulus presentation time and estimated spatial bias across all participants as well as the significance of stimulus duration as a variable in the statistical model (see Results). Participants indicated which side of the bisected line was longer (or shorter) by pressing a button on the keyboard. Each participant was asked to complete 4 blocks of the task. Each block consisted of 20 bisected horizontal lines for a total of 80 trials per participant. The task, including the practice trials, lasted roughly 10 minutes per participant.

The location of the bisecting vertical line was manipulated based on a staircase procedure. Each block began with a vertical bisecting line located 1° away to either the left or the right from the veridical midpoint of the horizontal line. The vertical bisecting line was shifted in a two-down, one-up manner. That is, each horizontal line was presented twice at a certain distance away from the veridical midpoint. If a participant responded correctly to both presentations of a stimulus with a certain offset, the vertical line was shifted closer to the veridical midpoint by setting the new offset to 80% of the previous offset. If the participant responded incorrectly, the vertical line was shifted away from the midpoint. Trials with bisecting vertical lines on the right and the left sides were randomly intermixed.

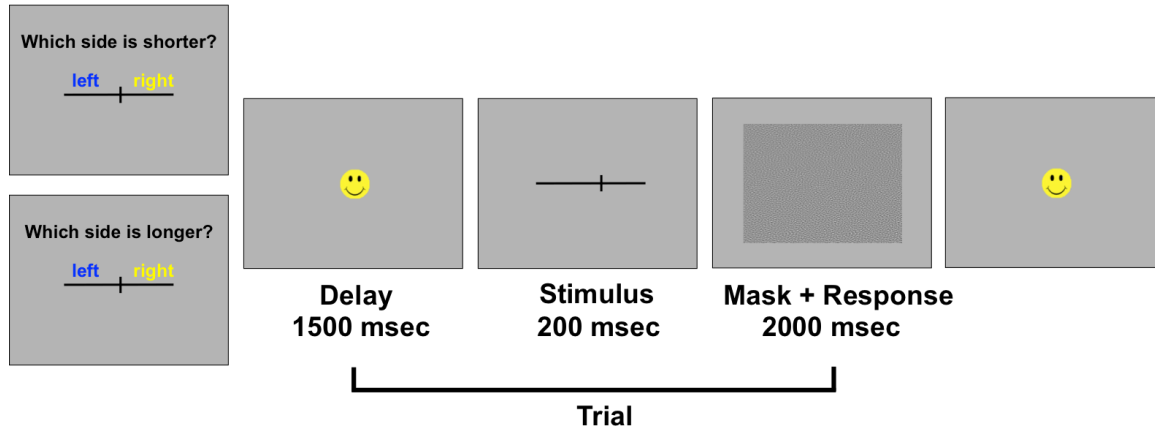


Figure 4.1. Experimental design. Each participant was prompted with an instruction screen at the beginning of each block. Each trial started with a delay during which a smiley face was shown to prepare the participant for the trial onset. A pre-bisected horizontal line was presented briefly, followed by a mask. Participants indicated their answer by button press. The location of the bisecting vertical line was varied following a staircase procedure.

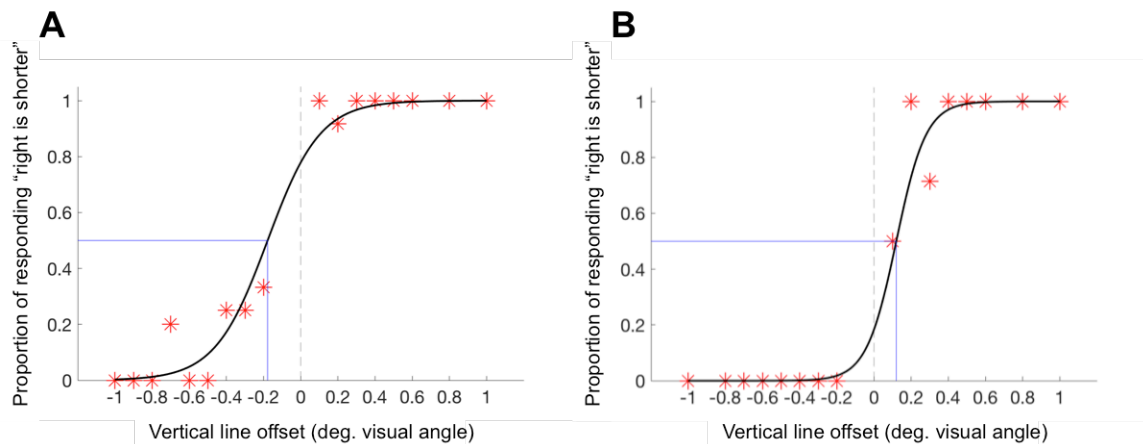


Figure 4.2. Examples of individual participants' psychometric curves. Vertical line offsets are indicated on the x-axis; zero is the veridical midpoint, negative values are offsets to the left, and positive values are offsets to the right. The proportion of responses for each vertical line offset was plotted on the y-axis. A psychometric curve (black solid curve) was estimated for each participant. The midpoint of the psychometric curve, at which $y = 0.5$, indicates the point where the participant judged the left and right segments to be of equal length (blue solid line). Each participant's spatial attention bias is estimated in degrees of visual angle based on the deviation of the point of subjective equality (i.e., the x-value of the curve's midpoint) from the veridical midpoint. Participant A shows a leftward bias and participant B has a rightward bias.

Estimating spatial bias

We estimated spatial attention bias in each participant by fitting a psychometric function and finding the point of subjective equality. Figure 4.2 illustrates this approach for two example participants. Trials from all four blocks were organized into bins based on the distance between the veridical midpoint and bisecting vertical line. In each participant, the proportion of the “the right side is shorter” response was calculated for each bin. The location of vertical lines was plotted on the x-axis (in degrees of visual angle) and the proportion of the participant’s “right is shorter” response was plotted on the y-axis. A psychometric curve was estimated from each participant’s data by using a general linear model with a logit link function [$\ln(\pi/(1-\pi)) = \beta \times X_i$]. We used MATLAB’s *glmfit* function, which received multiple inputs: the locations of the vertical line (x-value), the participant’s “the right side is shorter” responses (y-value), and the total number of trials for each data point (weight). The function used a weighted fit because the number of trials was different for each vertical line offset due to the staircase procedures. Thus, the function gave more weight to data points with more trials (i.e. more reliable data points) and less weight to data points with fewer trials (i.e. less reliable data points). The point of subjective equality refers to the midpoint of the psychometric curve where the y-value is 0.5 (indicated by the blue solid line). The participant’s leftward or rightward bias was determined based on the direction in which the x-value of the point of subjective equality deviated from the veridical midpoint, which is described as zero on the x-axis. The degree of the spatial attention bias was determined by the deviation from the veridical midpoint in degrees of visual angle, where a leftward spatial attention bias is described as a negative value (Figure 4.2A) and a rightward spatial attention bias a positive value (Figure 4.2B).

Analyses of spatial bias

In Part I, we used grade, instead of age, as our independent variable because grade is a better reflection of each child's educational background. We also report the results from age-based analyses at the end of the Results section.

We identified outliers from each grade and the adult population. Outliers were defined within each grade distribution as any data points that fell three standard deviations outside of the mean. A total of four participants were identified as outliers from the pediatric population (number of outliers for each grade indicated in Table 4.2) and one participant was identified as an outlier from the adult population. Outliers were removed from subsequent analyses.

We performed additional bootstrap hypothesis tests to compare the distributions of spatial attention biases and control for different sample sizes (e.g., when divided by handedness and gender). We performed bootstrap tests using the following procedures (Efron & Tibshirani, 1993). First, we calculated t-statistics comparing the original distributions. Then, we removed the mean difference between the two groups and generated 10,000 bootstrap samples from each group. We obtained a null distribution of t-statistics from the bootstrap samples. We then calculated the p-value based on where the t-statistic obtained from the original samples is located in the null distribution.

To model the relationship between a participant's grade and his or her behavioral spatial attention bias measure in the pediatric population, a linear regression model was applied to the data. Spatial bias was the dependent variable and grades the independent variable. The independent variable was log transformed to model a gradual shift in spatial attention bias towards an asymptote of zero, or the veridical equality point. This was based on previous findings suggesting that adults have a spatial attention bias that is normally distributed around

zero (Szczepanski & Kastner, 2013; Bio, Webb, & Graziano, 2018). T-test results of each grade coefficient for comparison with 0 were analyzed using the same fitted linear regression model to avoid multiple comparisons. Residuals from the model were examined to ensure that deviations between the actual data and model estimates were consistent. In addition, we performed another linear regression analysis, which included control variables describing the location where the data was acquired, stimulus duration, handedness, and gender, in addition to the same dependent and independent variables. This was done to control for possible variability induced by the variables.

In addition, we identified additional outliers based on the precision of line bisection judgments to ensure that less precise judgments did not affect the results. As a measure of the precision of line bisection judgments, we estimated the width of each participant's psychometric curve, which was measured by the difference between the vertical line offsets corresponding to the y-values of 0.25 and 0.5 (Supplementary Figure 4.1). A control analysis was conducted after excluding additional outliers with curve widths exceeding three standard deviations from the mean.

Finally, we further examined the developmental trajectory using age as the independent variable. Participants of ages 6 to 13 were included in the analyses based on age while participants age 5 (1 child) and age 14 (5 children) were excluded due to the small sample sizes. Outliers were defined within each age group as spatial bias measures that fell three standard deviations outside of the mean.

Results

The current study aimed to examine spatial attention bias in children from grades 1-8 (Table 4.1). A perceptual version of a line bisection task was used. In this task, participants viewed bisected horizontal lines and indicated whether the bisected lines were shorter (or longer) to the left or right of a bisecting vertical line (Figure 4.1). The location of the bisecting vertical line was manipulated by using a staircase procedure such that a psychometric curve could be obtained from each participant's responses by fitting a logistic function with a range of 0 to 1. The participant's leftward or rightward bias was determined based on the direction in which the x-value of the point of subjective equality ($y = 0.5$) deviated from the veridical midpoint ($x = 0$). The deviation from the veridical midpoint in degrees of visual angle indicated the degree of spatial attention bias. Negative values of spatial bias indicate leftward bias (Figure 4.2A), positive values indicate rightward bias (Figure 4.2B), and zero, no spatial bias.

Distribution of spatial attention bias in school children and adults

As a first step, we examined the overall distribution of spatial attention biases in school children in grades 1 to 8 and in the adult control group (college freshmen), excluding four outliers from the pediatric group and one outlier from the adult group (see Table 4.1 for demographics). One-sample t-tests against zero revealed that the children's spatial attention bias was skewed to the left of the veridical midpoint ($M = -0.13^\circ$, $SD = 0.29^\circ$; $t(331) = -8.28$, $p < 0.0001$). Adults also showed a leftward attention bias, albeit milder ($M = -0.087^\circ$, $SD = 0.19^\circ$; $t(59) = -3.48$, $p < 0.001$). Adults' average leftward bias was numerically closer to zero than children's, although the distributions of spatial biases did not significantly differ between children and adults [$F(1, 390) = 1.29$, $p = 0.26$].

In order to investigate whether our measures of spatial attention biases were affected by handedness, we examined the distributions of spatial biases separately for right- and left-handed participants (Figure 4.3A and 4.3B). Among children, the spatial biases in right-handed participants ($n = 299$, $M = -0.13^\circ$, $SD = 0.3^\circ$) did not differ from left-handed participants ($n = 32$, $M = -0.15^\circ$, $SD = 0.18^\circ$) [$F(2, 329) = 0.11$, $p = 0.9$]. One ambidextrous child was not included in this analysis. Likewise, right-handed adult participants ($n = 45$, $M = -0.092^\circ$, $SD = 0.19^\circ$) showed a similar distribution of spatial biases as compared to left-handed participants ($n = 15$, $M = -0.072^\circ$, $SD = 0.21^\circ$) [$F(1, 58) = 0.11$, $p = 0.75$].

The distributions of spatial biases were also examined separately by gender (Figure 4.3C and 4.3D). Among children, the spatial biases in male participants ($n = 165$, $M = -0.11^\circ$, $SD = 0.35^\circ$) did not differ from female participants ($n = 167$, $M = -0.15^\circ$, $SD = 0.22^\circ$) [$F(1, 330) = 1.13$, $p = 0.28$]. Likewise, male adult participants ($n = 19$, $M = -0.098^\circ$, $SD = 0.19^\circ$) showed a similar distribution of spatial biases as compared to female participants ($n = 41$, $M = -0.082^\circ$, $SD = 0.2^\circ$) [$F(1, 58) = 0.084$, $p = 0.77$].

A series of bootstrap analyses confirmed that there were no significant differences in spatial bias between children and adults ($p = 0.15$), or by handedness amongst children ($p = 0.50$), handedness amongst adults ($p = 0.76$), gender amongst children ($p = 0.33$), and gender amongst adults ($p = 0.80$).

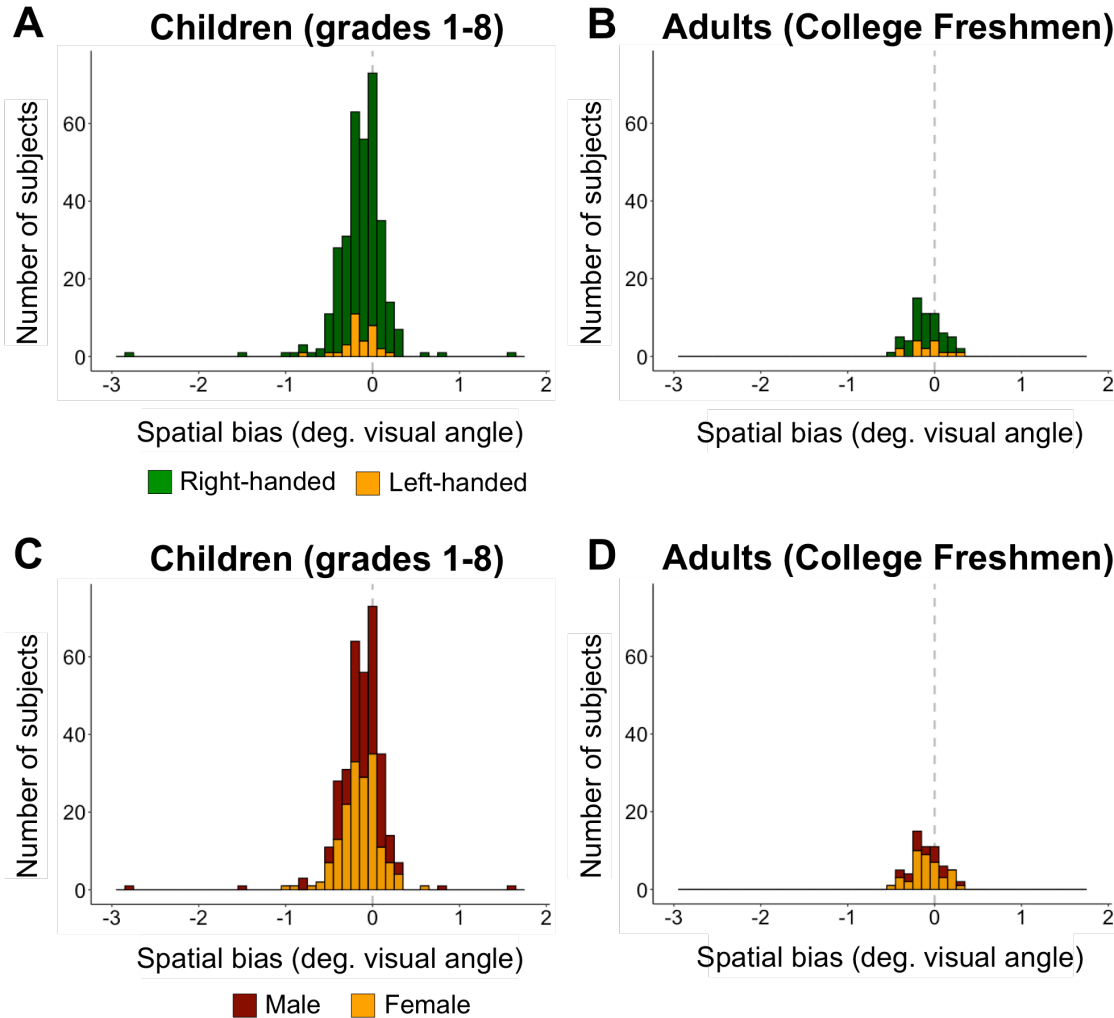


Figure 4.3. Spatial attention bias does not depend on handedness or gender. The distribution of spatial attention bias in participants across grades 1 through 8 (panels A and C) and adults (panels B and D) showed a leftward bias. Panels A and B show that such leftward attention bias was not related to participants' handedness. The distribution of attention biases in left-handed (colored in orange) and right-handed participants (colored in green) was similar. Panels C and D show that leftward attention bias was not related to participants' gender. The distribution of attention biases in male (colored in red) and females (colored in orange) was similar.

Developmental trajectory of spatial bias in school children

Next, we examined whether spatial biases changed, or remained relatively stable, as a function of grade by comparing spatial biases in younger children (grades 1 to 3; $n = 122$), older children (grades 6 to 8; $n = 147$), and adults (college freshmen; $n = 60$) (Figure 4.4). We found

that leftward biases were most expressed in younger children ($M = -0.2^\circ$), whereas the leftward spatial biases of older children were less expressed ($M = -0.098^\circ$) and not different from those observed in adults ($M = -0.087^\circ$). An ANOVA confirmed a main effect of Grade (grades 1-3 vs. grades 6-8 vs. adults), $F(2, 326) = 5.6, p = 0.004$. Tukey's HSD test revealed that the mean spatial biases differed between grades 1-3 and grades 6-8 (adjusted $p = 0.007$) and between grades 1-3 and adults (adjusted $p = 0.026$), but there was no difference in spatial bias between grades 6-8 and adults (adjusted $p = 0.97$). Thus, younger children (grades 1-3) showed greater leftward biases than older children (grades 6-8) and adults, while spatial biases of older children were similar to those of adults. Age-based analyses yielded similar results. There was a main effect of Age (ages 6-8 vs. ages 11-13 vs. adults, $F(2, 310) = 5.0, p = 0.007$). And younger children (ages 6-8) showed greater leftward biases compared to older children (ages 11-13; adjusted $p = 0.01$) and adults (adjusted $p = 0.04$).

Given that younger children showed a prominent leftward bias that was decreased in older children and adults, we hypothesized that the leftward bias in grades 1 to 3 gradually decreased towards a normal distribution around 0, typically observed in adults (Sczcepanski & Kastner, 2013) and indicative of a more balanced spatial attention system. In addition, since the older children's spatial bias was similar to that of the adults, it is possible that spatial bias reaches adult-level before grade 8. In order to test for a grade-related change in spatial bias, we used a linear regression model with a log-transformed independent variable (i.e., grade) that takes into account a possible asymptote in the grade-related trend.

