Preservation and plasticity in the neural basis of numerical thinking in blindness

by

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Abstract

Numerical reasoning pervades modern human culture and depends on a fronto-parietal network, a key node of which is the intraparietal sulcus (IPS). In this dissertation I investigate how visual experience shapes the cognitive and neural basis of numerical thinking by studying numerical cognition in congenitally blind individuals.

In Chapter 2, I ask how the cognitive basis of numerical thinking is shaped by visual experience. I test whether the precision of approximate number representations develops normally in the absence of vision and test whether the relationship between numerical approximation and math abilities is preserved in congenital blindness.

In Chapter 3, I ask how the neural basis of symbolic number reasoning is modified by visual experience by studying neural responses to symbolic math in congenitally blind individuals. This initial investigation revealed that the fronto-parietal number system is preserved in blindness but that some “visual” cortices are recruited for symbolic number processing in blindness. The following chapters unpack these two patterns preservation and plasticity.

In Chapter 4, I use resting-state data to ask whether functional connectivity with higher-cognitive networks is a potential mechanism by which “visual” cortices are reorganized in blindness. In Chapter 5, I work with individuals who became blind as adults to determine whether visual cortex plasticity for numerical functions is possible in the adult cortex or whether it is restricted to sensitive periods in development.

In Chapter 6, I investigated whether the IPS and newly identified number-responsive "visual" area of congenitally blind individuals possess population codes that distinguish between different quantities.

I find that the behavioral signatures of numerical reasoning are indistinguishable across congenitally blind and sighted groups and that the fronto-parietal number network, in particular the IPS, is preserved in the absence of vision. A dorsal occipital region showed the same functional profile as the IPS number system in congenitally blind individuals. Number-related plasticity was restricted to a sensitive period in development as it was not observed in adult-onset blind individuals. Furthermore, in congenital blindness, sub-specialization of the "visual" cortex for math and language processing followed the functional connectivity patterns of "visual" cortex.

Keywords: numerical reasoning, approximate number, symbolic math, blindness, cross-modal, plasticity, intraparietal sulcus, resting-state functional connectivity, sensitive period.

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Chapter 1

Introduction

1.1 Relationship between non-symbolic and symbolic representations of number

Humans can think about number in two distinct ways. One way uses number symbols (words or digits) to determine the precise numerosity of sets. We can perform exact computations over these number symbols, as when calculating the quotient of a long division problem, or a number's cubed root. This form of numerical thinking is uniquely human and depends on language, emerging slowly over the course of several years as children learn the meanings of number words, and continuing to be modified through mathematical education (Wynn, 1990; Dehaene et al., 1999; Pica et al., 2004). Another form of numerical thinking relies on a non-verbal system that allows observers to represent quantities only approximately, such as when estimating the rough number of apples on a tree or birds in a flock. The capacity to approximate number does not require formal schooling or linguistic experience; even newborn infants can match approximate numbers of images to approximate numbers of sounds (Izard et al., 2009), and numerical approximation abilities have been identified in various non-human animals including monkeys, birds, rodents, and fish (Meck and Church, 1983; Agrillo et al., 2008; Brannon and Merritt, 2011; Viswanathan and Nieder, 2013). Unlike the representations of the exact, symbolic number system, those of the Approximate Number System (ANS) are inherently imprecise. Without language to enable exact counting, it is not possible to determine whether there are exactly 16 or 17 people in a room, for example. Instead, a given magnitude is represented by a distribution of neural activity that is centered upon the true magnitude but is also characterized by some amount of variance (Feigenson et al., 2004). Thus, a set of 16 may sometimes be mistaken for 15 or 17 items. Furthermore, as quantities become more different, they exhibit less representational overlap and are therefore easier to discriminate.

Additionally, the variance in approximate number representations has been hypothesized to increase linearly with distribution means—a feature of the approximate number system termed scalar variability (Gallistel and Gelman, 1992; Whalen et al., 1999). This property predicts that a pair of smaller magnitudes, such as 8 and 12, will be more discriminable than a pair of larger magnitudes that are equally numerically distant, such as 30 and 34, because smaller magnitudes are characterized by less variability and thus exhibit less representational overlap than an equally distant pair of larger magnitudes (Gallistel and Gelman, 1992; Whalen et al., 1999). Instead, because variability scales with numerosity means, two pairs of magnitudes will be equally discriminable if the ratio between them is the same (e.g. 8 vs. 12 and 30 vs. 45). Thus, the discriminability of two quantities depends specifically upon the ratio and not the absolute magnitude difference between them (Gallistel and Gelman, 1992; Whalen et al., 1999). This feature gives rise to the approximate number system's key ratio-dependent signature (Gallistel and Gelman, 1992; Whalen et al., 1999).

It is also important to note that numerosity can be estimated apart from other magnitudes. In the natural environment, magnitudes such as cumulative area and density tend to co-vary with quantity. Although individuals utilize these correlated features when discriminating between quantities, we can reliably discriminate quantities when these features are uncorrelated with number (Dewind and Brannon 2012; Gebuis and Reynvoet 2012). Furthermore, infants are better at detecting changes in numerosity than changes in area. Infants prefer to look at streams of images that alternate between two quantities (that differ by at 1:3 ratio) while holding area constant than a concurrently presented stream of images alternating between two more distant areas (1:5 ratio) while number is held constant (Libertus et al., 2014). Infants even demonstrate similar interest in a threefold change in number and a tenfold change in area (Libertus et al., 2014). These results suggest that representations of numerosity are at least partially independent from those of area and that numerical approximation is not entirely dependent on area estimation (Libertus et al., 2014; Szkudlarek et al., 2017).

Despite the differences between the systems for representing symbolic and approximate number, symbolic number reasoning is thought to be rooted in the ANS, such that approximate number representations play a role even during symbolic math computation (e.g., Dehaene, Dupoux, & Mehler, 1990). Consistent with this idea, individual differences in the ability to approximate the number of items in an array without counting predicts performance on standardized math tests such as the Suite of Assessments (SAT) and the Woodcock-Johnson Test of Achievement (Bonny & Lourenco, 2013; Halberda, Mazzocco, & Feigenson, 2008; Libertus, Feigenson, & Halberda, 2011; Libertus, Odic, & Halberda, 2012; Lourenco, Bonny, Fernandez, & Rao, 2012; Wang, Halberda, & Feigenson, 2017; for review see Chen & Li, 2014; Feigenson, Libertus, & Halberda, 2013). The precision of approximate number representations is even predictive of future number knowledge--the precision with which 6-month-old infants discriminate visual quantities predicts their ability to acquire number words at age three (Starr et al., 2013). Even short-term training with quantity discrimination leads to improvements in the precision of approximate number representations that transfer to enhancements in math performance (Park and Brannon, 2013; Hyde et al., 2014; Wang et al., 2016).