As shown in Figure 4.5, the linear regression model demonstrated that the log-transformed independent variable grade had a significant relationship with the dependent variable spatial bias ($F = 17.88, p < 0.0001$, multiple $R^2 = 0.05$, adjusted $R^2 = 0.05$). That is,

there was a more prominent leftward bias in children in grades 1 to 3 in comparison to children in older grades, and the estimate of the spatial bias approached zero as children get older. Additionally, we obtained a model estimate for each grade and determined how the estimated spatial bias was different from zero (Table 4.2). These results from the regression model were consistent with our previous observations from the comparison among younger children, older children, and adults.

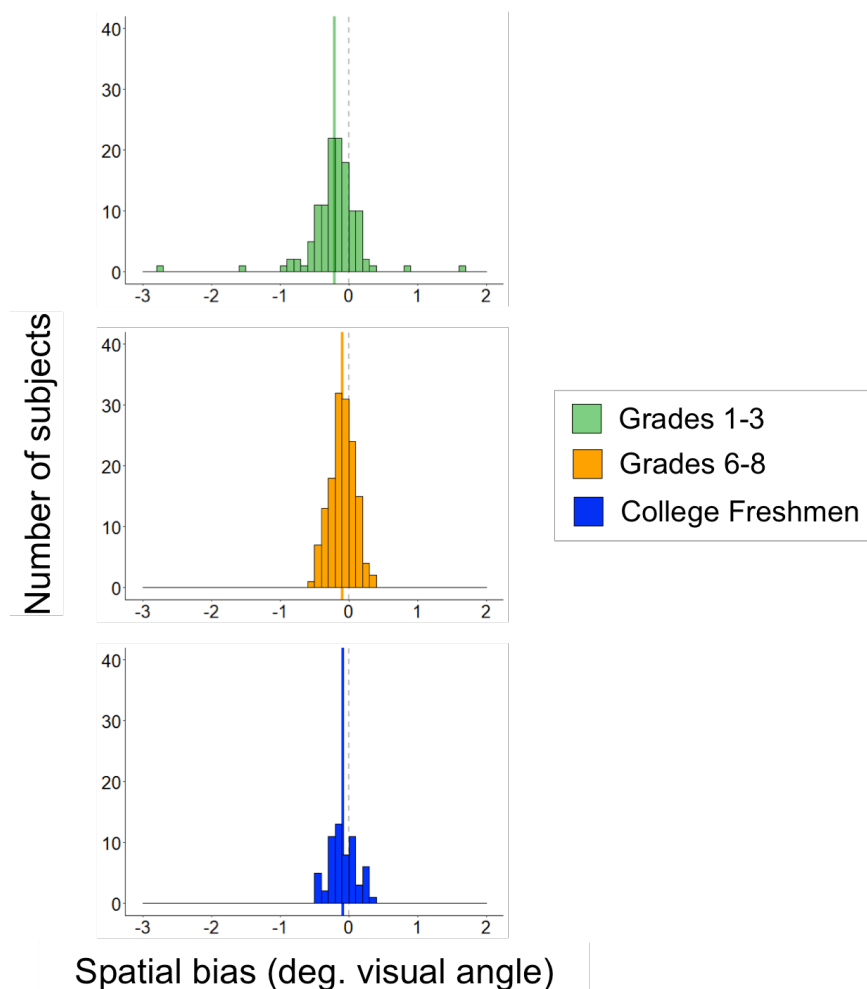


Figure 4.4. Children in early elementary school grades show an expressed leftward bias. The distributions of grades 1-3 (top panel; green), grades 6-8 (middle panel; orange), and college students (bottom panel; blue) are plotted. The veridical midpoint is found at zero, the location of the grey dotted line. The mean is the vertical line in each grade group's respective color. Grades

1-3 showed an expressed leftward bias (mean= -0.2). Grades 6-8 (mean= -0.098) show a distribution similar to that of college freshmen (mean= -0.087).

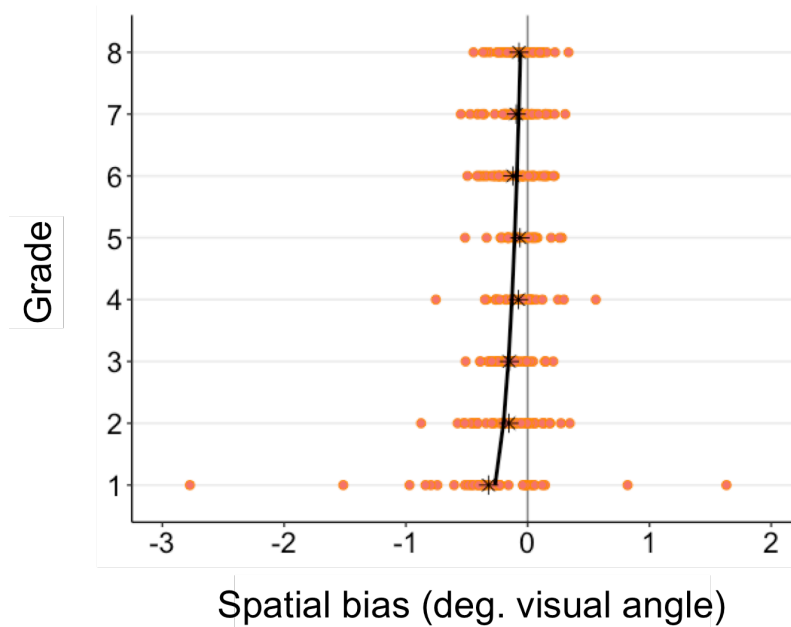


Figure 4.5. Early elementary grades show an expressed leftward spatial attention bias that gradually diminishes with advancing grade. Individual spatial biases were plotted by grade for Experiment 1. Negative values on the x axis indicate leftward attention bias, positive values rightward bias, and zero no bias. Similar to previous findings in adult populations (Szczepanski & Kastner, 2013; Bio et al., 2018), individual participants' spatial biases were widely distributed in each grade level. A linear regression model with a log-transformed independent variable demonstrated that early elementary school grades show an expressed leftward spatial attention bias, which gradually becomes more normally distributed around zero in higher grades. A solid black line represents the model fit. Black asterisks indicate an average spatial bias for each grade.

Table 4.2. Number of participants per grade and distribution of their spatial biases

Grade	Total number of subjects	Number of outliers	Distribution		t-statistics (Different from zero?)	Model estimate
			M	SD		
1	38	1	-0.32	0.65	$t(330) = -7.5$ $p < .0001$ ***	-0.27
2	44	1	-0.15	0.25	$t(330) = -8.9$ $p < .0001$ ***	-0.2
3	42	0	-0.15	0.15	$t(330) = -9.5$ $p < .0001$ ***	-0.16
4	30	0	-0.075	0.23	$t(330) = -8.4$ $p < .0001$ ***	-0.13
5	34	1	-0.063	0.16	$t(330) = -6.5$ $p < .0001$ ***	-0.11
6	56	0	-0.12	0.18	$t(330) = -4.8$ $p < .0001$ ***	-0.088
7	53	1	-0.093	0.18	$t(330) = -3.5$ $p < .001$ **	-0.073
8	39	0	-0.07	0.17	$t(330) = -2.6$ $p < .01$ *	-0.06
Total	336	4				

*** $p < 0.0001$; ** $p < 0.001$; * $p < 0.01$

One may ask whether the large variance among younger children may have driven the significance of the regression model by introducing greater leftward bias measures in younger grades relative to older grades. To address this issue, we probed whether the residuals (deviations between actual data points and estimated values) were particularly larger for younger grades that presented an overall greater leftward bias. We found that residuals from the regression model

were not particularly greater for younger grades than older grades, except for five outliers (Supplementary Figure 4.2). We confirmed that the developmental trajectory of spatial biases across grades remained the same, even when the outliers were excluded from the regression model such that residuals were consistent across different bias measures ($F = 34.73$, $p < 0.0001$, multiple $R^2 = 0.1$, adjusted $R^2 = 0.1$). The consistency in the residuals across model-estimated bias values for all grades indicates that the larger variance among younger children does not drive model estimates to be greater leftward biases.

Control analyses

The children's data were collected in two different locations outside the laboratory, a summer camp and a school. We checked whether the experiment venues affected data distributions by comparing spatial bias measures in children of grades 2, 3, and 7, because the number of participants from each location was comparable for those grades [grade 2: 23 (summer camp) vs. 20 (school); grade 3: 22 (summer camp) vs. 20 (school); grade 7: 27 (summer camp) vs. 25 (school)]. We found that the distributions of the data did not differ depending on whether they were acquired in the camp or the school (Mann-Whitney-Wilcoxon Test; $W = 2063$, $p = 0.23$).

As mentioned in the Methods section, the stimulus presentation time was adjusted to be longer (225-700 ms) for a total of 40 children in grade 1 ($n = 9$), grade 2 ($n = 18$), grade 3 ($n = 5$), grade 4 ($n = 3$), grade 5 ($n = 2$), and grade 6 ($n = 3$). These children were not able to perform the task with our standard presentation time of 200 ms. There was no significant correlation between the stimulus presentation time and estimated spatial bias across all participants (Pearson's $r = -0.09$, $p = 0.1$).

In order to verify that handedness, gender, location of data acquisition, and stimulus duration did not significantly predict spatial bias, those measures were added to a linear model with grade as a log-transformed independent variable and spatial bias as the dependent variable ($F = 3.2, p < 0.001$, multiple $R^2 = 0.06$, adjusted $R^2 = 0.04$). Only grade significantly predicted spatial bias ($p < 0.001$). Handedness, gender, location of data acquisition, and stimulus duration did not significantly predict spatial bias. Thus, grade was the only variable that significantly predicted spatial bias.

Lastly, we examined the linear regression model with an additional exclusion of outliers based on curve width in order to ensure that differences in the precision of line bisection judgments across different grade levels did not drive the results. We identified 2 additional outliers from the pediatric group based on the curve width estimations (> 3 SDs), which served as a measure of the precision of line bisection judgments. No additional outliers were identified from the adult group. Even after excluding these additional outliers, the results from the linear regression model with grade as a log-transformed independent variable and spatial bias as the dependent variable remained consistent ($F = 24.6, p < 0.0001$, multiple $R^2 = 0.07$, adjusted $R^2 = 0.07$).

Age-based analyses

In Part I, participants were recruited based on their grades because the initial goal of the study was to measure the developmental change in spatial biases based on children's educational experience, which was reflected better in grades than in ages. To ensure that we find a consistent developmental trend as a function of age, we conducted a linear regression analysis with log-transformed age as the independent variable (instead of grade). As shown in Figure 4.6, we

indeed found a developmental trajectory of spatial biases that is consistent with the analyses based on the grade ($F = 14.7$, $p < 0.001$, multiple $R^2 = 0.04$, adjusted $R^2 = 0.04$). The subsequent analyses in Part II were thus conducted based on age.

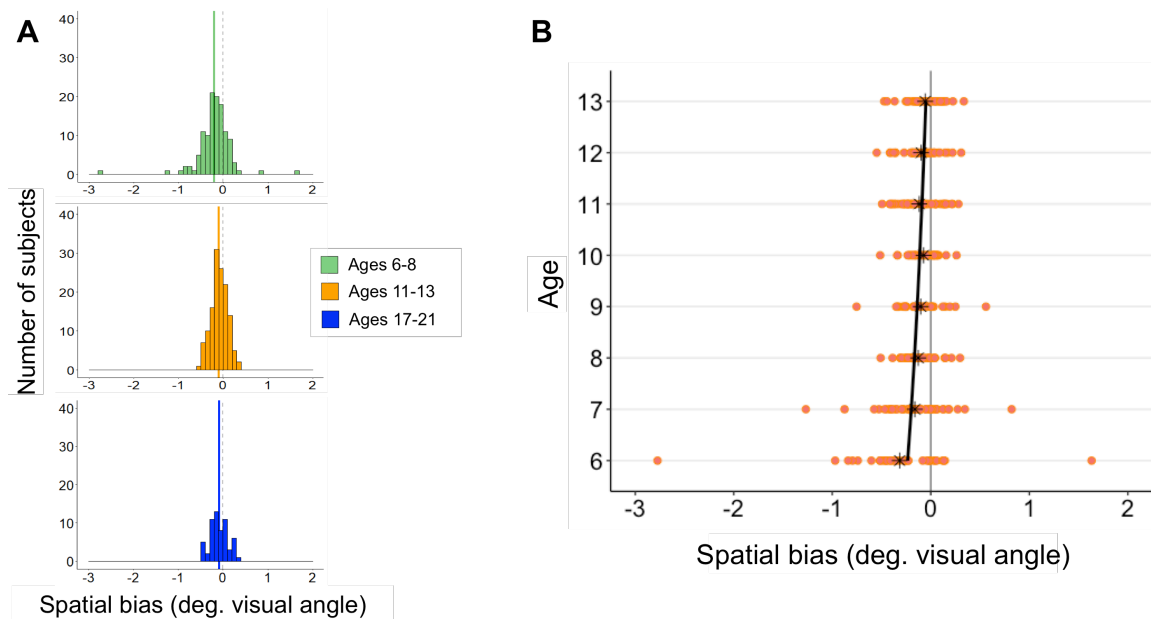


Figure 4.6. Spatial bias analyses based on age. Younger children ages 6-8 (top panel A; green) showed an expressed leftward bias (mean = -0.2°) in comparison to children ages 11-13 (middle panel A; orange; mean = -0.09°) and college students ages 17-21 (bottom panel A; blue; mean = -0.087°). A linear regression model with a log-transformed independent variable demonstrated that younger children show an expressed leftward spatial attention bias, which gradually becomes more normally distributed around zero, as they get older (panel B). A solid black line represents the model fit. Black asterisks indicate an average spatial bias for each age group. The analysis by age yielded similar results as compared to those based on grade.

Interim Summary

In Part I, we examined the development of spatial attention biases in school children by using a perceptual, computerized line bisection task. We found that children in early elementary grades showed a greater leftward bias that gradually diminished with advancing grade level. In contrast, the distribution of spatial biases among children in middle school was not different from that of adults. These spatial biases in children were independent of gender or handedness.

Our findings on behavioral spatial biases have implications for the development of the underlying neural mechanisms. In adults, neural attentional weights in the dorsal fronto-parietal network predict the behavioral spatial attention bias of an individual, as measured in the line bisection task (Szczepanski & Kastner, 2013). For example, if an individual has a leftward spatial bias, there are greater attentional weights produced by the right hemisphere, which controls spatial attention control in the left hemifield, than by the left hemisphere, which controls spatial attention in the right hemifield. Based on previous studies conducted in adults, we hypothesize that the right hemisphere produces greater attentional weights than the left hemisphere in younger children, thereby exerting greater control over the left than the right hemifield and resulting in greater leftward bias. As children get older, the attention network may achieve a better equilibrium such that the attentional weights produced by the two hemispheres become more similar and thereby control visual space in a more balanced fashion. In Part II, we will further investigate the link between spatial bias and the functional properties of the dorsal fronto-parietal network in children.

Part II: Linking spatial bias to the fronto-parietal attention network in the developing brain

In Part I, we found that children in early elementary grades (ages 6 to 8) exhibit a preference in directing attention to the left visual field over the right field. In the healthy adult brain, such bias in line bisection judgments has been associated with functional and anatomical differences between the two hemispheres within the dorsal fronto-parietal network (de Schotten et al., 2011; Szczepanski & Kastner, 2013). Based on these findings from adults, we hypothesized that the leftward bias in children might reflect a hemispheric asymmetry within the developing attention network, which exists in early elementary school ages and diminishes by middle school ages.

Here, we investigated how individual children's attention biases could be related to, or predicted by, the functional connectivity within the dorsal fronto-parietal network. We probed the brain-behavior relationship by using the Connectome-based Predictive Modeling method (CPM; Shen et al., 2017). This method has been shown to establish brain-behavior associations by building a linear model that predicts behavior based on functional connectivity patterns across the whole brain. Such whole-brain predictive models reliably predicted a variety of measures, such as sustained attention/ADHD symptoms (Rosenberg, Finn, Scheinost, Constable, & Chun, 2017), fluid intelligence (Finn et al., 2015), and reading comprehension (Jangraw et al., 2018). To test our hypothesis about the specific relationship between spatial bias and fronto-parietal attention network, we took an approach that is similar to the seed-based CPM developed by Goldfarb and colleagues (Goldfarb, Rosenberg, Seo, Constable, & Sinha, 2020). Instead of building a predictive model from the whole brain, we included a specific set of brain areas in the

frontal and parietal cortices, which have been mainly associated with attention control, including the frontal eye fields (FEF), intraparietal sulcus (IPS), and superior parietal lobule (SPL). Furthermore, we used a different set of nodes that are associated with large-scale brain networks, based on the 7-network definition made by Yeo and colleagues (2011), in order to examine whether the behavioral prediction is found at the level of a broader network and whether the prediction is specific to the dorsal fronto-parietal network.

Methods

Participants

A total of 58 children between ages 6 and 12 years were recruited to participate in the study, which was approved by the Institutional Review Board of Princeton University. All participants had normal or corrected-to-normal vision and no history of neurological or psychiatric illnesses. Informed consent was obtained from parents or guardians and informed assent from children. There were two criteria for data exclusion: the quality of fMRI data regarding head motion (see fMRI data preprocessing for detail) and the quality of spatial bias measures (see Spatial bias exclusion criteria). A total of 21 children were excluded: 3 did not complete the line bisection task, 10 had excessive head motion, and 8 for unreliable estimations of spatial bias.

The final sample consisted of 37 participants (19 female, mean age 9.7 ± 1.8 years, range 6.05-12.7 years, 4 left-handed, 1 no handedness information). All children were attending English-speaking institutions at the time of their participation. English was the first language to all participants except two children whose native language was French. Based on parents' reports, 3 children had a diagnosis of reading disorder, 4 children had a diagnosis of ADHD, and

one child had both diagnoses, all of which were made by clinicians or schools. We did not exclude or group children based on their diagnostic labels because, as in Part I, the goal of the study was to examine the general population of children with a similar proportion of each diagnosis (roughly 10 percent). We obtained measures of children's reading and inattention/hyperactivity behavior via behavioral tests or parent questionnaires, as described below.

Data Acquisition: Procedure

Study participation involved two visits on two separate days. On the first visit, children completed a mock scanner session (Psychology Software Tools' MRI Simulator). In addition to the mock scanner session, we administered a battery of behavioral tests, including (1) the Rapid Automatized Naming Test (RAN; Wolf & Denckla, 2005), (2) the Test of Word Reading Efficiency, second edition (TOWRE-2; Torgesen, Wagner, & Rashotte, 2012), and (3) the Kaufman Brief Intelligence Test, second edition (KBIT-2; Kaufman & Kaufman, 2004). RAN and TOWRE-2 both measured skills critical for reading, such as the efficiency in naming aloud familiar stimuli aligned in rows (RAN) and the efficiency in reading aloud words and pseudo-words (TOWRE-2). KBIT-2 provided verbal, nonverbal, and composite IQ scores. Finally, the parents were asked to fill out a questionnaire that included the Vanderbilt ADHD Parent Rating Scale (VAPRS; Wolraich et al., 2003).

During the second visit, children completed both the MRI session and the line bisection task. The second visit was typically scheduled 1-2 days after the first visit or within two weeks in case of scheduling conflicts. Two participants were exceptions; their spatial biases were measured 11-13 months later than the scan. We decided to include these two participants in our

analyses because these data points would be still meaningful for probing individual variability in behavior. Based on our large-scale behavioral study (Part I), we observed that the age-related change in spatial biases was greatest below age 8. Because the ages of the two participants were 8.9 and 9.4 years on the day of the MRI scan (group mean age 9.7 ± 1.8 years), differences across individuals would be greater than intra-individual differences that occurred in 11-13 months between the scan and the estimation of spatial biases.

Behavioral data acquisition: line bisection task

The procedures for administering the line bisection task and estimating a spatial bias in each participant were described in detail in Part I.

Spatial bias exclusion criteria

To ensure the reliability of the spatial bias measure, we compared three measures: the curve width (see Part I, Supplementary Figure 4.1) and R^2 value of the estimated psychometric curve, and the absolute difference of the spatial bias estimations between the two halves of each participant's data (i.e., first half versus second half). The curve width and R^2 were both precision measures of psychometric curve fitting, and the absolute difference obtained from split data was a reliability measure for bias estimations. We decided exclusion criteria by comparing these three quality measures of the participants in Part I (Supplementary Figure 4.3A). We found that both curve width measures and the absolute differences substantially diverged below the R^2 of 0.5. Thus, we excluded any participants whose R^2 value of the psychometric curve was below 0.5. Six participants were excluded based on this criterion. Similarly to Part I, we excluded 2 additional participants for their bias measures exceeding three standard deviations from the

group mean. Using these two criteria, a total of 8 participants were excluded (Supplementary Figure 4.3B).

MRI data acquisition

Data were collected for the whole brain on a Siemens 3T MAGNETOM Prisma using a 64-channel head/neck coil. Functional and diffusion data were collected using multi-band accelerated echo planar imaging (EPI) sequences (release R012c) provided by a C2P agreement with University of Minnesota (Auerbach et al., 2013; Cauley et al., 2014; Moeller et al., 2010; Setsompop et al., 2012; Sotiropoulos et al., 2013; Xu et al., 2013).

For the structural MRI scan, a whole-brain T1-weighted volume was collected (3D magnetized prepared rapid gradient echo (MPRAGE) sequence; 192 sagittal slices; 1.0 mm³ resolution; FOV = 192 mm; FOV phase = 93.8%; base resolution = 192; slice oversampling = 25%; TR/TE = 2400/2.08 ms; inversion time (TI) = 1000 ms; flip angle = 8°; fat suppression = water excitation fast; PE direction = anterior/posterior; IPAT mode = GRAPPA; acceleration factor = 2; bandwidth = 220 Hz/Px; ES = 7.5 ms; TA = 5m 11s).

For functional MRI scans, two runs of 420 measurements each were collected during resting state (72 interleaved transverse slices; in-plane resolution = 2.0 mm; slice thickness = 2.0 mm with no inter-slice gap; FOV = 208 mm; base resolution = 104; TR = 800 ms; TE = 37 ms; FA = 52°; fat suppression: enabled; bandwidth = 2290 Hz/Px; ES = 0.58 ms; multiband acceleration factor = 8; sum of squares image reconstruction; excite pulse = 6600 us; TA = 5m 46s). To retrieve signal in spatially compressed regions due to susceptibility-induced distortions, each run was collected in the opposing phase encode directions (anterior/posterior and posterior/anterior), and three spin echo volume pairs were acquired with matching slice

prescription, FOV, base resolution, fat suppression, bandwidth, ES, and image reconstruction (TR/TE = 8000/66.60 ms; FA/RFA = 90/180°; real/fake multiband acceleration factor = 1/8; TA = 32 s) (Andersson et al., 2003).

fMRI data preprocessing

Functional MRI data were preprocessed by using a customized script based on AFNI's `afni_proc.py` (Cox, 1996). The first three volumes from each run were discarded. Data were first examined for signal outliers (3dToutcount), and a volume with the minimum outlier proportion was selected as a base volume for subsequent motion correction and registration. We removed signal deviation > 2.5 SDs from the mean (3dDespike) and corrected for slice timing (3dTshift). To correct for distortions, we used AFNI's blip-up/down non-linear warp procedure (3dQwarp). Because the two runs were collected in the opposing phase encode directions (anterior/posterior and posterior/anterior), the median of 10 volumes from each run was obtained as a reference for each direction. Data were then warped into the midpoint between the two reference images. All volumes in each run were aligned to the base volume, the native anatomical image, and then to the MNI152 standard space using 3dvolreg.

To remove additional noise variables, data were further processed with a nuisance regression model including: white matter, cerebrospinal fluid, global mean signal time courses, and 24 motion parameters (i.e., frame-wise displacement measures from 6 angles, their temporal derivatives, quadratic terms, and 6 quadratic expansions of the derivatives of motion estimates) (Friston, Williams, Howard, Frackowiak, & Turner, 1996). Volumes that were identified as motion artifacts (framewise displacement in an Euclidean norm > 0.2 mm) or signal outliers (more than 10% of the voxels were detected as outliers by 3dToutcount) were censored and

replaced with zero such that the affected volumes did not influence correlation results (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Power et al., 2014). These preprocessing steps have been demonstrated to reduce motion-induced artifacts while reducing the loss in temporal degrees of freedom (Ciric et al., 2017; Parkes, Fulcher, Yücel, & Fornito, 2018).

While this denoising pipeline has been suggested to reduce motion-related artifacts, participants with too many censored volumes will have a great loss in temporal degrees of freedom, which leads to spurious connectivity measures (Ciric et al., 2017; Parkes et al., 2018). Thus, we excluded participants who had less than 70% of the fMRI data (7.8 minutes of data) available after censoring (Supplementary Figure 4.3C). A total of 10 children were excluded based on these criteria.

Definition of regions-of-interest (ROIs)

Regions of interest (ROIs) were defined using two different atlases (Figure 4.7). To investigate the link between spatial bias and functional connectivity among visual topographic areas in the frontal and parietal cortices, we used a probabilistic atlas that was developed from topographic mapping sessions in a large cohort of adults (Wang et al., 2015). We included 8 areas (FEF in the frontal cortex and IPS0-5 and SPL1 in the parietal cortex) in each hemisphere, which made a total of 16 regions. The volume-based full probability map for each area was obtained in the MNI152 standard space. We adjusted the threshold for each area's probabilistic map such that all of the ROIs are of similar sizes. The thresholds ranged from 15% to 40% (probability of a voxel being included in each topographic area across individual participants; Supplementary Table 4.1).

For network-level analyses, we used the 400 parcellation scheme of the whole brain (Schaefer et al., 2018). This scheme divides the cortical volume into 400 nodes in a data-driven way based on both local transitions and global similarity in functional connectivity patterns. Parcellation schemes with different numbers of nodes (100 to 1000) were available. We chose the 400-node parcellation because other whole-brain parcellation schemes generated from data-driven algorithms have also yielded between 300 and 400 areas in the human cortex (Craddock, James, Holtzheimer, Hu, & Mayberg, 2012; Shen, Tokoglu, Papademetris, & Constable, 2013; Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012). The volume-based parcellation was obtained in the MNI152 standard space. We used the provided 7-network labels to identify the nodes corresponding to each of the networks (Yeo et al., 2011).

Figure 4.7 illustrates the overlay of the probabilistic atlas-defined topographic areas (filled) and the 400-node parcellation color-coded by the 7-network labels (outlined). For the network-level predictive modeling analyses, a separate map of the corresponding nodes was generated for each of the following networks: Dorsal Attention, Ventral Attention, Control, and Default Networks. Among those networks, the Dorsal Attention Network (green) showed the greatest overlap with the topographic fronto-parietal areas although the boundaries of individual areas did not match with the probabilistic atlas-defined areas.

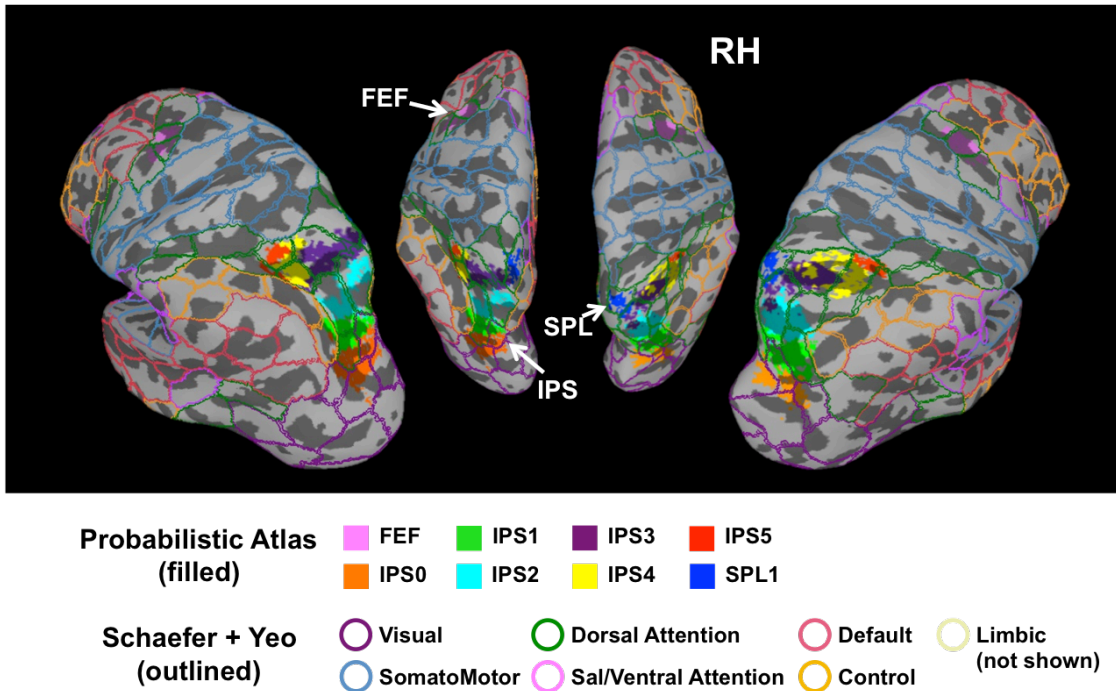


Figure 4.7. Two sets of regions-of-interest (ROIs) used for predictive modeling. Visual topographic areas in frontal and parietal cortices were defined by using a probabilistic atlas (filled; Wang et al., 2015). We also used a whole-brain parcellation scheme developed by Schaefer and colleagues (2018). The 400 nodes of the parcellation were outlined in different colors based on the 7 network definitions established by Yeo and colleagues (2011). Both atlases are displayed on an inflated surface reconstruction of the MNI152 standard brain. RH: right hemisphere, FEF: frontal eye fields, IPS: intraparietal sulcus, SPL: superior parietal lobule.

Building a predictive model

We used a modified version of publicly available connectome-based predictive modeling (CPM) code ([https://github.com/ YaleMRRC/CPM](https://github.com/YaleMRRC/CPM)) for the following procedures. Pairwise Pearson correlations were computed from all possible pairs from the set of ROIs using AFNI's 3dNetCorr. The predictor data were Fisher-transformed correlation matrices from individual participants in a given ROI map. The outcome data were behavioral spatial biases from individual participants. ROI pairs, or edges (i.e., model features), were selected if they showed above-threshold Spearman correlations with behavior. Edges showing positive correlations with

behavior were selected as positive features (“positive network”), and those showing negative correlations were selected as negative features (“negative network”). To determine a p threshold for feature selection, we generated predictive models using five different p thresholds (0.01, 0.02, 0.03, 0.04, 0.05) and selected a threshold that gave the best prediction performance. The variability of the model performance at each threshold is included in Supplementary Figure 4.4.

The prediction performance was initially built and validated by the leave-one-subject-out (LOO) cross validation procedure. For every LOO loop, model features were selected from $N-1$ participants. The selected edges’ Spearman correlation coefficients with behavior were summed into network strengths, separately for the positive network (“positive network strength”) and for the negative network (“negative network strength”) in each participant. A general linear model was fit to positive and negative network strengths from the $N-1$ participants. This model was applied to predict the behavioral measure of the left-out participant based on the participant’s network strength values. After all LOO iterations, a Spearman’s rho (r_s) was obtained between the predicted and observed behavioral measures of all participants.

To obtain a p value of the prediction performance, we repeated the LOO procedure with shuffled behavioral measures for 1,000 iterations. A null distribution of Spearman’s rhos (i.e., predicted vs. observed behavior) from 1,000 iterations served as a reference to calculate a p value of the true prediction r_s . If no edges were selected at this threshold (as when behavior was randomly shuffled for permutation analyses), we selected the 10 edges with the highest Spearman rhos (for positive edges) and 10 edges with lowest Spearman rhos (for negative edges) and submitted to the subsequent validation steps.

Additional analyses for model validation and feature selection

To account for potential biases in LOO cross validation (Poldrack, 2012), we further evaluated predictive power of the model by using 6-fold cross validation. On each fold, the model was trained (on $N = 31$ participants) and tested on the left-out subset ($N = 6$). This process was repeated 1,000 iterations with participants randomly assigned into folds. We obtained the average Spearman's rho value across all iterations as a measure of predictive power, and computed effect size (Cohen's d) by comparing the distribution of Spearman's rho values from models predicting true spatial bias measures to a null distribution (1,000 iterations of models predicting randomly shuffled spatial bias measures) as in recent studies (Goldfarb et al., 2020; Rudolph et al., 2018).

Model features (i.e. edges whose connectivity strengths were correlated with spatial bias) in each of 6,000 predictive models (6-fold for 1,000 iterations) were examined to assess how consistently each edge was selected based on the proportion of the edge's inclusion among the 6,000 predictive models. If a feature were selected randomly or by noise, we would not expect to see the feature selected in a high proportion of models generated during the iterative processes of model training.

Comparison of predictive models

Models were trained to predict the spatial bias in each participant from functional connectivity defined using 5 separate sets of nodes: one map for the 16 topographic areas in the frontal and parietal cortices, and the other four network-level maps (i.e., Dorsal Attention, Ventral Attention, Control, and Default) based on the 400-node parcellation. In other words, 5 models were trained and tested using the LOO and 6-fold cross validation procedures described

above. Because our main hypothesis was specific to the link between spatial bias and the dorsal fronto-parietal network, the main results are those two predictive models based on the 16 fronto-parietal areas and on the nodes associated with the Dorsal Attention Network, which were not independent from each other. Models from the other three networks were included as comparison analyses. Thus, instead of assessing p values adjusted for multiple comparisons, we checked the consistency of features selected during model training (as described in the previous paragraph) as an indicator of robustness and reliability of each predictive model.

Results

In Part II, we investigated the link between spatial bias and the dorsal fronto-parietal network in children, in order to understand the neural correlates of leftward biases observed in school children. By applying the connectome-based predictive modeling (CPM) method, we built a model that predicts each child's spatial bias based on the child's functional connectivity patterns across the dorsal fronto-parietal network. We first used a set of visual topographic areas in the frontal and parietal cortices defined by a probabilistic atlas (Wang et al., 2015) and then used a whole-brain parcellation scheme (Schaefer et al., 2018) to include additional areas that are often included in the same network (Dorsal Attention Network; Yeo et al., 2011). In order to assess whether spatial biases were specifically and exclusively related to fronto-parietal areas, we additionally examined predictive models built from several different large-scale brain networks.

Behavioral data analysis

We found an overall leftward distribution of spatial attention biases in children ($M = -0.13^\circ$, $SD = 0.18^\circ$; $t(36) = -4.24$, $p < 0.001$) as shown in Figure 4.8. The leftward biases in children replicates the observation from a larger cohort reported in Part I (Mann–Whitney–Wilcoxon test; $W = 7576$, $p = 0.65$). The distributions of spatial biases did not differ based on gender or handedness [gender: $F(1, 35) = 0.31$, $p = 0.58$; handedness: $W = 59$, $p = 0.83$], which is consistent with our observations in Part I (Figure 4.8A and B).

Our previous study using a large sample demonstrated that leftward biases were greatest in children in early elementary school grades (i.e., roughly age 6 to 8) and that the biases diminished and became adult-like in children in grades 6 to 8 (i.e. roughly age 10 to 13). Statistical analyses on our current sample did not reveal any age-related change in spatial biases (Figure 4.8C and D; linear regression with log-transformed age; $p = 0.44$). This is possibly because the sample size for each age may have been too small to reveal age-related differences, given that the dataset in Part I consisted of at least 30 children for each age. In addition, it is important to note that the final sample consisted of only five 6 to 8-year-old participants although it was the age range that exhibited the greatest change in spatial bias as a function of age.

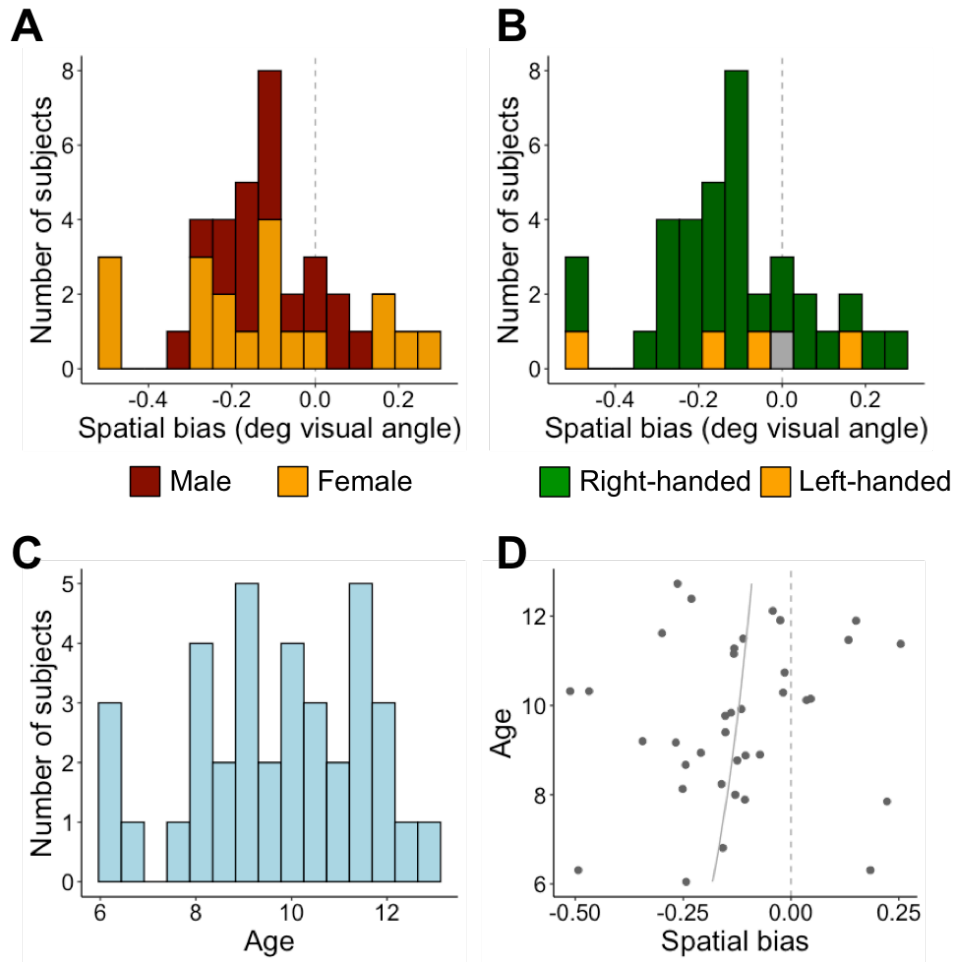


Figure 4.8. Distributions of age and spatial bias of the final sample. A total of 37 children age 6 to 12 years were included in the analyses. This independent group of participants showed an overall leftward distribution of spatial biases (Mean = -0.13°), replicating the large-cohort study in Part I (panels A and B). The distribution of spatial biases did not vary depending on the gender (panel A) or handedness (panel B; gray color indicates one child with no handedness information). Panel D illustrates the spatial biases and ages across individual participants. The age-related change in spatial biases in the current dataset was not statistically significant, possibly due to the small sample size relative to Part I. However, a regression line fit to the data points (solid gray line) indicated a direction that is consistent with our previous observations.