Symbolic and approximate number reasoning also share similar neural substrates. Reasoning about both approximate and exact number depends on a fronto-parietal network, a key node of which is the intraparietal sulcus (IPS) (Dehaene, 1999; Menon et al., 2000; Zago et al., 2001; Dehaene et al., 2003; Lemer et al., 2003; Venkatraman et al., 2005; Piazza et al., 2007a; Prado et al., 2011). Parts of the IPS are more active when participants solve math problems than when they passively read sentences or symbolic numbers (Zago et al., 2001; Piazza et al., 2007a). In addition, bilateral IPS are preferentially recruited when participants process the meaning of mathematical stimuli compared to matched non-mathematical, linguistic stimuli (Amalric and Dehaene, 2016; Liu et al., 2017a). These IPS regions are more active when participants process meaningful compared to meaningless math statements and when participants perform computations over numerical magnitudes than when reasoning about abstract arithmetic principles (Amalric and Dehaene, 2016; Liu et al., 2017a). Activity in the IPS also increases with the number of operands in subtraction and multiplication problems (e.g. 1+2=3 vs. 6-2+5=8) (Menon et al., 2000; Zago et al., 2001).

Parts of the IPS that are localized with math calculation tasks are also active during numerical magnitude estimation (Piazza et al., 2007a; Prado et al., 2011). During numerical discrimination tasks, in which participants must select the larger of two sets of items, activity in the IPS of both adults and children is modulated by the difference between numerosities, showing more activity for more numerically similar sets than numerically distant sets (Ansari et al., 2006; Kucian et al., 2011). However, IPS responses during numerical approximation tend to be more right-lateralized relative to exact and symbolic number tasks, which tend to recruit more left-lateralized circuits, presumably due to interactions with language networks (Pesenti et al., 2000; Andres et al., 2005; Piazza et al., 2006; Pinel and Dehaene, 2010; Bugden et al., 2012).

Furthermore, the IPS shows sensitivity to the actual quantity of items in a set. For example, numerical magnitudes, such as sets of 4, 8, 16 or 32 objects, evoke different spatial patterns of activity in the IPS of sighted individuals (Eger et al., 2009; Harvey et al., 2013; Lyons et al., 2014; Bluthe et al., 2015; Cavdaroglu et al., 2015; Harvey and Dumoulin, 2017). After training with these different activity patterns, machine learning classifiers can actually predict which quantity the participant saw just based on neural patterns in the IPS (Eger et al., 2009). Furthermore, neural representations in the IPS exhibit more overlap for more similar quantities (e.g. 4 vs. 8) than more distant quantities (e.g. 4 vs. 16), as predicted by behavioral signatures of the ANS (Eger et al., 2009).

Consistent with these findings, repeated presentations of visual sets of the same quantity cause neural adaptation in the IPS with ratio-dependent recovery in activity in response to deviant quantities (Piazza et al., 2004, 2007b). This finding further suggests that the IPS develops population codes for representing approximate quantities. An especially compelling piece of evidence for this idea comes from the discovery of neurons in the IPS of monkeys that are tuned to specific quantities, even in the absence of training (Nieder et al., 2002, 2006, Nieder, 2005, 2012; Viswanathan and Nieder, 2013). These neurons exhibit the most activity in response to their preferred quantity (e.g. 4 items) and show monotonically decreasing activity for more distant quantities (e.g. less activity for 3 items and even less for 2 items) (Nieder et al., 2002, 2006, Nieder, 2005, 2012; Viswanathan and Nieder, 2013).

Finally, there is evidence that the IPS is functionally relevant for numerical thinking. Temporary deactivation of the IPS with transcranial magnetic stimulation (TMS) impairs performance on both approximate and symbolic number tasks (Cappelletti et al., 2007; Dormal et al., 2008, 2012; Sandrini and Rusconi, 2009; Andres et al., 2011; Montefinese et al., 2017). For example, participants were slower to judge whether the magnitude of a symbolic number or visual quantity was greater than or less than 65 after TMS was applied to the left IPS (Cappelletti et al., 2007). Together these data suggest that the IPS supports both non-symbolic and symbolic numerical reasoning.

1.2 Links between numerical processing and vision

The above evidence suggests that representations of symbolic and approximate number develop in the IPS but little is known about the developmental origins of the IPS number system. How does the IPS come to be involved in numerical processing in the first place? IPS activity during numerical processing is seen in children as young as 4-years-old, but these children have had years of experience with numerical information, both experience with estimating the number of items in sets and experience with number words (Cantlon et al., 2006). How does the nature of very early experience affect the development of number representations in the IPS? In the upcoming studies, I investigate this question by probing the development of numerical representations following atypical sensory experience. Specifically, I investigated the role of visual experience in the development of numerical representations by working with individuals who are blind from birth.

Blindness is an interesting test-case for studying the development of numerical cognition because vision is an important source of numerical information. Vision permits hundreds of items to be estimated in parallel within just seconds (Dakin et al., 2011; Anobile et al., 2014). By contrast, humans are limited in the number of tactile and auditory items they can simultaneously individuate in space. For example, participants cannot accurately enumerate more than 5 simultaneous tactile stimuli on the body (Ferrand et al., 2010).

Thus, one possibility is that vision plays a foundational role in the developmental of approximate number representations because it is able to provide an enhanced experience with numerical information that is absent in other modalities. If IPS representations of number develop as a result of accumulated experience with seeing sets of items, the neural basis of numerical thinking may be affected by blindness.

Some evidence for role of vision in the development of the number system comes from studies finding behavioral links between non-symbolic numerical processing abilities and visual abilities in sighted individuals (Tibber et al., 2013; Zhou et al., 2015). Individuals who are more precise at approximating numbers of items in a set are also better at estimating the cumulative area of objects in an array and visually matching objects based on shape (Lourenco et al., 2012; Zhou et al., 2015; but see Odic et al., 2013).