Prediction of spatial bias within the fronto-parietal areas

We examined whether children's spatial biases are indeed related to functional interactions across the topographic areas in the frontal and parietal cortices, by applying the connectome-based predictive modeling (CPM) approach. The first set of ROIs consisted of 16 areas defined by a probabilistic atlas (Supplementary Table 4.1; Wang et al., 2015): frontal eye fields (FEF), intraparietal sulcus (IPS0-5), and superior parietal lobule (SPL) in each hemisphere (Figure 4.7). Among the 120 possible connections from the 16 areas, we first identified edges that are correlated with spatial biases (Figure 4.9A) under the threshold of $p < 0.03$ (see Methods and Supplementary Figure 4.4 for choosing a threshold). The “positive network” consisted of the edges showing a positive correlation between the functional connectivity and spatial biases (i.e., stronger connectivity in rightward biases), and the “negative network” consisted of the edges showing a negative correlation with spatial biases (i.e., stronger connectivity in leftward biases).

To investigate whether these selected edges are also predictive of spatial biases, we used a general linear model and leave-one-out (LOO) cross validation (Figure 4.9B). From the training set ($n = 36$), we submitted individual participants' positive and negative strengths and their spatial biases to a general linear model, which was then applied to predict the spatial bias of the left-out subject. The model's predictive power was assessed by the Spearman rho between the observed and predicted spatial biases across all participants. We found that the model successfully predicted spatial biases ($r_s = 0.57$, $P_{perm} = 0.003$) as shown in Figure 4.9C. We additionally conducted a 6-fold cross validation, which provided further evidence for the model's prediction of spatial bias (Mean $r_s = 0.48$, Cohen's $d = 3.17$).

We expected that edges connecting between the frontal and parietal areas (e.g., FEF and IPS2) in each hemisphere would be selected to predict the degree of spatial bias towards the

contralateral side, based on previous findings in adults (Szczepanski et al., 2013). For example, leftward biases would be predicted by stronger connectivity between the FEF and IPS2 in the right hemisphere. This was indeed the case for leftward biases; edges connecting between the right FEF and right IPS areas (e.g., IPS2) were part of the negative network (red in Figure 4.9A). The negative network also included cross-hemisphere connections between the right FEF and left IPS areas as well as interhemispheric edges between the left and right parietal areas. The right FEF was identified as a hub for the negative network for being associated with the greatest number of negative edges. In contrast, the positive network did not include edges between the FEF and IPS areas in the left hemisphere (blue in Figure 4.9A). For the positive network, a hub was found in the left parietal lobe, specifically area IPS4 as defined by the probabilistic atlas. This area's connections with left and right posterior IPS areas (e.g., IPS0-1) were selected as positive edges predicting rightward biases.

In the process of selecting relevant edges (i.e., feature selection), we did not perform any correction for multiple comparisons in deciding the statistical significance of correlation between each edge's functional connectivity and spatial bias. Thus, to assess the reliability of each edge's inclusion in the predictive model, we calculated the proportion of each edge's inclusion during the 1,000 iterations of the 6-fold cross validation (i.e., among a total of 6,000 models). For the final model (Figure 4.9A), we included the edges that were selected more than 50% of the models generated during the 1,000 iterations. Table 4.3 displays the proportion of each edge selected to be positively or negatively correlated with spatial biases for the true distribution (i.e., models to predict true spatial biases) and for the null distribution (i.e., models to predict randomly shuffled spatial biases). We confirmed that these edges were selected exclusively when the model was generated to predict true spatial biases. In contrast, the same edges were included

less than 1% of the 6,000 models predicting the shuffled measures. Negative network edges were more consistently selected than positive network edges. The majority of the negative network edges were selected by more than 90% of the models. For the positive network, however, only two edges (left IPS4-right IPS2 and left IPS4-right SPL1) were selected for 97% and 94% of the models, and other positive edges were selected less frequently.

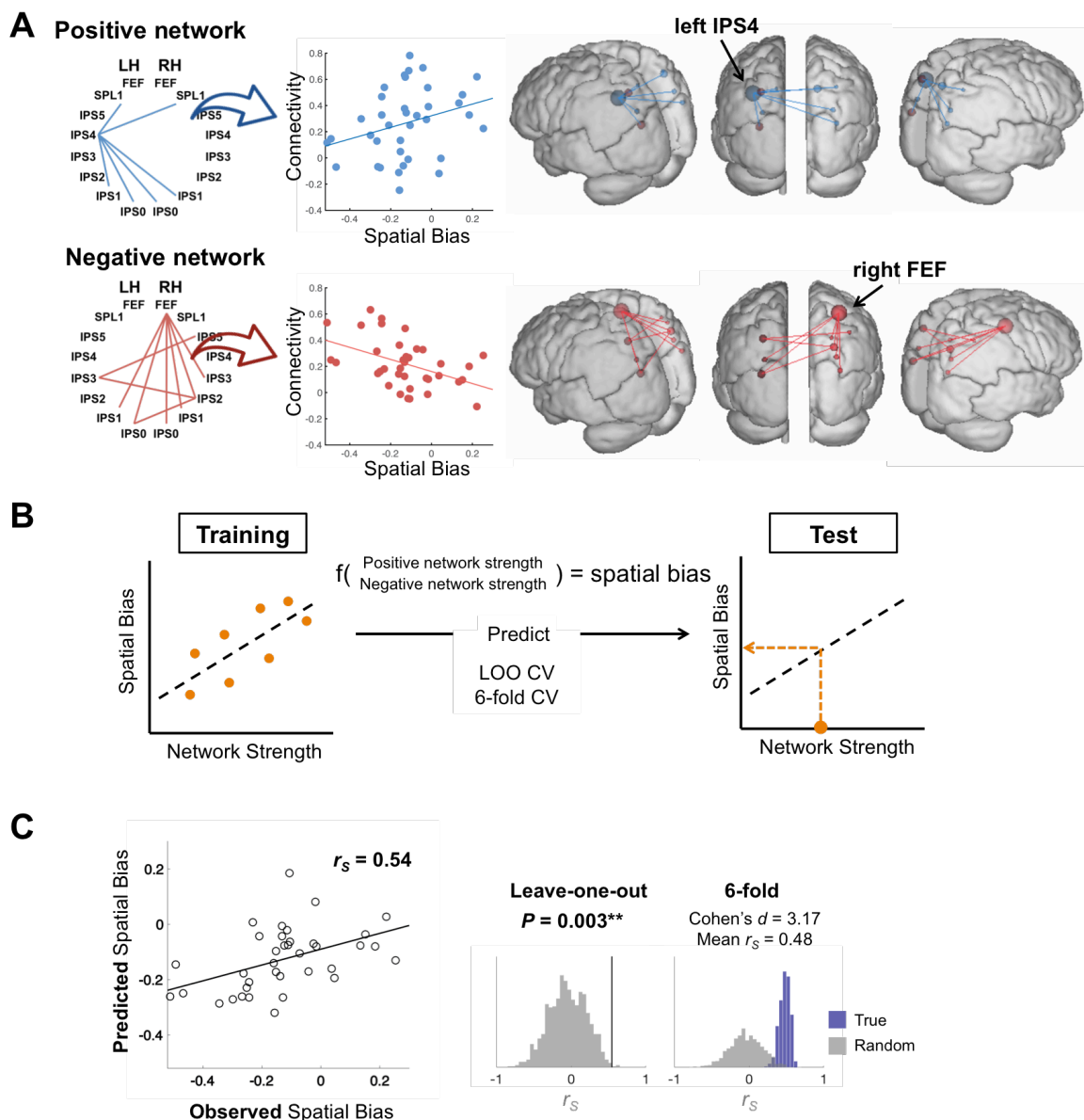


Figure 4.9. Children’s spatial biases were predicted by functional connectivity across the fronto-parietal areas. (A) Feature selection for a connectivity-based predictive model among the 16 topographic fronto-parietal areas. Displayed are selected features (i.e., edges) that showed functional connectivity either positively (blue) or negatively (red) correlated with spatial biases across individual participants, with a threshold of $p < 0.03$. The nodes of the model (spheres) were sized based on their total number of connections. For the positive network (i.e., stronger connectivity in rightward biases), left IPS4 was identified as a hub associated with the biggest number of selected edges. For the negative network (i.e., stronger connectivity in leftward biases), the right FEF was identified as a hub. (B) Schematic of the procedures for building a predictive model and evaluating its predictive power. A general linear model was estimated from the training set (LOO: $N = 36$; 6-fold: $N = 31$) and applied to predict the spatial bias of the testing set (LOO: $N = 1$; 6-fold: $N = 6$). The predictive power was evaluated by the correlation between the observed and model-predicted spatial biases. (C) Summary of model prediction. Both leave-one-out and 6-fold cross validation procedures supported that individual children’s spatial biases were successfully predicted by functional connectivity across the fronto-parietal areas.

Table 4.3. The reliability of feature selection across the models generated from the 6-fold cross validation.

Edges	True	Null
Positive Network		
left IPS4-left IPS0	64%	0.6%
left IPS4-left SPL1	88%	0.3%
left IPS4-right IPS0	86%	0.6%
left IPS4-right IPS1	97%	-0.4%
left IPS4-right IPS2	52%	0.2%
left IPS4-right SPL1	94%	-0.1%
Negative Network		
right FEF-left IPS0	94%	-0.4%
right FEF-left IPS1	98%	0.1%
right FEF-right IPS1	100%	0
right FEF-right IPS2	95%	-1%
right FEF-right IPS3	92%	0
right IPS2-left IPS3	93%	-0.7%
right IPS5-left IPS3	68%	0.3%

Negative proportions indicate the edge’s inclusion in the opposite network.

Prediction of spatial bias in large-scale brain networks

In addition to topographic areas in the frontal and parietal cortices, we investigated whether spatial biases are specifically and exclusively linked to the dorsal fronto-parietal areas, or linked to broader areas of the brain. We used the 400-node parcellation of the whole brain (Schaefer et al., 2018) in combination with the 7-network definition developed by Yeo and colleagues (Yeo et al., 2011). For this specificity analysis, we examined the following four networks: Dorsal Attention, Salience/Ventral Attention, Control, and Default Networks.

Among the four networks, the Dorsal Attention Network showed the greatest overlap with topographic fronto-parietal areas that were included in our main predictive model. Thus, we expected that the predictive model based on this network would also be predictive of spatial bias. Indeed, we found that functional connectivity within the Dorsal Attention Network ($N_{\text{nodes}} = 46$ across the two hemispheres) was predictive of the spatial biases ($r_s = 0.43$; $P_{\text{perm}} = 0.04$), although the predictive power was weaker than the model built based on the set of fronto-parietal areas (Figure 4.10 top panel). Importantly, this model also consisted of edges across the fronto-parietal areas. Consistent with the model based on the topographic fronto-parietal areas, edges between the right FEF and bilateral posterior parietal areas, as well as interhemispheric edges between the right and left parietal areas, were selected in the negative network. Edges between the right and left parietal areas were selected in the positive network. This further supports the link between spatial biases and the dorsal fronto-parietal network in children's brain.

In addition to the edges among the fronto-parietal areas, the Dorsal Attention Network model also selected nodes and edges outside the topographic fronto-parietal areas. We identified the selected nodes and edges based on the anatomical landmarks, Harvard-Oxford cortical atlas, and the probabilistic atlas used to define topographic fronto-parietal areas (Wang et al., 2015).

One of the prominent nodes in this model was located in the left ventral temporal cortex, including the fusiform gyrus. Two nodes located in the left ventral temporal cortex were connected with six other areas: left IPS4 (as part of the positive network), left IPS2, right supramarginal gyrus, right IPS2, and right FEF (as part of the negative network).

Furthermore, we were not able to build predictive models for spatial bias based on functional connectivity within the other three networks (Figure 4.10 bottom panel). This was not driven by differences in the amount of data because the number of nodes included in the Ventral Attention ($N_{\text{nodes}} = 47$) and Control Networks ($N_{\text{nodes}} = 52$) were similar to the Dorsal Attention Network ($N_{\text{nodes}} = 46$), except the Default Network consisting of more nodes ($N_{\text{nodes}} = 91$) than the three networks. Thus, the prediction of spatial bias was specific to the dorsal fronto-parietal network.

Control analyses

In order to rule out the possible confounding effect of head motion, we investigated whether the same sets of ROIs that we used to predict spatial bias were able to predict the amount of head motion across participants. The Euclidean norm of displacement was calculated for each time point relative to the previous time point, and the average head motion was obtained by averaging across all time points in each participant. We found that neither the 16 fronto-parietal areas ($P_{\text{perm}} = 0.55$) nor the Dorsal Attention Network nodes ($P_{\text{perm}} = 0.90$) predicted head motion. Thus, motion-related artifacts in functional connectivity measures did not drive the results from the predictive models.

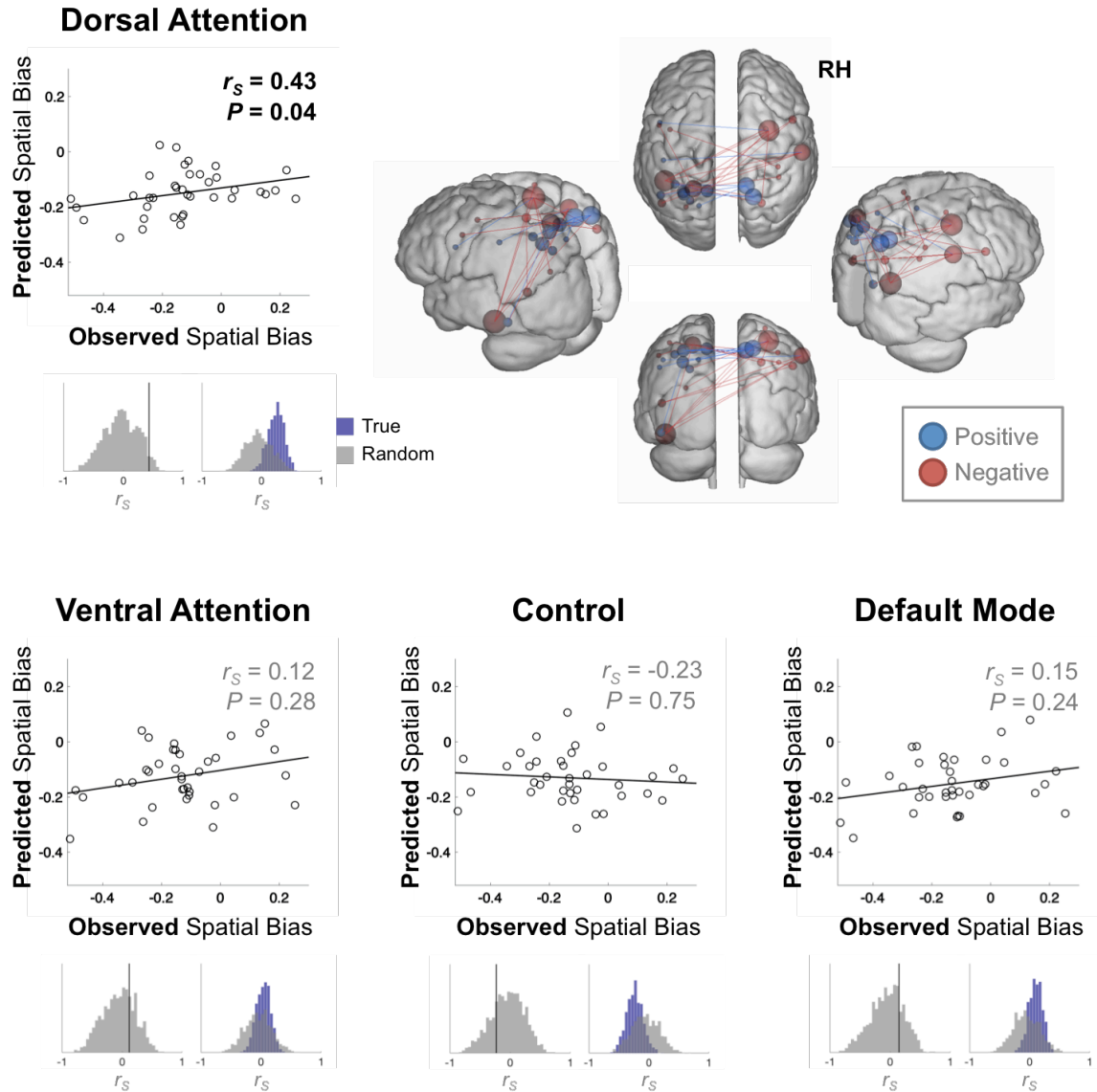


Figure 4.10. Prediction of spatial bias was specific to the Dorsal Attention Network. In order to test the network-level specificity, we generated predictive models using the nodes associated with four of the large-scale brain networks (see Figure 4.7 for node and network definitions). As expected, the nodes of the Dorsal Attention Network, which overlaps most with the attention-related fronto-parietal areas, predicted spatial bias (top panel). Displayed on the top right panel are positive features (i.e., stronger connectivity in rightward biases; blue) and negative features (i.e., stronger connectivity in leftward biases; red) selected in the model. The nodes of the model (spheres) are sized based on their total number of connections. Despite the difference in area boundaries, this model consisted of fronto-parietal connections that were consistent with the fronto-parietal model described in Figure 4.9. However, models based on the other three networks did not predict spatial bias, suggesting that the prediction of spatial bias was specific to the dorsal fronto-parietal network (bottom panels).

Interim Summary

In Part II, we demonstrated the link between spatial attention biases and functional connectivity within the dorsal fronto-parietal network in children of ages 6 to 12. Individual children's spatial biases were successfully predicted from functional connectivity across the topographic areas in the frontal and parietal cortices. Specifically, stronger connectivity between the right FEF and the bilateral posterior parietal areas predicted leftward biases, whereas stronger connectivity between left IPS4 and the bilateral posterior parietal areas were associated with rightward biases. This is broadly consistent with the idea that stronger attention signals from the right hemisphere lead to a leftward bias and stronger signals from the left hemisphere lead to a rightward bias. However, the edges predicting leftward and rightward spatial biases were not symmetrical. These results suggest that, although all of the areas participate in allocating attention across visual space, the right FEF and its interactions with parietal areas become stronger and induce leftward biases during the early elementary years, which is followed by greater engagement of left parietal areas in balancing out the left-biased attention via interhemispheric connections between the left and right parietal regions during the later elementary years.

Furthermore, the prediction of spatial bias was specific and exclusive to the nodes and edges associated with the Dorsal Attention Network. Earlier studies have associated the extreme spatial biases in hemineglect patients with more lateral fronto-parietal areas, including the temporoparietal junction, superior temporal sulcus, and middle frontal gyrus, which are referred to as the salience network or the Ventral Attention Network (Corbetta, Kincade, Lewis, Snyder, & Sapis, 2005; Corbetta & Shulman, 2011; He et al., 2007). In cases of hemineglect, however, it is unclear whether their spatial biases indicate deficits in spatial attention control *per se*.

Hemineglect is a heterogeneous syndrome, and some cases have been attributed to deficits in visual awareness or more general functions, rather than a specific dysfunction of spatial attention (also see Beck & Kastner, 2014). Our results suggest that spatial bias was more strongly predicted by the Dorsal Attention Network than the Ventral Attention Network even though the number of nodes was matched between the two networks. Despite the previous finding on the relationship between attention bias and between-network connections (de Schotten et al., 2011; He et al., 2007), a model combining the nodes from the two attention networks was not successful in predicting spatial bias. Thus, at least in school children, individual variability in spatial attention biases was specifically and exclusively associated with the dorsal fronto-parietal network.

In addition to fronto-parietal connections, the Dorsal Attention Network model selected edges associated with nodes in left ventral temporal cortex. The left ventral temporal cortex includes a region that selectively responds to the perception of words and is often referred to as the visual word form area (VWFA) (Cohen et al., 2002; McCandliss, Cohen, & Dehaene, 2003). Given that it is one of the key areas that develop with the improvement of reading skills (Maurer, Brem, Bucher, & Brandeis, 2005), strong connections between the VWFA and fronto-parietal regions have suggested a link between reading and visuo-spatial attention across development (Franceschini, Gori, Ruffino, Pedrolli, & Facoetti, 2012; Stevens & Bavelier, 2012). This led us to the question whether and how leftward biases in children are related to reading development, which will be further explored in Part III.

Part III: Interaction between Visuo-spatial Attention and Reading Development

Thus far, we have shown that school children, especially in early elementary grades (grades 1 to 3; equivalent to ages 6 to 8), show leftward biases in spatial attention control, and that these spatial biases can be linked to functional connectivity patterns within the dorsal fronto-parietal network. One remaining question is why and how children show such leftward spatial biases. We hypothesized that the significant leftward bias observed in children of early elementary grades might be related to the acquisition of reading skills. As reading is first introduced during early elementary grades, the leftward spatial bias may reflect an interaction between the attention network and the emerging reading network.

A study from our laboratory tested this hypothesis by following up the behavioral findings in Part I (Cheng & Kastner, 2020; Hoyos, Kim et al., 2020). This study recruited an independent cohort of 123 children in grades 1 to 3 who speak and read primarily in English and examined their spatial biases and two standardized measures of their reading fluency and word identification skills (see Methods for the procedures for both measures). The results demonstrated that the degree of leftward spatial biases was predictive of better reading fluency (Figure 4.11). The relationship with word identification skills was not found. This supports our hypothesis that leftward biases in young children might arise to facilitate the early phase of reading development, as children improve their ability to scan text in a coordinated manner.

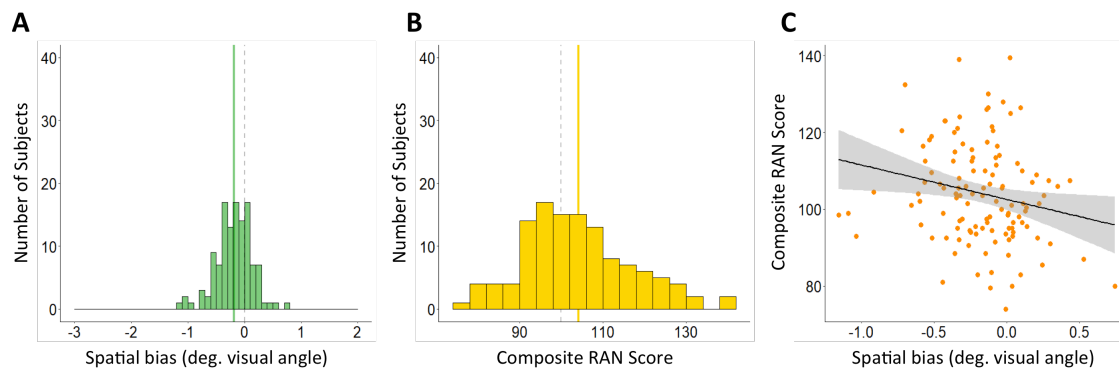


Figure 4.11. Degree of leftward spatial bias predicts reading fluency measured with the Rapid Automatized Naming (RAN) test. We conducted a follow-up study by recruiting an independent dataset consisting of children in grades 1 to 3 ($N_{\text{total}} = 123$; Cheng & Kastner, 2020; Hoyos, Kim et al., 2020). (A) The distribution of spatial attention biases in this independent cohort showed an overall leftward bias, thereby replicating our findings in Part I (see Figure 4.3). (B) The distribution of composite RAN scores of participants in this independent cohort (grades 1–3). See Methods for more details about the RAN test. (C) Relationship between individual participants’ spatial biases and their composite RAN scores. Participants who showed leftward biases (negative values) tended to have better composite RAN scores, when controlled for other variables (e.g., age, testing location). The regression line with a 95% confidence interval is indicated. This figure is adapted from Hoyos, Kim et al. (2020).

The dorsal visual stream, from the primary visual cortex through the MT complex on to the posterior parietal cortex, plays an important role in visuo-spatial attention (e.g., Buschman & Kastner, 2015; Fiebelkorn & Kastner, 2020), and has also been linked to reading development. For example, it has been found that dorsal visual stream functioning measured by frequency doubling sensitivity can be predictive of early reading skills in first graders (Kevan & Pammer, 2009). The frequency doubling stimulus involves the counterphase presentation of two low spatial frequency gratings that appear to have twice the spatial frequency when flickered rapidly. Children who were less sensitive to this illusion at a kindergarten age were tended to show poorer reading skills at the end of the first grade. These and other findings have led to proposals that have linked reading ability to attentional mechanisms controlled by the dorsal visual stream (Franceschini et al., 2012; Vidyasagar & Pammer, 2010). The idea that visuo-spatial attention

and reading function influence each other during development is also reflected in the estimated 25-40% bidirectional comorbidity between ADHD and dyslexia (Bental & Tirosh, 2007; Willcutt & Pennington, 2000). Indeed, a longitudinal study demonstrated that poor performance on visuo-spatial attention tasks in pre-readers predicts later reading deficits, providing compelling evidence for the causal role of attention in the acquisition of reading skills (Franceschini et al., 2012).

Indeed, there is some overlap between the attention network and activation maps associated with reading. For example, it has been observed that visual word form area (VWFA) in the left extrastriate cortex exhibits stronger functional connectivity to the fronto-parietal network at rest, even compared to other areas related to reading (Moulton et al., 2019; Vogel, Miezin, Petersen, & Schlaggar, 2012). The connectivity with the fronto-parietal network, specifically the IPS region, increases with age and reading experience. Indeed, when the cerebral cortex of the human adult brain is divided into seven networks, the VWFA is grouped with topographic fronto-parietal areas into one network, which is referred to as the Dorsal Attention Network (Yeo et al., 2011). To visually inspect the overlap between the attention network and reading-related activity, we compared a map of reading-associated activation derived from NeuroSynth with the 7-network identification (Figure 4.12). In addition to the VWFA, the reading-related activation map overlaps with the Dorsal Attention Network (outlined in green) in the parietal and precentral/inferior frontal regions as well as in visual area V5/MT.

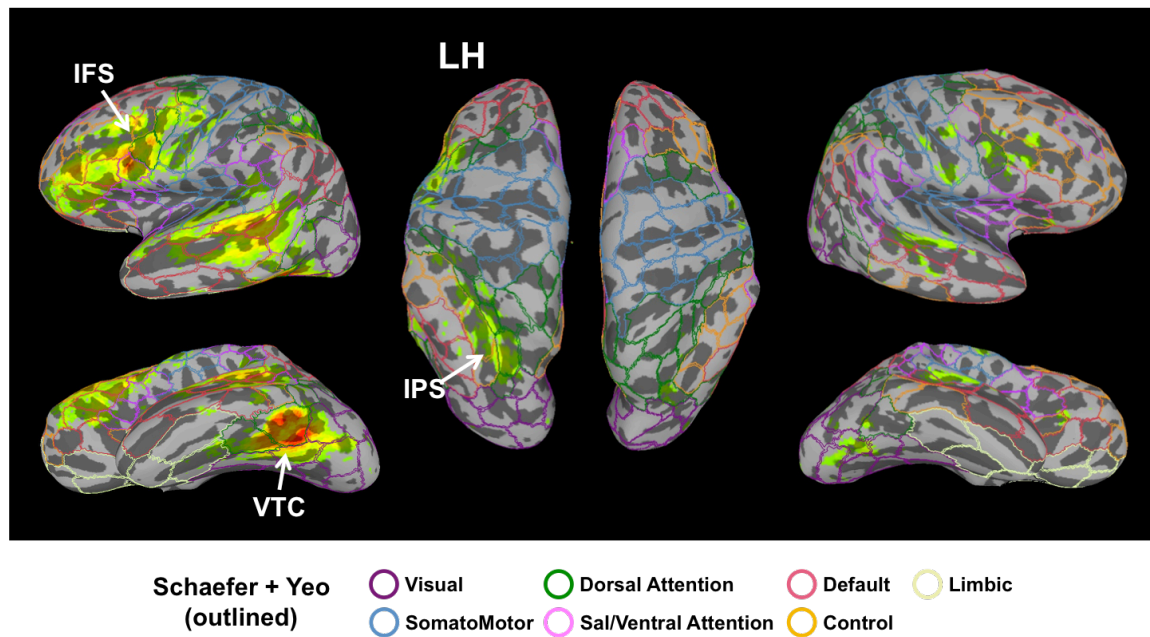


Figure 4.12. Comparison of reading-related activation and large-scale brain networks.

Displayed is NeuroSynth’s “association test map” for the topic of reading (Version 4, topic 15/100; top-load terms: reading, words, language, phonological). The map visualizes voxels where activation is found consistently for studies that mention the relevant terms (the threshold was set at an FDR-corrected $q = 0.01$) (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). The red-green gradient of the map represents Z scores, red indicating higher Z scores (i.e., more consistently found in studies on reading-related topics). The Dorsal Attention Network, which overlaps with topographic frontal and parietal areas, is outlined in green. The reading-related activation map overlapped with the nodes of the Dorsal Attention Network in the left IPS areas, left inferior frontal sulcus, and left ventral temporal cortex. LH: left hemisphere, IFS: inferior frontal sulcus, IPS: intraparietal sulcus, VTC: ventral temporal cortex.

Here, we continued to probe the interactions between visuo-spatial attention and reading networks across development by exploring the link between the dorsal fronto-parietal network and children’s reading behavior. Using the predictive modeling approach and the same sets of areas that we used in Part II, we tested whether reading skills could be related to, or predicted by, the same networks that were predictive of spatial biases. Based on the behavioral finding (Figure 4.11), we expected that children’s reading fluency might be linked to the same network that predicted spatial biases.

Methods

This study is a re-analysis of the same dataset described in Part II. The methods for the experimental paradigms, MRI data acquisition, and data analysis can be found in Parts I and II. Below we provide the procedures for each of the standardized behavioral tests related to reading.

Participants

The final sample used in Part II ($N = 37$, 19 female, mean age 9.7 ± 1.8 years, range 6.05-12.7 years) was included. As described in Part II, we administered the following tests during the first visit (i.e., in addition to the mock scanner session).

Reading assessment: Rapid Automatized Naming (RAN)

The RAN test assesses the speed at which individuals can name visual stimuli (e.g., letters or numerical digits) presented in serial, left-to-right row order (Wolf & Denckla, 2005). This acts as a measure of reading ability by requiring participants to exercise many of the same processes involved in reading, including saccadic eye movements, left-to-right serial processing of visual information, and the rapid conversion of visual stimuli to a verbal output (Manis, Seidenberg, & Doi, 1999; Wimmer, Mayringer, & Landerl, 1998). Performance on the RAN test has been shown to be a robust predictor of current and future reading ability in children (Siddaiah & Padakannaya, 2015) and is also predictive of children's performance on word- and pseudoword-reading tests (Warmington & Hulme, 2012).

The RAN test consisted of four subtests (Numbers, Letters, Objects, Colors), each of which presents a unique type of stimuli. We only examined the Letters and the Numbers subtests in the current analysis, in order to be consistent with our previous studies (Cheng & Kastner,

2020; Hoyos, Kim et al., 2020). Each subtest consists of a stimulus card containing 5 rows of 10 stimuli each. The Letters subtest uses alphabet letters as stimuli, and the Numbers subtest uses numerical digits as stimuli. During each subtest, the experimenter first pointed in random order to each of the items in a set of practice stimuli to ensure that participants were familiar with the stimuli that they would be exposed to during the test phase. During the test phase, participants were then instructed to name the stimuli on the stimulus card (5 rows of 10 stimuli each) as quickly as they could, in row order. Subjects were given raw scores based on the number of seconds they took to finish naming all the test stimuli. These raw scores were then adjusted for age and standardized to a mean of 100 and standard deviation of 15 by using scoring procedures given by Wolf and Denckla (2005), who normed the RAN subtests using a large, nationally representative sample of school-aged children in the United States. The average of the standard scores on the Letters and the Numbers subtests was then taken to derive a single composite RAN score for each participant.

Reading assessment: Test of Word Reading Efficiency, Second Edition (TOWRE)

The TOWRE assesses the speed and accuracy at which individuals can read aloud words and pseudo-words presented in serial, top-to-bottom column order (Tarar, Meisinger, & Dickens, 2015). This test consisted of two subtests that were designed to measure two word-level reading skills, sight word reading and phonological decoding, respectively. In the Sight Word Efficiency subtest, each participant was instructed to read aloud real words presented in columns as fast and accurately as possible. The number of real words that participants read accurately within 45 seconds was recorded as a raw score. This subtest was to measure the ability to perceive words as single orthographic units and identify them quickly and easily. The Phonemic Decoding

Efficiency subtest was administered in a similar format except that participants read pseudo-words instead of real words. The number of pseudo-words that participants read correctly within 45 seconds was recorded. This subtest measured each participant's ability to utilize graphophonic knowledge to sound out unknown words. The raw scores from the two subtests were combined to yield a Total Word Reading Efficiency index. Similar to RAN, these raw scores and the combined index were adjusted for age and standardized to a mean of 100 and standard deviation of 15 using a large, nationally representative sample in the United States. In the current study, we used the Total Word Reading Efficiency index as a measure of word identification skills in each participant.

Results

The current analysis aimed to examine the link between the developing attention network and children's reading skills. We first investigated the relationship among the behavioral measures in the current dataset to explore potential associations at the behavioral level. We then tested whether individual children's scores on the RAN and TOWRE tests could be predicted by functional connectivity across the same sets of areas that we found to predict spatial biases in Part II.

Behavioral data analysis: spatial biases vs. reading measures

First, we checked the distributions of RAN and TOWRE scores, both of which were standardized for age with a mean of 100 and standard deviation of 15. We obtained a composite RAN score for each participant by averaging the standardized scores on the Letters and Numbers subtests, since the scores on the two subtests were highly correlated (linear regression, $p <$

0.001). The average composite RAN score of our final sample ($M = 103.9$, $SD = 13.3$) was close to the national average (i.e., 100), and the scores ranged from 76.5 to 131, which would be evaluated to be ‘poor’ to ‘very superior’ based on the score guidelines (M. Wolf & Denckla, 2005). The average TOWRE score of our final sample ($M = 105.4$, $SD = 15.4$) was also close to the national average, and the scores ranged from 76 to 147. A linear regression analysis demonstrated that the composite RAN and TOWRE scores in our sample were predictive of each other [$F(1, 35) = 10.7$, $p = 0.002$, multiple $R^2 = 0.23$, adjusted $R^2 = 0.002$], ensuring that children who performed better on one of the reading tests were more likely to receive a higher score on the other.

As described earlier, our previous study on an independent dataset has shown that leftward biases of children in grades 1 to 3 were associated with better reading fluency skills measured with the composite RAN scores, but not with the TOWRE scores (Cheng & Kastner, 2020; Hoyos, Kim et al., 2020). In the present dataset, however, we did not find a significant association with spatial bias either for the RAN composite scores [$F(1, 35) = 2.0$, $p = 0.17$] or for the TOWRE scores [$F(1, 35) = 0.24$, $p = 0.63$]. Given that the age range of our final sample was older than the previous study, this may suggest that the association between spatial bias and the RAN score is specific to early elementary grades. It should be noted that the size of our final sample ($n = 37$) was much smaller than the sample size in the previous study ($n = 123$).

Predictive models for the RAN and TOWRE scores

Although we did not find a significant correlation between behavioral spatial biases and the reading scores in our final sample, predictive models for those behavioral measures may reveal the commonalities in the neural correlates for spatial attention and reading.

Predictive models for spatial biases have demonstrated the link between the behavioral measures and the dorsal fronto-parietal areas, or Dorsal Attention Network (Part II). We explored whether the same sets of functional connections in the brain may be related to individual children's reading skills, by using the same predictive modeling approach and the same ROI maps: 16 fronto-parietal areas defined by the probabilistic atlas (Wang et al., 2015) and three large-scale networks of similar sizes defined by the 400-parcellation (Schaefer et al., 2018) and by the 7-network identification (Yeo et al., 2011): Dorsal Attention, Ventral Attention, and Control Networks.

First, we examined predictive models for the composite RAN scores. As in Part II, we identified edges that were correlated with the RAN scores, and then applied a general linear model and leave-one-out (LOO) cross validation to evaluate whether those edges were also predictive of the RAN scores. In every LOO iteration, a linear model was fitted to the training set ($n = 36$) and applied to predict the RAN score of the left-out subject. The model's predictive power was assessed by the Spearman rho between the observed and predicted RAN scores across all participants. Among the four sets of ROIs, individual children's RAN scores were most strongly and reliably predicted by the model based on the Dorsal Attention Network ($r_s = 0.58$; $P_{perm} < 0.001$; corrected) as shown in Figure 4.13. The P value was determined by comparing to the null distribution, which we obtained by repeating the procedure for 1,000 iterations with randomly shuffled data (histogram in grey). The additional 6-fold cross validation demonstrated

a large effect size (Mean $r_s = 0.41$, Cohen's $d = 2.05$), further supporting the predictive power of the model. Models based on the topographic fronto-parietal areas ($r_s = 0.33$; $P_{perm} = 0.056$), on the Ventral Attention Network ($r_s = 0.08$; $P_{perm} = 0.32$), and on the Control Network ($r_s = -0.17$; $P_{perm} = 0.67$) were not successful in predicting the RAN scores.