In addition, although representations of quantity and area do not entirely overlap, as discussed earlier, the visual dimensions of a stimulus can affect numerosity perception. For example, individuals are slower to select the greater of two symbolic numbers if the luminance of the numerals is incongruent with the numerical magnitude of the numerals (e.g. bright 2 vs. dim 4) (Kadosh et al., 2008). Similarly, other studies find that physical size interferes with numerical magnitude judgments (Kaufmann et al., 2005). These findings suggest that representations of irrelevant visual features are automatically activated when individuals make numerical judgments, possibly pointing to shared underlying representations (Kaufmann et al., 2005; Kadosh et al., 2008). Individuals also perform better on numerical approximation tasks when the more numerous array is greater in cumulative area or is visually denser (Fuhs & McNeil, 2013; Gebuis & Reynvoet, 2012a, 2012b; Gilmore, Attridge, & Inglis, 2011; Halberda & Feigenson, 2008; Rousselle, Palmers, & Noël, 2004; Soltész, Szücs, & Szücs, 2010).

Moreover, some researchers have suggested that visual numerical approximation is, itself, a form of visual perception (Burr and Ross, 2008; Ross and Burr, 2010). Like other primary visual features, including color and contrast, numerosity is susceptible to adaptation--exposure to a large quantity of dots causes a subsequent quantity to be perceived as less numerous than its true quantity, suggesting that numerosity is a visual feature that is extracted early in processing (Burr and Ross, 2008; Ross and Burr, 2010). Numerosity judgments are also influenced by the visuo-spatial frequency of arrays, suggesting that numerical estimation may tap a form of visual texture perception (Dakin et al., 2011; Morgan et al., 2014).

Symbolic number reasoning, too, is linked to various forms of visual perception. Individuals who are better at math are also better at sustaining attention in an object tracking task (Anobile et al., 2013), have better visual working memory (De Smedt et al., 2009; Le Fevre et al., 2010; Bull et al., 2011), and are better at visuo-spatial mental rotation (Reuhkala, 2001), visual movement perception (Sigmundsson et al., 2010), and basic visual perception tasks including discriminating the orientation of lines, comparing objects' shapes, and comparing visual area across arrays (Lourenco et al., 2012; Tibber et al., 2013; Zhou et al., 2015).

Neural evidence is also consistent with the idea that number and visuo-spatial representations are linked. Overlapping regions in the IPS are recruited both during visual numerical estimation and when participants make judgments about other visual magnitudes, such as luminance and physical size (Cohen Kadosh et al., 2005; Kaufmann et al., 2005, 2006). Intracranial recordings from the IPS of monkeys reveals that representations of numerosity and length overlap at the level of individual neurons, with some IPS neurons encoding both features (Tudusciuc and Nieder, 2007, 2009). Furthermore, the IPS is located along the dorsal visual stream, raising the possibility that vision plays a foundational role in the initial development of the ANS (Dehaene & Changeux, 1993; Piazza & Eger, 2016; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Roggeman, Santens, Fias, & Verguts, 2011; Uddin et al., 2010). Consistent with this idea, computational modeling shows that neural networks spontaneously construct representations of numerosity following accumulated experience with simple visual sets (Stoianov and Zorzi, 2012).

The links between visual processing and representations of number suggest that visual experience with object sets may play a critical role in the development of representations of number in the IPS. Furthermore, vision provides a unique experience with numerical information that may not be able to be effectively substituted by input from other modalities. If this is true, there is a strong possibility that the neural and behavioral signatures of numerical processing will be affected by blindness from birth (i.e. congenital blindness).

By contrast, if representations of number develop independently of visual experience, perhaps due to evolutionary precursors in the IPS, the IPS number system may be preserved in congenital blindness. This alternative is supported by some findings that, in sighted adults, the neurobiological underpinnings of numerical thinking are similar across sensory modalities and input formats. The IPS is active not only when adults estimate the quantity of visual objects but also when they estimate the number of of tones in a sequence or view number symbols (Eger et al., 2003; Venkatraman et al., 2005; Piazza et al., 2006, 2007a; Prado et al., 2011). Furthermore, some neurons in the IPS of monkeys are tuned to specific numerosities across visual and auditory modalities (Nieder, 2012). The ability to compare quantities across modalities is present very early in development (Kobayashi et al., 2005; Izard et al., 2009). Just hours after birth, newborn infants are able to match small numbers of images to numbers of sounds (Izard et al., 2009). Together, these findings raise the possibility that representations of number in the IPS are not exclusively visual, even very early in development.

In the next section, I raise specific questions regarding how the absence of vision in congenital blindness might affect the development of numerical representations and how these potential outcomes would speak to the developmental origins of the IPS number system.

1.3 Open questions regarding role of visual experience in development of number system

The data discussed in Chapter 1.2 raise several open questions regarding the role of visual experience in the development of the cognitive and neural basis of numerical thinking.

First, given the unique experiences that vision is able to offer with respect to numerical information relative to other modalities, one question is whether vision is necessary for tuning representations of approximate number. In sighted populations, the precision of approximate number representations increases markedly over development. For example, whereas sighted infants require a 1:2 or 2:3 ratio between arrays in order to successfully discriminate numerosities, children and adults can make more fine-grained discriminations between smaller ratios (Xu and Spelke, 2000; Lipton and Spelke, 2003; Halberda and Feigenson, 2008; Izard et al., 2009; Halberda et al., 2012). Improvement is observed even before educational experience and before the emergence of linguistic competence (Halberda & Feigenson, 2008; Libertus & Brannon, 2009; Libertus & Brannon, 2010; Lipton & Spelke, 2003; Odic et al., 2013).

These early developmental increases in the precision of approximate number representations might be partly driven by visual experience with quantities. If so, we would expect the precision of approximate number representations to be affected in congenitally blindness and would predict that congenitally blind individuals will perform worse than sighted individuals on numerical estimation tasks.

Second, in Chapter 1.2 I discuss findings that suggest that representations of approximate number and symbolic math abilities are both strongly linked to visual abilities. These findings have raised the hypothesis that the observed correlations between numerical approximation performance and symbolic math abilities are mediated by a shared dependence on visual-spatial processing (Tibber et al., 2013). If so, the relationship between numerical approximation and math performance may not be preserved in congenitally blind individuals, for whom neither approximate nor symbolic number representations are rooted in vision.

In Chapter 2, I investigate the behavioral signatures of numerical cognition in congenital blindness. I ask whether vision plays an important role in tuning approximate number representations by comparing the precision of these representations across congenitally blind and sighted groups. I also ask whether the relationship between the precision of approximate number representations and symbolic math abilities is preserved in congenitally blind individuals.