To assess individual edges that were included in the predictive model for the RAN scores, we obtained all of the model features from 6,000 iterations during the 6-fold cross validation process. We used the proportion of each edge's inclusion (out of 6,000 models) as a measure of how reliably the edge's connectivity strengths could be associated with the RAN scores. A total of 56 edges, out of 1,035 possible pairs, were selected in more than 50% of the iterations: 29 positive edges (blue in Figure 4.13) and 27 negative edges (red in Figure 4.13). Most reliable positive edges (i.e., stronger connectivity in participants with higher RAN scores; selected more than 90% of the iterations) included connections among the right IPS areas, between the right IPS0 and the left mid-IPS areas (left IPS2-3, SPL1), and between the right FEF and the left parietal cortex near the superior temporal sulcus. The left IPS0 and right IPS0 appeared to be hubs of the positive edges. Although less reliable (54-69%), edges between the left ventral temporal cortex (near VWFA) and right parietal areas were also included as positive features. For negative edges (i.e., stronger connectivity in participants with lower RAN scores), one of the most prominent hubs was found in the right ventral temporal area. The area's connections with the left and right frontal areas and with the left and right parietal areas were negatively correlated with the RAN scores. The node identified as the left supramarginal gyrus was also one of the hubs for negative edges; its connections with the right ventral temporal area and with the left/right IPS areas were included as negative features. The left IPS3 and IPS4 had edges with the left and right parietal nodes that were included as negative features.

Although both the spatial biases (Figure 4.10) and RAN scores (Figure 4.13) were predicted by models based on the Dorsal Attention Network, the specific features included in the two models were distinct from each other. The main features of the model predicting spatial biases consisted of more “dorsal” edges, between the right FEF and superior parietal regions. On the other hand, the main features of the model predicting RAN scores included connections between more “lateral” parietal areas. Both models included edges among the nodes along the IPS. This suggests that spatial biases and reading fluency skills indicated by the RAN scores rely on different neural circuits, but they are strongly interacting with each other.

None of the predictive models were successful in predicting the TOWRE scores (fronto-parietal: $r_s = -0.15$, $P_{perm} = 0.65$; Dorsal Attention: $r_s = -0.10$, $P_{perm} = 0.59$; Ventral Attention: $r_s = -0.23$, $P_{perm} = 0.75$; Control: $r_s = -0.33$, $P_{perm} = 0.84$). This was consistent with the observation from our previous study that demonstrated the relationship between spatial biases and the RAN scores, but not with the TOWRE scores, in early elementary school children (Cheng & Kastner, 2020; Hoyos, Kim et al., 2020). Even though those two reading-related scores were related to each other both in our dataset and the cohort in the previous study, spatial biases were specifically related to the RAN scores, which measured how fluently children were able to scan text in the left-to-right direction.

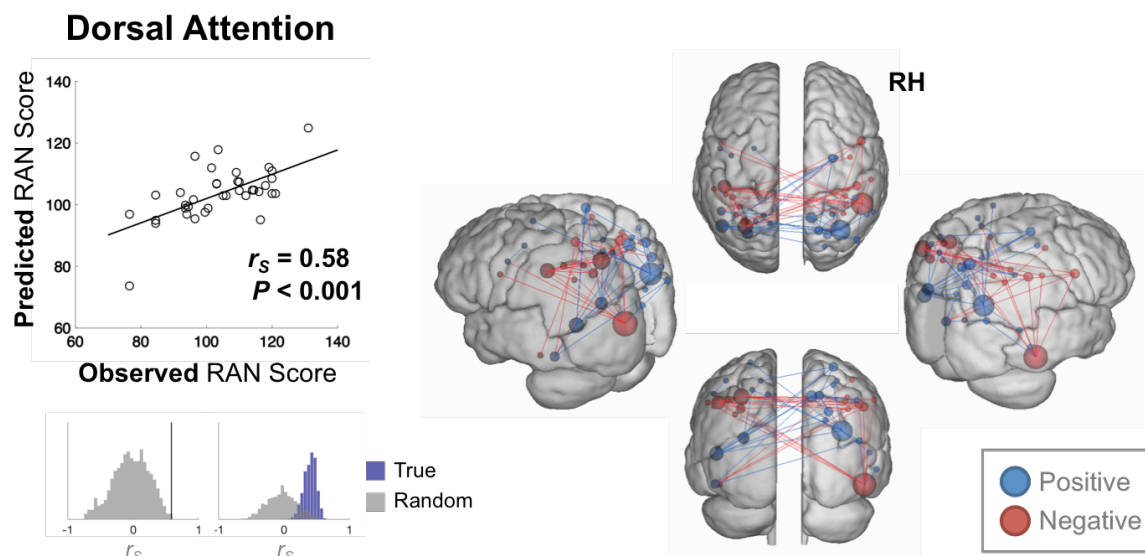


Figure 4.13. Children’s reading fluency measured with the Rapid Automatized Naming (RAN) test was predicted by functional connectivity within the Dorsal Attention Network. A model based on the Dorsal Attention Network nodes of the 400-parcellation (Schaefer et al., 2018; Yeo et al., 2011) successfully predicted individual children’s RAN scores based on their functional connectivity patterns. This was the same set of nodes as the model predicting spatial bias (Figure 4.10). The right panel indicates the positive features (i.e., stronger connectivity in participants with higher RAN scores; blue) and negative features (i.e., stronger connectivity in participants with lower RAN scores; red) selected in the model for the RAN scores. The nodes of the model (spheres) are sized based on their total number of connections. Like the model for spatial bias, this model included edges across the IPS. However, this RAN model was based on more lateral or posterior parietal nodes, such as IPS0 and supramarginal gyrus) while the spatial bias model selected more dorsal parietal nodes, such as superior parietal lobule. Despite the differences in the selection of specific model features, these results suggest that the Dorsal Attention Network could be linked to children’s reading skills, particularly their ability to scan visual information along the horizontal axis.

Interim Summary

Building upon the behavioral evidence that children’s leftward biases are related to their reading fluency, we demonstrated an association between children’s dorsal fronto-parietal network and reading fluency measured with the Rapid Automatized Naming (RAN) test. We found that individual children’s RAN scores were predicted by functional connectivity within the

Dorsal Attention Network nodes. However, another model based on the topographic fronto-parietal areas, which showed the strongest predictive power for spatial bias, exhibited only a trend. In addition, the RAN model and the spatial bias model consisted of distinct features (i.e., connections) even if they were both generated from the Dorsal Attention Network nodes. This suggests that spatial attention and reading rely on different neural resources, but they show strong functional interactions both at rest and during task conditions. Given that both behavioral and neuroimaging analyses revealed a relationship with spatial bias only for the RAN scores, but not for the TOWRE scores, spatial attention appeared to be related to a particular set of cognitive facilities required for the RAN performance, such as the ability to scan visual stimuli horizontally in the left-to-right direction.

Discussion

This chapter examined the development of the dorsal fronto-parietal network in school-aged children with a focus on asymmetry in spatial attention and interhemispheric interactions within the network. Using a perceptual version of line bisection task, we found that children in early elementary grades (equivalent to ages 6 to 8) show a leftward spatial bias (Part I). The leftward bias diminished with increasing grades and became more balanced and similar to adults by middle school ages (grades 6 to 8; ages 11 to 13). Next, we demonstrated that those spatial biases were related to functional interactions within the dorsal fronto-parietal network (Part II). The degree of spatial bias was predicted by functional connectivity patterns within the network across individual children. The behavioral prediction was specific to the Dorsal Attention Network involving the fronto-parietal areas and was not found in other brain networks of similar sizes. Interestingly, among children in early elementary grades, the degree of leftward bias was predicted by the child's reading fluency measured with the Rapid Automatized Naming test. Our additional analyses also revealed that the children's reading fluency scores were also predicted by functional connectivity patterns within the Dorsal Attention Network (Part III). Together, our work provides evidence for developmental changes in the interhemispheric interactions within the dorsal fronto-parietal network, which may be influenced by the acquisition and improvement of children's reading skills.

Leftward spatial biases and hemispheric asymmetry in the developing attention network

Our findings on behavioral spatial biases provide a lens to understand the developmental mechanisms for the dorsal fronto-parietal network (Part I). In the healthy adult population, biases in line bisection judgments have been shown to be a behavioral indicator of neural biases in

attention signals from areas across both hemispheres of the dorsal fronto-parietal network (Szczepanski & Kastner, 2013). Thus, leftward attention biases in children suggest that in children's attention network, the right hemisphere presents stronger signals towards the left-hand side of space than the left hemisphere counterparts' signals towards the right-hand side. The age-related change in spatial biases indicates that the network gradually achieves a better-balanced attention control system across middle childhood. Previous studies have characterized developmental changes in the attention network across childhood and adolescence based on the anatomical structure (Sowell et al., 2003), task-driven activity (Casey et al., 2004; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Klingberg, Forssberg, & Westerberg, 2002; Konrad et al., 2005; Luna et al., 2001), and functional connectivity (Fair et al., 2007; Farrant & Uddin, 2015; Rohr et al., 2017; Vinette & Bray, 2015). Our work adds a new angle to the existing literature by suggesting that achieving a better balance in the interhemispheric interactions may be a maturational process of the attention network.

Our results from the predictive modeling analyses provide some evidence for the brain-behavior association for children's spatial biases (Part II). Here we built a predictive model of individual children's spatial biases based on functional connectivity patterns measured during movie viewing—in a naturalistic state without any specific task. As the developmental changes in spatial biases were reflected in the patterns of intrinsic functional connectivity, spatial biases could also be related to hemispheric differences in evoked activity during attention tasks and in white matter tracts connecting between the frontal and parietal regions. It would be a fruitful future direction to take an integrative approach by examining the structural and functional properties of the attention network together in relation to children's spatial biases, in order to

achieve a fuller understanding of the interplay between structure and function in the developing attention network.

A crucial strength of using the perceptual version of line bisection task is that it avoids possible confounds of manual actions in bisecting lines. The traditional paper-and-pencil version of the line bisection task requires participants to move their hand across the page and coordinate hand/arm movements with visual information in order to indicate a midpoint. Confounding motor effects may be more critical in children than in adults. For example, it has been shown that children's spatial bias measures varied largely based on which hand they used to indicate the subjective midpoint (Bradshaw et al., 1987; Dellatolas et al., 1996). In particular, children indicated a midpoint to the right side of the veridical midpoint when they used the right hand (Dobler et al., 2001). This deviation was observed to the left of the veridical midpoint when the same children used their left hand. Adults were shown to be more consistent regardless of the hand used to bisect the line. Thus, spatial biases measured in this type of task are prone to motor-related confounds, particularly in younger children. To avoid such confounds, we developed a perceptual, computerized line bisection task that only required simple button presses after the perceptual judgment had been formed. We found that the distribution of spatial biases was consistent regardless of handedness. Therefore, the current study may provide more precise and reliable measures of spatial attention biases in children that are not confounded by motor-related parameters. The perceptual version of the line bisection task used in the current study will be particularly useful to test children with ADHD and/or dyslexia, as motor deficits are frequently observed in those populations (Gilbert et al., 2019; Kaplan et al., 1998).

It should be noted that our analyses were restricted to cortical structures, but growing evidence suggests the importance of subcortical structures in attention and cognitive functions.

For example, the thalamus plays a critical role in coordinating inter-areal communications in the attention network (Fiebelkorn & Kastner, 2020; Saalmann, Pinsk, Wang, Li, & Kastner, 2012). The cerebellum's involvement in cognition beyond motor control has been highlighted over the past decade (Buckner, 2013; Schmahmann, Guell, Stoodley, & Halko, 2019). These structures and their interactions with cortical areas significantly develop in childhood (Casey et al., 2004; Luna et al., 2001), and dysfunction in their circuits has been associated with attention deficits (Schmitt & Halassa, 2017; Stoodley, 2016). Future work should investigate how subcortical structures might be involved in the developmental mechanisms for the attention network and visuo-spatial attention functions in order to establish a more complete understanding.

Implications for the interaction between attention and reading across development

Why do children in early elementary grades show a leftward bias? We hypothesized that the significant leftward bias observed in early elementary school children might be related to the acquisition of reading skills. For example, children may develop these leftward attention biases when they learn to read left-to-right in English because these biases offer a perceptual advantage that facilitates the repetitive, left-to-right shifting of attention involved in reading. As children gain reading expertise, this leftward spatial attention bias could become less useful in facilitating reading and thus gradually diminish for a more even distribution, reflecting balanced attention control across visual space. Our results in Part III provide evidence for the potential interaction between visuo-spatial attention and reading development. On the behavioral level, leftward biases were associated with better reading fluency in first to third graders who begin to learn to read in English (Cheng & Kastner, 2020; Hoyos et al., 2020). The Dorsal Attention Network that was linked to spatial bias in Part II was also predictive of individual children's reading fluency

skills. These findings are consistent with previous studies suggesting the relationship between visuo-spatial attention and reading development (Franceschini et al., 2012; Gabrieli & Norton, 2012; Vidyasagar & Pammer, 2010).

If our interpretation of the relationship between leftward biases and reading is correct, we predict that children learning to read from right to left (e.g., Hebrew, Arabic) will show opposite, that is, rightward attention biases. Indeed, a prior study found that Israeli children of age 4.5 and 8 years had greater rightward biases, compared to French children of the same ages who appeared to have rightward biases yet to a lesser degree (Chokron & De Agostini, 1995). However, this study used a paper-and-pencil version of the line bisection task and could not rule out the confounding effect of handedness and other motor-related issues. Therefore, it remains an open question whether spatial attention biases are initially shaped by the experience of reading direction. Future studies involving pediatric populations from cultures with reading conventions different from the English language will be necessary to explore this important issue further.

If reading experience shapes spatial attention biases in early elementary school grades, this offers a hypothesis on a causal direction that is opposite to the prevailing focus in the literature that visuo-spatial attention function primarily influences reading development (e.g., Vidyasagar & Pammer, 2010). That is, reading may also have an impact on the development of visuo-spatial attention (also see Ferretti, Mazzotti, & Brizzolara, 2008). Comparisons to children prior to reading experience and longitudinal studies would be necessary to further explore how the evolving reading and the attention networks influence each other during the acquisition of reading skills.

General Discussion

The main goal of the work presented in this dissertation was to investigate the neural basis of visuo-spatial selective attention functions in children by using the theoretical framework of biased competition (Beck & Kastner, 2009; Desimone & Duncan, 1995). Visuo-spatial attention is a fundamental cognitive process that allows one to navigate the complex visual environment. However, research on the development of the neural mechanisms underlying visuo-spatial attention is still in its infancy. The results presented in the above chapters have highlighted that in middle childhood, roughly between ages 6 and 12, visuo-spatial attention is shaped by the interactions with perceptual organization mechanisms in the visual cortex and newly acquired cognitive skills, both of which continue to mature in this age range.

Biased competition in the developing visual cortex

The main principle of biased competition theory is that multiple objects in a visual scene give rise to competition in the visual system, which should be overcome or “biased” towards a target object. Competition can be biased both by bottom-up mechanisms that segment objects from the background and by top-down mechanisms that select targets related to the behavioral goal. We demonstrated that the visual cortex of children above age 8 exhibits adult-like sensory competition in response to multiple stimuli that are simultaneously displayed (Chapter 2). As the receptive field (RF) architecture in extrastriate areas becomes similar to adults by age 5 (Conner et al., 2004; Dekker et al., 2019; Gomez et al., 2018), competition in children’s brain was also closely tied to the RFs and modulated by the spatial distance among the competing stimuli.

These results offered a basis for further investigations of bottom-up and top-down factors that modulate the competition in children's visual cortex. Chapter 3 investigated perceptual grouping mechanisms in children's brain as one of the bottom-up modulations of sensory competition. Although the results were preliminary, younger children (ages 6 to 7) appeared to exhibit a weaker effect of grouping relative to older children (ages 11 to 12), which may provide a neural model for previous behavioral findings on the prolonged development of perceptual organization (e.g., Scherf et al., 2009).

How and to what extent sensory competition can be resolved by the top-down mechanisms in children's brain should be further investigated in future research. The effect of attention modulation in the visual cortex can be quantitatively measured by a reduction of competition when children covertly attend to one of the peripheral stimuli (in adults: Kastner et al., 1998). Such top-down modulation effect may be weaker in children, given that they are more vulnerable to nearby distracters than adults (Huang-Pollock, Carr, & Nigg, 2002; Jeon et al., 2010; Plebanek & Sloutsky, 2017; Rueda, Posner, & Rothbart, 2005). Building upon these findings, one could examine how such top-down mechanism interacts with bottom-up sensory-driven functions to overcome sensory competition in children's visual cortex. As described before, in the adult brain, the engagement of top-down attention is constrained by the remaining amount of competition after bottom-up filtering (Figure 1.2; Beck & Kastner, 2009). Weaker perceptual grouping in young children may demand for top-down factors to a greater extent. Due to the limited capacity of top-down selective functions, however, children may need greater cognitive effort to filter out distracters effectively by recruiting additional control areas, such as dorsolateral prefrontal cortex and anterior cingulate cortex.

The paradigms and results of this work could prove useful for investigations of developmental disorders that accompany deficits in visuo-spatial attention. Specifically, our paradigm allows systematic analyses of functional interactions within visual cortex in or outside the focus of attention, providing a compelling way of probing different components of visuo-spatial attention in developmental disorders. A growing body of research has highlighted the importance of characterizing low-level perceptual deficits in ADHD (Fuermaier et al., 2018; Mihali et al., 2018; Stevens et al., 2012) and autism spectrum disorder (ASD; Robertson & Baron-Cohen, 2017). We suggest that future research should examine how those atypical sensory functions could contribute to attention functions. For example, it has been observed that the receptive field sizes of extrastriate visual areas are larger in adults with ASD, and the receptive field sizes also correlate with the severity of autistic traits (Schwarzkopf, Anderson, de Haas, White, & Rees, 2014). According to biased competition theory, individuals with ASD may experience greater sensory competition due to the larger RF sizes, therefore requiring a greater demand for top-down modulation to resolve competition. In support of such a proposal, increased competition by incongruent flankers has been found in the Flanker task, as suggested by greater flanker effects in adolescents with ASD (Adams & Jarrold, 2012). A seemingly conflicting finding, however, is enhanced local processing in ASD (Plaisted, O’Riordan, & Baron-Cohen, 1998). It has also been suggested that adults with ASD show a sharper gradient of spatial attention (Robertson, Kravitz, Freyberg, Baron-Cohen, & Baker, 2013). When presented with a spatial cue followed by a target item at varying distances from the cue, both ASD and control groups performed better as the target appeared closer to the cue, but individuals with ASD showed a sharper decrease in performance when the target appeared far from the cue. Based on our theoretical framework, altered receptive field sizes and sharper gradient of

attention will affect both bottom-up and top-down modulations, thereby leading to impairments in selective attention functions in ASD.

Our studies have focused on group-level comparisons between children and adults (Chapter 2) or across three age groups (Chapter 3). Potential individual variability in the neural measures within the same age group was not addressed. In addition, it remains largely unknown how variability in the neural measures of sensory competition could be linked to behavioral performance. By recruiting a larger sample and a wider age range of children, one may be able to investigate variability in sensory competition as well as in the effects of bottom-up and top-down factors across individuals and across development. This individual variability in the neural measures could also be directly associated with behavioral performance on attention tasks (e.g., visual search).

Development of the fronto-parietal attention network and acquisition of reading skills

The top-down guidance of attention across visual space engages the dorsal fronto-parietal network. Our results in Chapter 4 demonstrated that this network develops to gradually achieve a better balance between the two hemispheres throughout elementary school ages, and thus achieve a more balanced attention control. This work extends the current literature by demonstrating developmental changes in interhemispheric interactions within the attention network, beyond the process of strengthening within-network connections and weakening between-network connections as a function of age (e.g., Fair et al., 2007).

Leftward biases in children suggest that in children's fronto-parietal network, the right hemisphere produces stronger biasing signals towards the contralateral side than the left hemisphere and that the two hemispheres reach a balance with increasing age. Indeed, fronto-

parietal activity during task conditions has been shown to change as a function of age throughout childhood and adolescence, which was associated with the improvement of working memory and reasoning capacities (Bunge & Wright, 2007; Crone et al., 2006; Klingberg et al., 2002).

However, it remains unclear how the developmental changes in fronto-parietal activity could also be linked to selective attention. Although our work examined the neural correlates of spatial attention bias based on functional connectivity, more work is needed to identify developmental changes in the degree of task-evoked activation in individual areas of the attention network and their behavioral outcomes. If children's top-down attention makes a weaker release of competition in the visual cortex as mentioned above, this might be related to weaker activation in frontal and parietal cortices evoked by attention allocation. As fronto-parietal activity becomes stronger as a function of age, the top-down mechanisms for resolving sensory competition may become more effective in childhood.

Because our work targeted children above age 6, it still remains unanswered how functional interactions within the attention network emerge in earlier ages. For example, if reading development is the main factor that shapes spatial biases in novice readers, the network would begin with more symmetric connectivity profiles prior to reading. Alternatively, the leftward biases in children could be an outcome of intrinsic developmental mechanisms for the attention network regardless of reading development; that is, the right hemispheric areas might develop faster than the left hemisphere counterparts regardless of their reading directions, generating temporary leftward biases in early childhood. This question can be further addressed by investigating spatial biases in children who are beginning to read in the right-to-left direction (e.g., Hebrew). Longitudinal studies starting from younger ages prior to much reading experience

or comparison of the attention network before and after intensive reading intervention programs (e.g., Huber, Donnelly, Rokem, & Yeatman, 2018) could provide further insight.

Since the current study aimed to examine the general population of school children, we were agnostic to atypical development in our participants. According to the National Center for Learning Disabilities, it is estimated that 1 in 5 children in the United States have learning and attention difficulties. Studies have suggested that children with ADHD or dyslexia show rightward spatial attention biases relative to age-matched controls (Bellgrove et al., 2008; Chan et al., 2009; Sireteanu et al., 2005). In Chapter 4, we assume that participants with an atypical developmental trajectory are normally distributed in the general population and that our findings therefore reflect a population-level development of spatial attention biases in children. As a result, the developmental trajectory of the general population discussed here may provide a useful reference for future studies that aim to explore differences in the development of spatial biases in children with atypical development.

To conclude, these studies show that children's attention functions interact with sensory processing and cognitive skills that undergo further refinement and maturational processes, suggesting dynamic developmental mechanisms of visuo-spatial selective attention. Thus, this dissertation work lays a foundation for future investigations of attention functions in typical and atypical development.

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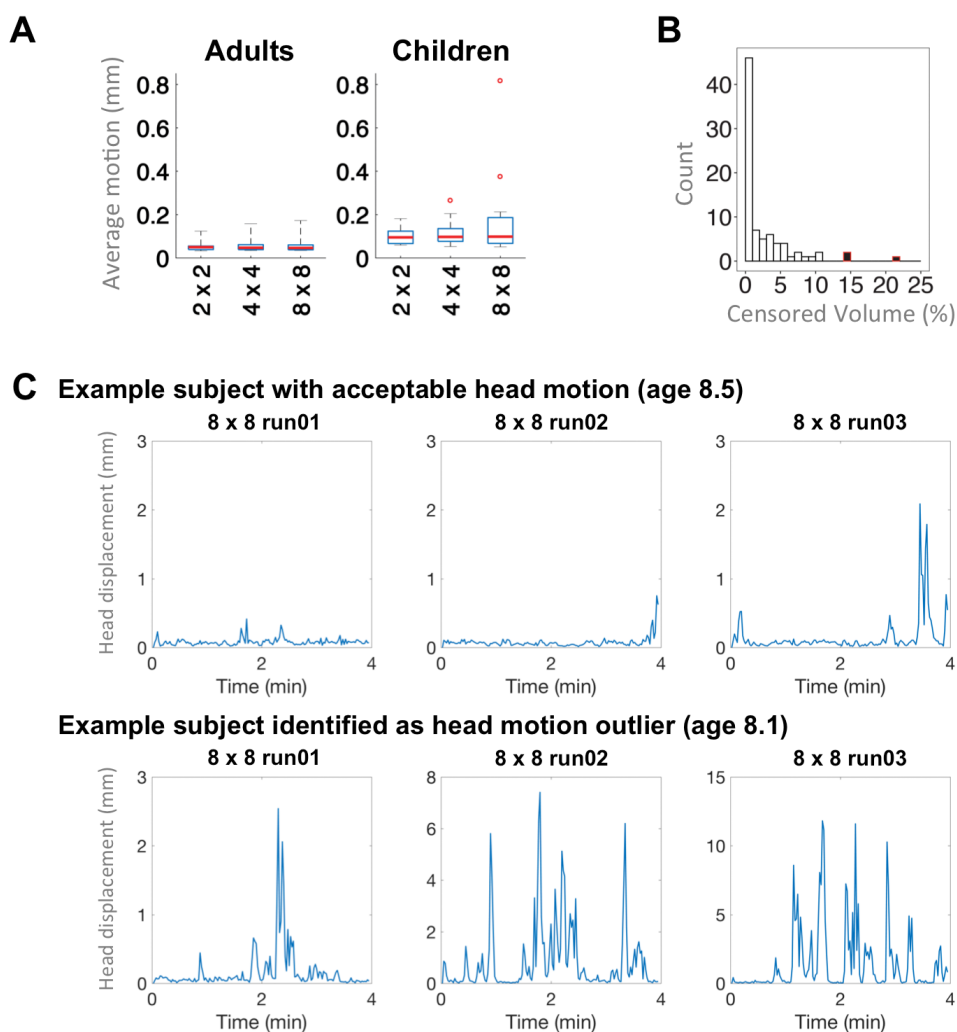
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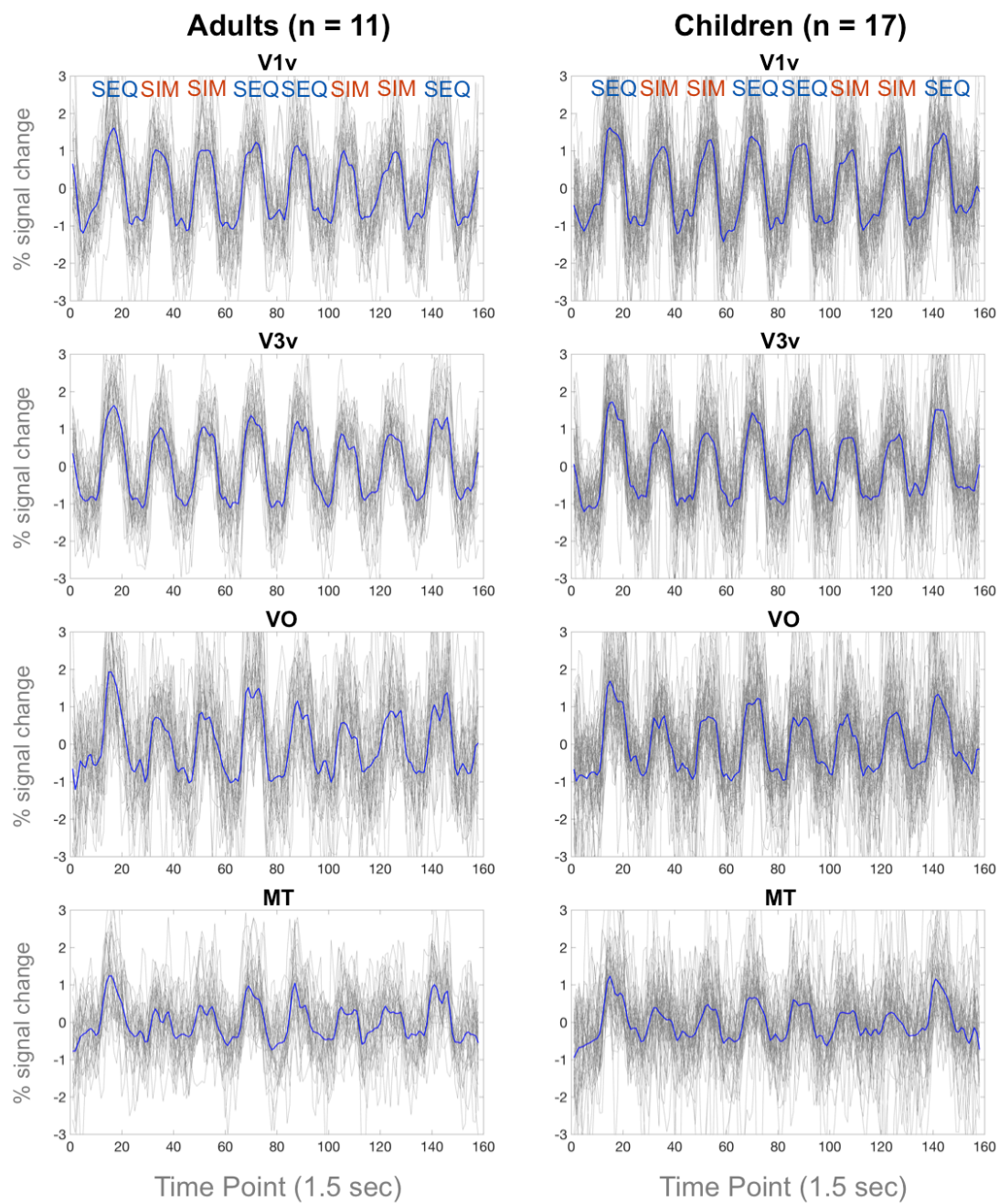
Supplementary Information



Supplementary Figure 2.1. Head motion and the identification of outliers. (A) Frame-to-frame displacement (i.e. motion for each time point relative to the previous time point) was calculated and averaged for each display condition in individual participants. Outliers were identified for each display condition (indicated as red circles); one child for the $4 \times 4^\circ$ condition and two children for the $8 \times 8^\circ$ condition. (B) The number of censored volumes (>2 mm displacement; corrected via interpolation) was obtained for each display size condition for each participant. The histogram summarizes the proportion of data censored at the level of display size conditions. If a participant completed three display size conditions, the participant was counted three times in this histogram. The three participants identified as outliers in panel A are indicated in black. In those participants, a higher proportion of data (> 3 SDs) was censored compared to other participants. (C) Frame-to-frame head motion in an example participant with acceptable head motion parameters and in an outlier participant of similar age.