In the subsequent chapters, I study how visual experience modifies the neural basis of numerical cognition. Even if congenitally blind individuals demonstrate the same behavioral signatures on numerical tasks as sighted individuals, it is possible that their behavior is supported by different neural mechanisms. As discussed in Chapter 1.2, representations of approximate number may develop in the IPS because the IPS receives visual input that is rich in numerical information, by virtue of its neuroanatomical location in the dorsal visual stream. One question this hypothesis raises is whether the IPS develops similar numerical representations in individuals who have never experienced numerical information visually.

I first test this hypothesis in Chapter 3 by asking whether fronto-parietal responses to symbolic math are preserved in congenital blindness. Specifically, I ask whether the IPS develops similar sensitivity to mathematical difficulty in the absence of vision. In Chapter 6, I further investigate whether the IPS develops a spatial code for auditory approximate quantities in congenitally blind individuals, as has been previously shown for visual quantities in the IPS of sighted individuals (Piazza et al., 2004, 2007a; Eger et al., 2009). Furthermore, I test whether, across congenitally blind and sighted individuals, the IPS similarly codes for auditory quantities in a ratio-dependent format, with more neural overlap for quantities that differ by a smaller ratio.

Finally, the absence of vision could modify the neural basis of numerical thinking by incorporating deafferented visual cortices into the fronto-parietal number network in congenital blindness. I will discuss this possibility in more detail in the next section.

1.4 Higher-cognitive repurposing of visual cortices in congenital blindness

1.4.1 The "metamodal" view of visual cortex plasticity

Apart from addressing questions about the role of vision in the development of numerical representations, studying the neural basis of numerical thinking in blindness also provides an opportunity to investigate theories of plasticity and brain development.

Studies of blindness have long been a test-case for understanding the mechanisms of functional organization and re-organization in the human brain. In typical development, structure and function are tightly linked across individuals. For example, in sighted individuals, the functional organization of category-selective ventral visual cortices, such as face- and place-selective regions, aligns with cytoarchitectonic divisions at the cellular level (Van Essen et al., 1992; Lorenz et al., 2015; Gomez et al., 2017; Weiner et al., 2017). The intrinsic anatomical connectivity of the brain also predicts the localization of cortical functions even at the level of individual subjects (Saygin et al., 2011, 2016; Osher et al., 2016).

Studies of blindness suggest, however, that this tight structure to function link can be altered by early experience. In blindness, "visual" areas of the occipital cortex respond to auditory and tactile stimuli, a phenomenon termed cross-modal plasticity (Kujala et al., 1995; Sadato et al., 1996; Bavelier and Neville, 2002). One of the earliest studies on this phenomenon used positron emission tomography (PET) to show greater activation in primary visual cortices during Braille reading and non-Braille tactile discrimination compared to rest in early-blind individuals but not sighted control participants (Sadato et al., 1996). Studies have also shown responses to auditory stimuli, such as pure tones, in the visual cortex of congenitally blind individuals (Kujala et al., 1995; Watkins et al., 2013).

Although "visual" cortices become responsive to input from non-visual modalities, some instances of visual cortex plasticity in blindness point to the idea that the link between structure and function is maintained even in cases of cross-modal plasticity (Pascual-Leone and Hamilton, 2001; Amedi et al., 2002; Poirier et al., 2005, 2006, Renier et al., 2010, 2013; Reich et al., 2011; Striem-Amit et al., 2012; Collignon et al., 2013a; Abboud et al., 2015). For example, area MT/MST processes visual motion in sighted individuals and auditory and tactile motion in blindness (Poirier et al., 2005, 2006; Saenz et al., 2008; Bedny et al., 2010; Wolbers et al., 2011). The visual word form area (VWFA) is involved in processing the visual orthography of written language in sighted individuals and shows sensitivity to non-visual Braille reading in congenital blindness (Reich et al., 2011).

The large-scale organization of category-selective areas (e.g. face-, scene-, object- and body-selective regions) in ventral visual cortex is also thought to be preserved in congenital blindness (Amedi et al., 2007, 2010; Reich et al., 2011; Abboud et al., 2015; van den Hurk et al., 2017). Typically in sighted individuals, regions of ventral visual cortex become specialized for visual recognition of specific object categories such as faces, places and objects (Malach et al., 1995; Kanwisher et al., 1997; Epstein and Kanwisher, 1998; Grill-Spector et al., 1999, 2001; Downing et al., 2001; Kanwisher and Yovel, 2006). Furthermore, the organization of these category-selective regions within the ventral visual stream is highly consistent across sighted individuals (Malach et al., 2002; Hasson et al., 2003).

Surprisingly, although congenitally blind individuals do not engage in visual object recognition, they appear to develop category-selective regions in the ventral visual cortex with very similar functional profiles and topographical layout as sighted individuals (van den Hurk et al., 2017). For example, the "FFA" is more active when congenitally blind individuals listen to sounds that faces make (e.g. laughing and chewing) than when listening to sounds made by body parts (e.g. clapping), objects (e.g. washing machine) or scenes (e.g. train station) (van den Hurk et al., 2017). These findings suggest that cortical areas have intrinsic cognitive functions that may be preserved even in the absence of vision.

One interpretation of these findings is that cortical areas have intrinsic computational functions that are fixed. Furthermore, some argue that these intrinsic computations are “metamodal” in nature and can therefore operate over input from any modality (Pascual-Leone and Hamilton, 2001; Lomber, 2017). In sighted individuals, visual regions primarily operate over visual information because they receive overwhelming amounts of bottom-up visual input. However, this view predicts that in blindness “visual” areas will preserve their metamodal functions but simply perform these functions over non-visual input (e.g. visual motion responsive MT/MST becomes responsive to auditory and tactile motion). Thus, according to the “metamodal” view of plasticity, even cross-modal plasticity is narrowly constrained by the intrinsic cognitive predispositions of cortex. That is, experience is capable of changing the dominant sensory modality of input (e.g. from vision to touch and sound), but not the underlying cognitive operations of cortex (Pascual-Leone and Hamilton, 2001; Lomber, 2017).

1.4.2 The “pluripotent” view of visual cortex plasticity

One piece of evidence that appears to contradict the “metamodal” hypothesis comes from studies of the neural basis of language processing in blindness. A number of studies suggest that, in blindness, parts of the visual cortex are recruited for language processing (Röder et al., 2002; Bedny et al., 2011; Lane et al., 2015; Kim et al., 2017). For example, Braille reading elicits stronger responses in early visual areas than non-Braille tactile discrimination (Sadato et al., 1996). Primary visual cortex, V1, is recruited during verbal memory processing in blind individuals and exhibits greater activity in blind individuals with better memory performance (Amedi et al., 2003; Raz et al., 2005). There is evidence that, in blind individuals, “visual” cortex activity during verbal tasks is functionally relevant: temporarily disrupting activity in some visual areas using transcranial magnetic stimulation (TMS) causes impairments in verb generation and Braille reading in blind individuals (Cohen et al., 1999; Amedi et al., 2004).

Recent evidence further suggests that language-responsive visual cortices are sensitive to high-level linguistic information. Specifically, parts of the “visual” cortex respond to the meanings of words and the grammatical structure of spoken sentences (Röder et al., 2002; Bedny et al., 2011; Lane et al., 2015; Kim et al., 2017). For example, the lateral occipital cortex of congenitally blind individuals shows a preference for semantic information even in the absence of syntactic structure, showing greater responses to lists of words than lists of nonwords (Bedny et al., 2011). Furthermore, language-responsive lateral occipital cortex is sensitive to the presence of syntax in a linguistic stimulus, responding more to sentences and jabberwocky (sentences in which content words are switched with non-words) than lists of words (Bedny et al., 2011). Language-responsive lateral occipital and ventral occipito-temporal cortices also show greater responses to sentences with a more complex syntactic structure than sentences with a simpler syntactic structure (Lane et al., 2015; Kim et al., 2017).

These findings suggest that the human cortex may be more functionally flexible than previously recognized, i.e. capable of assuming functions as distinct as vision and language. One interpretation of these findings is that cortical areas are functionally pluripotent at birth and their cognitive function is heavily influenced by the input that they receive from other cortical systems during early development. This input, itself, is jointly determined by the anatomical connectivity of the receiving cortical area (i.e. where it gets input from), the functional capacities of the "sending" cortical systems and, crucially, by early experience (Bedny, 2017).

This "pluripotency" hypothesis makes specific predictions about visual cortex reorganization in congenital blindness. Rather than preserving elements of their original "visual" functions, deafferented occipital areas should assume the functions of those cortical regions that are most strongly connected to them. Given that visual cortices receive a lot of top-down feedback from fronto-parietal networks, the "pluripotency" framework predicts that "visual" cortices will assume higher-cognitive functions in the absence of vision, rather than sensory functions that are analogous to the "typical" operations of visual cortices.

In sighted individuals, the lateral geniculate (visual) nucleus of the thalamus is a strong source of input to the visual cortex. However, fronto-parietal and fronto-temporal networks also send a significant amount of top-down feedback to the visual cortex (Gilbert and Li, 2013; Muckli and Petro, 2013). For example, studies using diffusion tractography imaging (DTI) in humans and chemical tracers in animals find anatomical tracts connecting intraparietal regions with "visual" cortices (Blatt et al., 1990; Nakamura et al., 2001; Uddin et al., 2010a; Greenberg et al., 2012).

In sighted individuals, these fronto-parietal inputs exert top-down control over visual processing, for example by directing visual attention or modulating category selectivity (Kastner et al., 1999; Kastner and Ungerleider, 2003; Tong, 2003; Miller and D'Esposito, 2005; Ruff et al., 2008; Lauritzen et al., 2009; Muckli, 2010; Miller et al., 2011; Lee and D'Esposito, 2012; Bray et al., 2015). For instance, unilateral prefrontal cortex lesions in monkeys impairs their ability to switch between different visual cues in the affected hemifield but not in the contralesional hemifield (Rossi et al., 2007, 2009). Similarly, temporarily suppressing activity in a lateral intraparietal area affects the ability of monkeys to detect visual targets in the contralesional hemifield (Wardak et al., 2004). These findings provide further evidence for the existence of top-down feedback connections from fronto-parietal networks to visual cortices.

In the absence of bottom-up visual input from the LGN in blindness, “visual” cortices may become more functionally coupled with fronto-parietal networks via these top-down feedback connections, and could subsequently be repurposed for higher-cognitive functions. The evidence reviewed above regarding responses to linguistic information in “visual” cortices of blind individuals supports this hypothesis.

However, it remains possible that language-related visual cortex plasticity can still be accounted for under the metamodal view of cortical function. One proposition, for example, has been that high-level language functions do not directly invade the visual cortex of congenitally blind individuals, but that language builds upon plasticity for Braille processing (Bavelier and Neville, 2002). According to this hypothesis, parts of the visual cortex possess metamodal computations for discriminating features at a fine-grained spatial scale. In sighted individuals, these computations typically support visual processing and in blindness, these computations may transfer to Braille reading. Braille reading could subsequently provide a gateway for more high-level language functions to develop in the visual cortex. Thus, even plasticity for language may reflect a preservation of the intrinsic functions of the visual cortex. Furthermore, the higher-cognitive takeover hypothesis was proposed as an explanation for language-related plasticity in the visual cortex of congenitally blind individuals. Can this hypothesis predict new, as yet unobserved, patterns of plasticity in visual cortex? Studies of the neural basis of numerical cognition in blind individuals provide an opportunity to answer this question.

The fronto-parietal number network is a strong candidate for invading the visual cortex of blind individuals. As noted above, in sighted individuals, the visual system is strongly modulated by inputs from fronto-parietal cortices in general, as well as intraparietal regions in particular (Kastner et al., 1999; Tong, 2003; Kastner and Ungerleider, 2003; Miller and D'Esposito, 2005; Ruff et al., 2008; Lauritzen et al., 2009; Muckli, 2010; Miller et al., 2011; Greenberg et al., 2012; Lee and D'Esposito, 2012; Bray et al., 2013, 2015; Muckli and Petro, 2013; Vinette and Bray, 2015). In this dissertation, I test the hypothesis that, in congenital blindness, the fronto-parietal number system recruits parts of the "visual" cortex for numerical processing.

In addition to being well positioned for functionally repurposing visual cortices with respect to connectivity, numerical processing is a good test-case for investigating visual cortex plasticity for higher-cognitive functions because it is functionally and anatomically distinct from language processing. As noted in Section 1.1, previous studies have found distinct neural correlates for numerical and linguistic processing, even when symbolic math stimuli are closely matched to linguistic stimuli (Monti et al., 2012; Amalric and Dehaene, 2016; Liu et al., 2017a). Therefore, if we identify responses to number in visual cortex, these could be distinguished from responses to language. Furthermore, I can then test the hypothesis that "visual" cortices of blind individuals show sub-specialization for different higher-cognitive functions i.e. language and number.