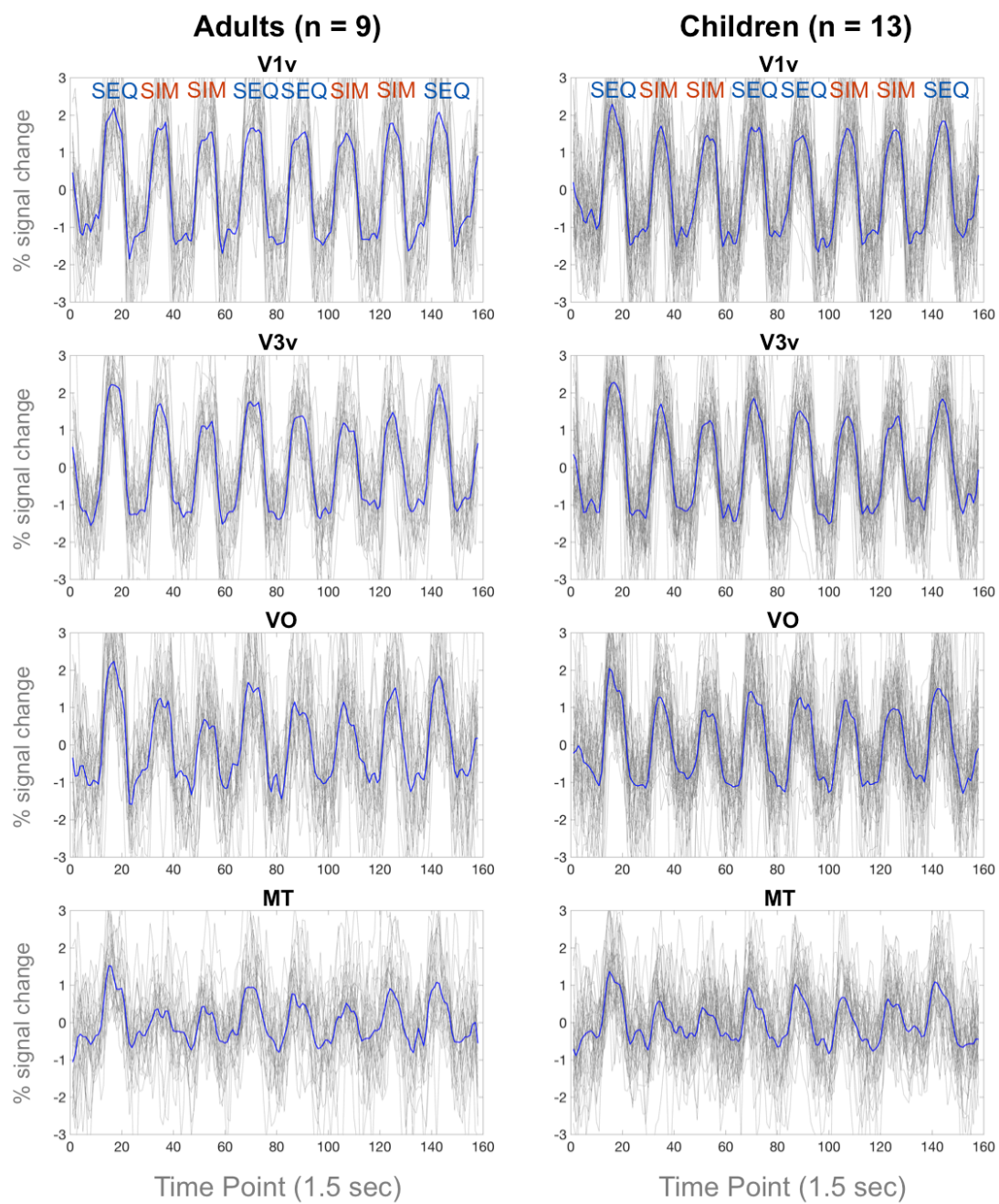
Supplementary Figure 2.2A

2 x 2 display



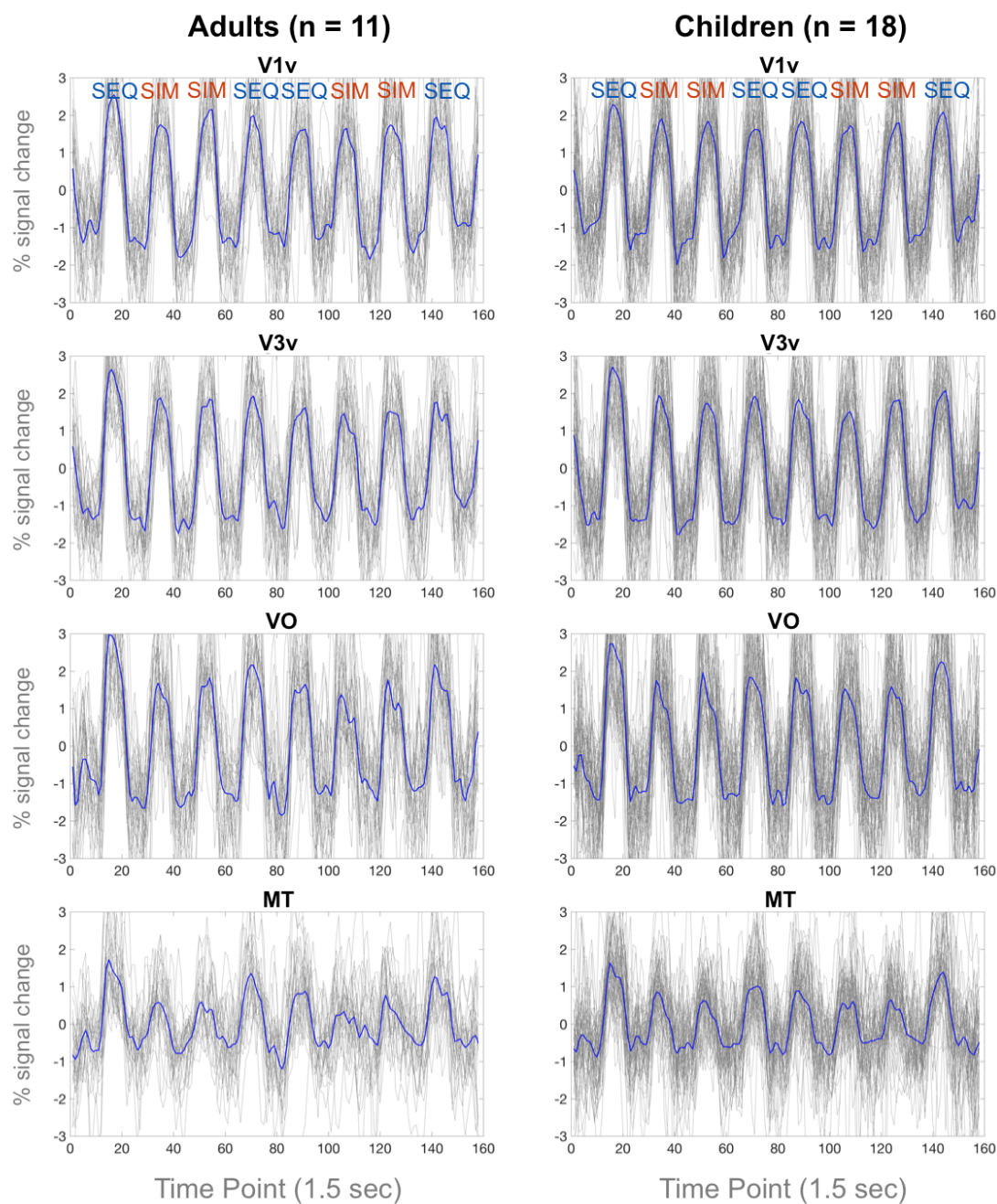
Supplementary Figure 2.2B

4 x 4 display



Supplementary Figure 2.2C

8 x 8 display

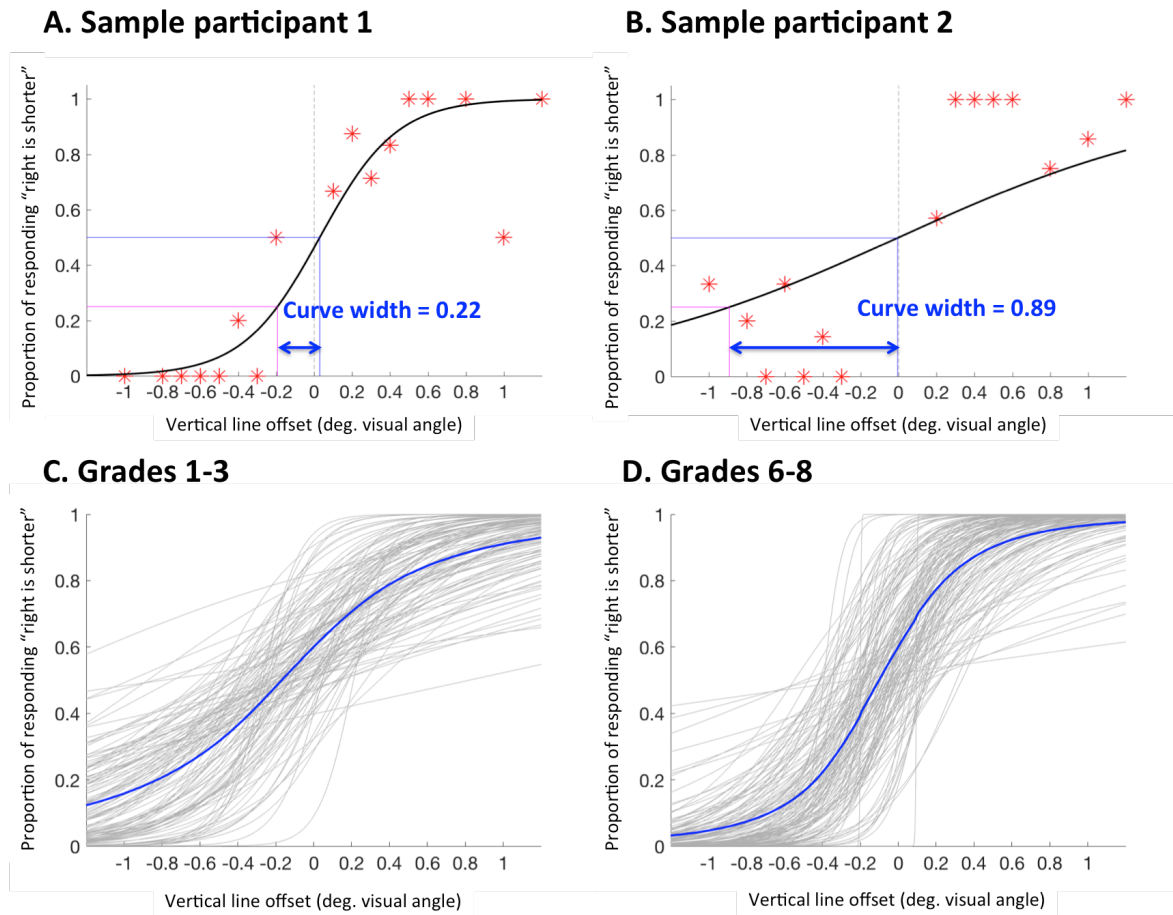


Supplementary Figure 2.2. Extracted time courses for the 2 × 2° display (A), 4 × 4° display (B), 8 × 8° display (C) condition. Each run's time course from all individual participants was extracted from visually responsive voxels and normalized. Time courses from all runs and all

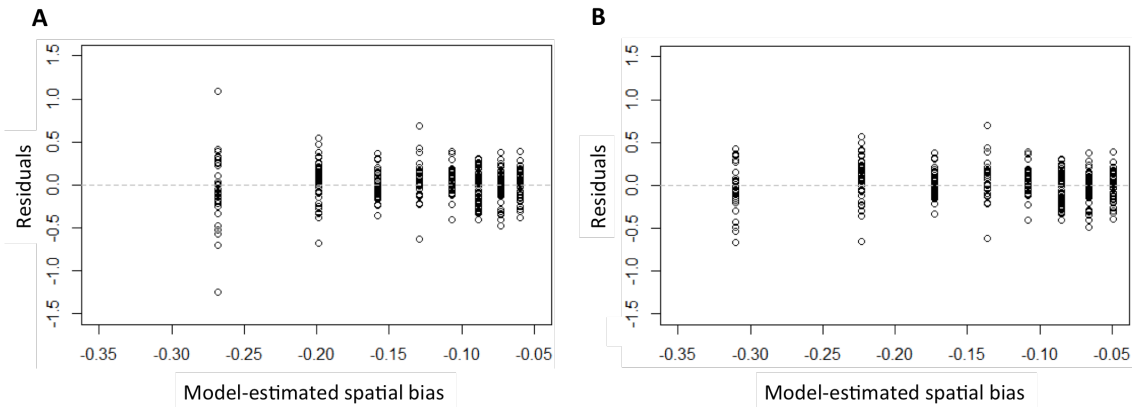
participants were combined for each area and for each display size condition in the same plot. The blue solid line indicates the average time course in each plot. Every run had 8 visual stimulation blocks of 12 s that were interleaved with 15 s blocks of blank presentation. The 8 visual stimulation blocks (sequential and simultaneous presentation blocks) were always in the following order: SEQ-SIM-SIM-SEQ-SEQ-SIM-SIM-SEQ. Sensory suppression effects (SEQ > SIM) can be observed from the average time courses. Peak signal changes from visual presentation blocks are summarized in Figure 2.5.

Supplementary Table 2.1. Evaluation of probabilistic atlas in children’s brains. Visually-responsive voxels were identified from whole-brain contrast maps (peripheral stimuli > blank, $Z > 1.96$) and assigned to each topographic area based on either the child’s retinotopic map (labeled “Ret”) or probabilistic atlas (labeled “Atlas”). The table represents the number of voxels (2 mm cubic voxel) identified by the two procedures and the overlap.

	Subject 1						Subject 2					
Display	2 x 2			4 x 4			2 x 2			4 x 4		
Area	Ret	Atlas	Overlap	Ret	Atlas	Overlap	Ret	Atlas	Overlap	Ret	Atlas	Overlap
V1	33	37	29	95	61	55	41	65	39	151	173	144
V2	85	57	53	213	176	146	96	135	93	198	174	161
V3	67	90	56	212	193	140	47	95	39	178	116	101
V4	51	44	32	89	114	60	21	74	11	82	277	74
VO	9	28	6	124	125	95	52	53	18	216	235	108
V3A	42	33	10	142	78	78	47	91	47	247	228	219
MT	67	96	59	12	9	9	10	46	10	196	192	189
	Subject 3						Subject 4					
Display	4 x 4			8 x 8			2 x 2			8 x 8		
Area	Ret	Atlas	Overlap	Ret	Atlas	Overlap	Ret	Atlas	Overlap	Ret	Atlas	Overlap
V1	108	100	89	154	105	102	84	89	58	92	61	54
V2	68	87	54	157	162	116	172	218	161	211	249	197
V3	132	143	103	248	217	186	19	45	17	61	75	55
V4	55	62	31	142	175	122	26	43	20	65	67	43
VO	107	80	61	176	100	94	110	136	96	149	127	123
V3A	132	119	103	231	170	158	115	93	88	87	84	84
MT	.	.	.	.	.	.	127	180	102	61	61	61

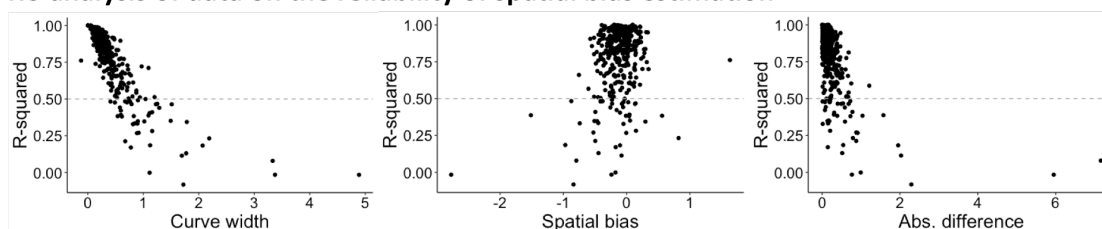


Supplementary Figure 4.1. Curve width estimations. To control for precision of line bisection judgments, we estimated the width of each participant's psychometric curve. For each participant, spatial bias was measured by the midpoint of the psychometric curve where the y-value is 0.5 (blue solid line). To estimate the curve width, we found the first quartile point where the y-value is 0.25 (pink solid line) and calculated the difference between the vertical line offsets corresponding to the two points. Panel A is an example of a psychometric curve with a smaller curve width. Panel B shows an example of a flatter psychometric curve with a greater curve width. Although these two sample participants' spatial biases were estimated to be similar to each other (A: 0.03° , B: -0.005°), the widths of their psychometric curves differed from each other. As a control analysis, we additionally excluded two participants for curve widths that were greater than three standard deviations from the mean. Even after excluding these additional outliers, the results from the linear regression model with grade as a log-transformed independent variable and spatial bias as the dependent variable remained consistent (see Results for more details). The lower panels compare average psychometric curves between the youngest group (Panel C; grades 1-3; $N = 147$) and the oldest group (Panel D; grades 6-8; $N = 120$) in children. In panels C and D, gray lines indicate individual participants' psychometric curves and the blue solid curve indicates the average from each group.

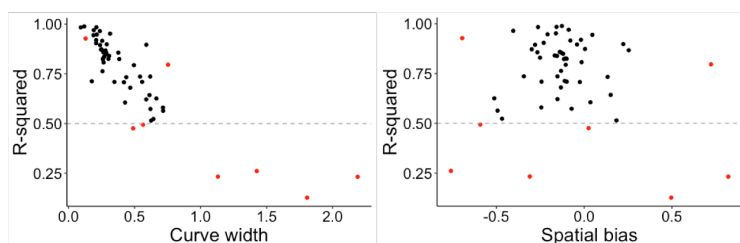


Supplementary Figure 4.2. Residuals for the model estimate for each grade. From the linear regression model with a log-transformed independent variable (log-transformed grade vs. spatial bias), we obtained the residuals from the model estimate for each grade. The x-axis shows the regression model's estimated biases (indicated by black solid line in Figure 4.5), and the y-axis shows residuals for individual participants' actual biases versus the model's estimated biases for their grade. As the model's estimates gradually became closer to zero from grade 1 to grade 8, the clustered data points indicate data points for each grade level; Panel A shows grade 1 on the left (x-value = -0.26) to grade 8 on the right (x-value = -0.055). Residuals for early grades (especially grades 1,2, and 3) were not greater than for older grades. In Panel B, five data points with the most extreme residual values are excluded such that the residuals are normally distributed. The model remains significant after this exclusion. This indicates that the larger variance among younger children did not drive more negative model estimates.

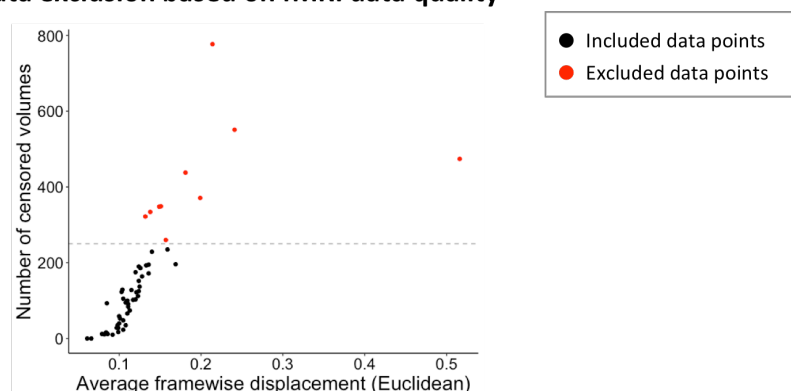
A. Re-analysis of data on the reliability of spatial bias estimation



B. Data exclusion based on spatial bias estimation



C. Data exclusion based on fMRI data quality



Supplementary Figure 4.3. Data exclusion criteria (Parts II and III). In order to ensure the reliability of spatial bias estimation, we re-analyzed data from Part I to establish data exclusion criteria based on three quality measures: the R-squared of each fitted curve, curve width (as examined in Supplementary Figure 4.1), and the absolute difference in estimated spatial bias between the first and second halves of data for each participant (Panel A). In Part II (Panel B), we excluded when the R-squared value of the psychometric curve was below 0.5 because the curve width and absolute difference measures diverged greatly below the R-squared of 0.5, indicating less reliability in bias estimations for those participants. Two additional participants were excluded for their bias measures exceeding three standard deviations from the group mean, leading to the exclusion of 8 participants in total. We also excluded participants with poor MRI data quality (Panel C). We used the number of censored volumes as a criterion because it reflects both head motion and other factors leading to signal outliers. A total of 10 children were excluded for having less than 70% of the fMRI data (7.8 minutes of data) available after censoring were excluded.

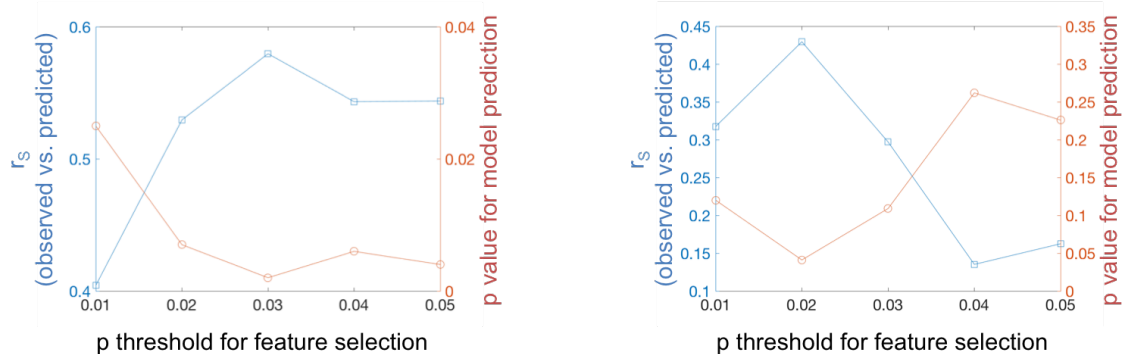
Supplementary Table 4.1. Size of regions of interest (ROIs)

Fronto-parietal areas based on probabilistic atlas		
Area of Interest	P Threshold*	Number of Voxels (MNI152; 2-mm isotropic voxels)
FEF	40%	LH: 154 RH: 109
IPS0	40%	LH: 264 RH: 235
IPS1	25%	LH: 200 RH: 181
IPS2	20% (LH) 15% (RH)	LH: 164 RH: 206
IPS3	15%	LH: 157 RH: 158
IPS4	15%	LH: 99 RH: 163
IPS5	18%	LH: 78 RH: 68
SPL1	20%	LH: 99 RH: 112
Schaefer 400-node parcellation and 7-network definition		
Network Label (Yeo et al., 2011)	Number of Parcels (Range of Parcel Size)**	
Visual	LH: 31 RH: 30	
Somatomotor	LH: 37 RH: 40	
Dorsal Attention	LH: 23 (115-612 voxels) RH: 23 (137-738 voxels)	
Salience/Ventral Attention	LH: 22 (137-629 voxels) RH: 25 (152-647 voxels)	
Limbic	LH: 13 RH: 13	
Control	LH: 22 (125-732 voxels) RH: 30 (131-898 voxels)	
Default Mode	LH: 52 (89-816 voxels) RH: 39 (56-654 voxels)	
Total	LH: 200 RH: 200	

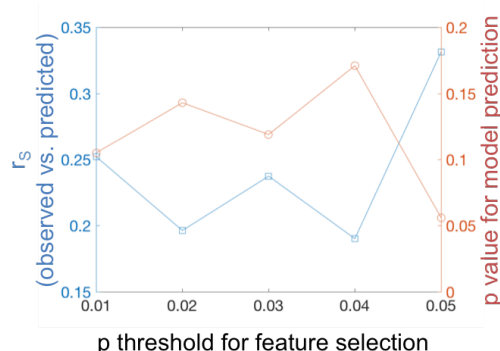
* Thresholds were kept the same between the left and right hemispheres unless noted.

** The number of 2 mm isotropic voxels in each parcel was counted in the MNI152 volume.

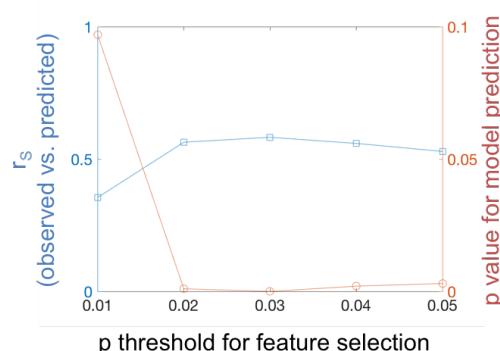
A. Fronto-parietal model predicting spatial bias **B. DAN model predicting spatial bias**



C. Fronto-parietal model predicting RAN



D. DAN model predicting RAN



Supplementary Figure 4.4. Prediction performance under different p thresholds for model feature selection. We chose a p threshold for feature selection in order to find the best possible predictive model for a given set of nodes and behavioral measure. We first generated predictive models using five different p thresholds (0.01, 0.02, 0.03, 0.04, 0.05). Based on the p threshold, the predictive model included varying numbers of features (i.e., edges). Among those five models generated using five different thresholds, one model with the best prediction performance was selected, as indicated by the highest r_s value (blue curve) and lowest p value (red curve). Displayed is the performance of each model at different feature selection thresholds, generated from the fronto-parietal areas (16 topographic areas defined by probabilistic atlas; Wang et al., 2015) and the Dorsal Attention Network (DAN) nodes (based on the 400-node parcellation; Schaefer et al., 2018) predicting spatial bias or reading fluency (Rapid Automated Naming scores; RAN). In the main manuscript, the feature selection threshold of $p < 0.03$ was used for the fronto-parietal model predicting spatial bias (panel A), $p < 0.02$ predicting the DAN model predicting spatial bias (panel B), $p < 0.05$ for the fronto-parietal model predicting RAN score (panel C), and $p < 0.03$ for the DAN model predicting RAN score (panel D).