In Chapter 3, I first investigate whether the “visual” cortices of blind individuals are recruited during symbolic number processing and whether visual cortex responses to number are anatomically and functionally distinct from responses to language. To foreshadow, I find that, indeed, parts of dorsal occipital cortex are recruited for symbolic number processing in blindness. Furthermore, I find that language and number tasks recruit different portions of the “visual” cortex in blindness.

In Chapter 4, I more directly test the hypothesis that functional repurposing of visual cortex in blindness is related to connectivity with fronto-parietal networks. I do this by asking whether math- and language-responsive “visual” regions show dissociable patterns of functional connectivity with canonical math- and language fronto-parietal networks. Previous studies have shown that resting-state correlations between “visual” cortex and fronto-parietal networks increase in congenital blindness (Liu et al., 2007, 2017b; Striem-Amit et al., 2012; Watkins et al., 2012; Wang et al., 2014; Deen et al., 2015; Hasson et al., 2016). For example, a number of studies find increased functional coupling between parts of the visual cortex and language networks at rest in congenital blindness (Bedny et al., 2011; Watkins et al., 2012; Striem-Amit et al., 2015). Furthermore, the “visual” region that becomes more synchronized with language networks at rest is the same region that develops sensitivity to semantics and grammar in congenital blindness (Bedny et al., 2011).

Do “visual” areas with different functional profiles (i.e. those responsive to number as opposed to language) also show dissociations in functional connectivity patterns? I test the prediction that number-responsive regions within the “visual” cortex will be preferential synchronized with the fronto-parietal number network, while language-responsive “visual” cortex will show functional connectivity with inferior frontal language regions.

One open question regarding the functional repurposing of visual cortices for higher-cognitive functions in blindness concerns the limits to this reorganization. Specifically, is the human cortex capable of such dramatic plasticity later in development or is this capacity circumscribed to a sensitive period in development? Studies of traumatic amputation find that amputation of the hand causes corresponding sensori-motor cortices to respond to stimulation of other body parts, such as the face, suggesting that the adult cortex can reorganize to some extent within a modality (Pascual-Leone et al., 1996). However, whether the adult cortex can support more dramatic functional changes remains to be tested. In Chapter 4, I investigate this question by asking whether visual cortices are recruited during numerical processing even in individuals who become blind as adults (adult-onset blind individuals).

Finally, as discussed in Chapter 1.1, representations of symbolic and non-symbolic number are co-localized to the IPS in sighted individuals. Thus, one critical question is whether representations of approximate number become co-localized with responses to symbolic math in the “visual” cortex of congenitally blind individuals as well. In Chapter 6, I ask whether the “visual” region that is recruited during symbolic math calculation in congenital blindness also develops a more fine-grained population code for approximate numerosity.

Chapter 2

Precision of approximate number system (ANS) and its link to the symbolic number system develop independent of visual experience

2.1 Introduction

In this Chapter, I begin to investigate whether visual experience plays a critical role in the development of numerical representations by asking if the behavioral signatures of the Approximate Number System (ANS) are preserved in the absence of vision. As noted in Chapter 1.1, the precision of approximate number representations improves over development (Libertus and Brannon, 2010; Odic et al., 2013). The sources of this developmental improvement remain largely unknown. Although math education has been shown to hone the preision of approximate number representations, improvements in numerical approximation are observed even between 6 and 9 months of age (Libertus and Brannon, 2010; Piazza et al., 2013).

One possibility is that accumulated experience with estimating visual sets tunes representations of approximate number. As noted in Chapter 1.2, vision is uniquely efficient at conveying large, parallel numerical quantities. Thus, early experiences with visual input that is rich in numerical information may play a role in honing the precision of approximate number representations. If the tuning of approximate number representations does depend on visual experience, we would expect the precision of approximate number representations to be compromised in congenitally blind individuals, who have never experienced numerical sets visually.

Alternatively, given that auditory and tactile estimation primarily occur sequentially, whereas visual estimation often occurs simultaneously, blind individuals might substantially outperform sighted individuals on sequential numerical approximation tasks with which they are putatively more practiced. Blind individuals have previously been shown to outperform sighted individuals on some auditory perception tasks (e.g., peripheral sound localization) (Lessard et al., 1998; Röder et al., 1999; Fieger et al., 2006). A parallel finding could be obtained for auditory numerical approximation if the ANS is not, in fact, a unitary cognitive system, but rather comprised of multiple modality-specific or format-specific (i.e., sequential vs. simultaneous) systems. In fact, there is some evidence that sequential and parallel quantity processing depend on partially non-overlapping neural substrates (Dormal, Andres, Dormal, & Pesenti, 2010; Nieder, Diester, & Tudusciuc, 2006). If sequential and simultaneous approximate number systems are independent, we might expect blind individuals to exhibit specific improvements in sequential auditory number estimation.

Here I measured the precision of approximate number representations by asking participants to discriminate auditory quantities that differ by varying ratios. I then fit a psychophysical model to participants' discrimination performance to obtain a Weber fraction, which characterizes the amount of noise in a participant's underlying approximate number representations.

Two previous studies have compared numerical approximation across blind and sighted participants (Castronovo and Seron, 2007; Castronovo and Delvenne, 2013). Contrary to the proposal that vision is required for ANS development, these studies found that blind individuals actually outperformed the sighted on sequential estimation tasks that involved producing a particular number of actions without counting (e.g., footsteps, key presses) or estimating the number of tones played in a sequence (Castronovo and Seron, 2007; Castronovo and Delvenne, 2013). One possible concern with these findings, however, is that participants in these studies may not have relied exclusively on the approximate number representations to perform the task. Although participants were instructed not to count, their near-perfect accuracy with very large target quantities suggests that they likely engaged resources beyond the approximate number system. For instance, blind individuals were potentially better able to rapidly verbally count numbers of items in these tasks relative to sighted individuals. Indeed, blind individuals outperform sighted on some verbal tasks (e.g., verbal working memory), suggesting the possibility that their enhanced performance may not reflect approximate number precision but rather use of alternative strategies (Amedi et al., 2003; Raz et al., 2007).

Therefore, in the current study I asked whether congenitally blind participants show similar ANS precision as sighted participants when counting is rigorously prevented.

A second goal of the current study involves understanding the nature of the relationship between the approximate number system and symbolic math abilities. In Chapter 1.1, I describe behavioral links between numerical approximation abilities and math performance. Individuals who demonstrate better precision on numerical approximation tasks also perform better on various assessments of math abilities (Halberda et al., 2008; Libertus et al., 2012; Feigenson et al., 2013). Precision of approximate number representations in infancy is even predictive of future number knowledge (Starr et al., 2013). However, the nature of the relationship between the ANS and symbolic math abilities has been a matter of recent debate. Given the links between visual perception and both symbolic math and numerical approximation, one open question concerns whether there a meaningful relationship between the approximate number system and math abilities. One possibility is that the link between the ANS and exact symbolic number is specific, potentially reflecting shared abstract number content (albeit in different representational formats). Alternatively, the relationship between these systems may be a byproduct of individual differences in visual processing abilities that independently predict both numerical approximation and math performance.

Evidence from congenitally blind individuals offers a unique opportunity to answer this question. Unlike sighted individuals, congenitally blind individuals have never experienced approximate numerical information through vision—therefore, vision could not "bootstrap" the relationship between the ANS and symbolic number processing during development. Thus, the second aim of this Chapter was to ask whether individual differences in ANS precision correlate with math performance among congenitally blind individuals who have never experienced number visually.

In this study, a group of congenitally blind participants and a group of sighted participants completed an auditory numerical approximation task and a timed symbolic math task using spoken numerals. In the approximate number task, participants judged which of two tone-sequences was more numerous. In the symbolic math task, participants completed as many subtraction problems as they could in four minutes and as many division problems as they could in another four minutes.

I first measured ANS precision in congenitally blind and sighted groups by using psychophysical modeling to determine the noise in participants' underlying approximate number representations. I then tested whether ANS precision was different across congenitally blind and sighted groups and tested whether this precision was predictive of symbolic math performance in both groups.

To determine the specificity of any observed relationship between ANS precision and symbolic math performance, I also tested participants on a series of control tasks. I administered a standardized test of math concepts that tests participants' knowledge of math facts. Previous work suggests that ANS precision does not relate to rote memory for mathematical information (for review see Chen & Li, 2014). I therefore predicted that knowledge of math facts would not correlate with ANS precision (Dehaene, Piazza, Pinel, & Cohen, 2003). I also tested participants' working memory, reading, and verbal knowledge; this allowed us to partial out the effect of these skills from the relationship between ANS precision and symbolic math performance.

2.2 Materials & Methods

2.2.1 Participants

Twenty-four congenitally blind and fifteen sighted participants contributed data. Sighted and blind groups were matched on average age and education (see Table 2.1). All blind participants had, at most, minimal light perception and reported never having seen shapes, color or motion. One additional blind participant was excluded after testing because further screening revealed non-congenital blindness. Three additional participants were tested but excluded from the final sample due to performance on the ANS task. One sighted participant was excluded because their performance on the ANS task was two standard deviations away from the sighted mean and was unusually poor relative to published samples of ANS performance in sighted participants (Halberda et al., 2012). Two blind participants were excluded because their ANS performance was poorly fit by the psychophysical model ($R2 \leq 0$).

Working memory data from one blind participant were not included because the participant confused the sounds of letter stimuli in the letter span task. One blind participant did not complete the analogies subtest of the oral vocabulary task. This participant's vocabulary score consisted of the mean of their synonym and antonym scores.

2.2.2 Auditory Approximate Number Discrimination Task

Blind and blind-folded sighted participants heard pairs of auditory tone sequences over headphones and indicated which sequence was more numerous by pressing one of two buttons on a response pad (blind) or computer keyboard (sighted controls). The second test sequence was smaller than the first on half of the trials (small test) and larger on the other half (large test). The number of tones in the first and second sequence differed by one of 5 ratios: 1.08, 1.15, 1.2, 1.44 or 2 (e.g., 20 vs. 40 is a ratio of 2, where ratio is the larger numerosity divided by smaller numerosity). Each of the 5 ratios was presented 16 times over the course of the experiment and was instantiated as 8 unique numerosity pairs, each of which occurred twice (all pairs shown in Table 2.2).

Table 2.1. Participant demographic information

Participant	**Age**	**Education**	**Cause of Vision Loss**
CB_01	23	Some College	LCA
CB_02	48	JD	LCA
CB_03	44	BA	ONH
CB_04	34	BA	ONH
CB_05	33	Some College	ROP
CB_06	29	MA	ROP
CB_07	43	Some College	ONH
CB_08	26	Some College	LON
CB_09	57	MA	CG
CB_10	26	BA	LCA
CB_11	30	Middle School	Unknown
CB_12	28	BA	AN
CB_13	43	High School	RB
CB_14	29	Some College	ONH
CB_15	32	BA	PCA
CB_16	39	BA	AN
CB_17	44	MA	SOD
CB_18	27	Some College	Aniridia
CB_19	42	BA	LCA
CB_20	27	PhD	MO
CB_21	44	JD	Unknown
CB_22	33	BA	ROP
CB_23	40	PhD	ROP
CB_24	25	MA	LCA
Group Average	**Age**	**Years of Education**	
Congenitally Blind	35	16.94	-
Sighted	37	17.60	-

AN=Anopthalmia; CG=Congenital Glaucoma; LCA=Liebers Congenital Amaurosis; MO=micro-opthalmia; ONH=Optic Nerve Hypoplasia; RB=Retinal Blastoma; ROP=Retinopathy of Prematurity; SOD=Septo-optic Dysphasia; BA=Bachelor of Arts; JD=Juris Doctor; MA=Master of Arts; PhD=Doctor of Philosophy

Table 2.2 Numerosity pairs in the auditory approximate number discrimination task

ratio	sample	small test	large test
1.08	14	13	15
	16	15	17
	18	17	18
	20	19	22
1.15	14	12	16
	16	14	18
	18	16	20
	20	18	23
1.2	14	11	17
	16	13	19
	18	15	22
	20	17	24
1.44	14	9	20
	16	11	23
	18	13	26
	20	14	29
2	14	7	28
	16	8	32
	18	9	36
	20	10	40

To prevent participants from relying on duration to make their responses, I controlled the total duration of sound presented within a given pair of tone sequences (i.e., the sums of individual tone durations). This is analogous to visual experiments that control the total area of presented dots. On half the trials the total duration of sound was congruent with respect to the ratio between the two numerosities (i.e., the more numerous sequence was longer) and on half the trials it was incongruent (i.e., the more numerous sequence was shorter). Thus relying on total sound duration to judge number would systematically yield the incorrect answer on half the trials.

Frequency was also not a reliable cue to numerosity, as inter-tone interval was randomly selected from geometric distribution (mean ISI=158.83 ms, min=100 ms, max=806 ms). Thus, participants could not use frequency (ISI) as a reliable cue to numerosity because they were not correlated. Note that controlling for total sound duration and ISI duration precluded us from also controlling for total sequence duration (i.e., total sound duration + total ISI duration). However, subsequent analyses showed that participants were reliably above chance at judging numerosity, even when numerosity was incongruent with total sequence duration (see Results).

While the average duration of tones and ISIs was controlled, the durations of individual tones and ISIs were jittered to preclude participants from counting. Both individual tone duration and the interval between tones varied randomly within and across trials. This procedure has been shown to effectively preclude participants from counting (see Cordes, Gallistel, Gelman, & Latham, 2007).

To further prevent counting, on each trial, participants verbally repeated a different two-letter sequence (e.g., “D-F”) during the presentation of the stimulus sequences. Previous work has found that similar verbal loads were successful in preventing participants from counting (Cordes et al., 2001).

To ensure that the two tone sequences were separately perceived, the first tone sequence always consisted of 400 Hz tones to the left ear and the second sequence always consisted of 500 Hz to the right ear. Each individual tone ramped up in volume, reached a plateau and then ramped down. Immediately after their response on every trial, participants heard auditory feedback to indicate whether their response was correct (“ding” sound) or incorrect (buzzer sound).

Participants pressed the space bar on a keyboard to begin each trial. Each trial began with a unique pair of spoken letters for participants to begin repeating (0.87-1.55

sec), followed by the first tone sequence (see above), a delay interval (2 sec), the second tone sequence (see above), a response period (3 sec), and a feedback tone (0.41-0.5 sec). Participants then waited the remainder of the 3-second response period before starting the next trial.

Trials on which a participant's response time was more than two standard deviations away from their own mean (across all ratios) were dropped from all analyses (blind: M=3.46 trials dropped, SD=1.47; sighted: M=4 trials dropped; SD=2).

2.2.3 Psychophysical modeling of performance on auditory ANS task

I assessed individual differences in the precision of participants' approximate number representations using Weber fractions. The Weber fraction (w) is a number greater than 0 that indexes the amount of noise in ANS representations for a given individual. Each participant's Weber fraction was determined using a least squares method to fit their accuracy (percent correct across trials) across ratios with a curve generated by the model shown below (Halberda et al., 2008; Libertus et al., 2012; Odic et al., 2013; Pica et al., 2004).

$$\frac{1}{2} erfc\left(\frac{n_1 - n_2}{\sqrt{2w}\sqrt{n_1^2 + n_2^2}}\right) \times 100$$

The model assumes that for a given trial, the numerosity of each of two stimulus arrays is represented by a Gaussian distribution (with means n_1 and n_2), and that comparing the two quantities involves a Gaussian subtraction of these two distributions in order to determine the magnitude of their difference. The probability of responding correctly following this subtraction is predicted by the complementary error function.

The Weber fraction, *w*, is the only free parameter in this model. The Weber fraction quantifies the variance in the Gaussian representation of each numerosity (the standard deviation for a distribution representing the numerosity n will be *w**n). Thus, a larger Weber fraction corresponds to larger variance in the numerical representation. Larger Weber fractions are worse because wider distributions exhibit more overlap, which makes numerosities less discriminable.

Goodness of fit of the Weber function was determined using the following formula: $1.0-(SS_{Regression}/SS_{Mean})$, where $SS_{Regression}$ is sum of squared distances between each data point and its predicted value based on the psychophysical model, and SS_{Mean} is the sum of squared distances between each data point and the mean of the data points. This formula produces a positive value (with 1 indicating a perfect fit) if the Weber function predicted a participant's accuracy better than a horizontal line through their mean accuracies. Negative values indicate that that the Weber function fit the participant's data worse than a horizontal line through the participant's mean accuracies.

2.2.4 Auditory symbolic math task

Previous research suggests that ANS precision is linked with only a subset of symbolic math abilities, suggesting that the link between the ANS and math reflects reliance of particular mathematical computations on magnitude representations, rather than reflecting the contribution of meta-cognitive or emotional factors, such as self confidence in math, or math anxiety. I tested participants on timed subtraction and division tasks and examined the correlation between ANS precision and performance on these two arithmetic operations separately. I chose to test participants on subtraction and division because they require active quantity manipulation more than addition and multiplication, which can often be solved by rote memorization (Dehaene & Cohen, 1997; Dehaene, Piazza, Pinel, & Cohen, 2003; Lee & Kang, 2002). Subtraction performance (tested independently and intermixed with addition problems) has been shown to correlate with ANS precision (Price et al., 2012; Wei et al., 2012). Subtraction also activates the IPS more than multiplication (Chochon et al., 1999; Lee, 2000). However, to our knowledge, division has not previously been shown to correlate with ANS precision (Chen & Li, 2014; Gebuis & van der Smagt, 2011; Lindskog, Winman, Juslin, & Poom, 2013).

Participants mentally solved as many subtraction or division problems as possible within two four-minute blocks. Participants heard the math problems over headphones, spoke their answers aloud, and pressed a button to advance to the next problem. Participants could use as much time as they needed for any problem (within the allotted four minutes), and could skip problems but could not return to skipped problems. There were 29 subtraction problems and 32 division problems, taken from the Kit of Factor-Referenced Cognitive Test (Ekstrom et al., 1976). Minuends in the subtraction task ranged from 18 to 98, subtrahends ranged from 11 to 65, and answers ranged from 4 to 70. Divisors in the division task ranged from 2 to 9, dividends ranged from 42 to 792, and answers ranged from 7 to 99. Participants did not receive any feedback on this task.

2.2.5 Working memory task

Forward and backward letter-span tasks were adapted from the Third Edition of the Wechsler Adult Intelligence Scale (WAIS-III) digit-span task. Digits 1-9 were assigned letters A-I. Participants heard strings of letters over headphones. In the forward span task, they repeated the letters back in the same order as they were presented, and in the backward span task they repeated the letters in the reverse order in which they were presented. Letter strings began with 2 letters and increased by one letter every two trials, with a maximum of 10 letters for the forward span and 8 letters for the backward span task. The task stopped when participants recited two letter strings of the same length incorrectly or when participants reached the maximum number of trials (max 16 and 14 trials for forward and backward letter span, respectively). Letters within a string were separated by a one second delay. All participants completed the forward and then the backward span task. Participants' forward and backward letter span scores were averaged to obtain a working memory score for each participant.

2.2.6 Woodcock-Johnson III Quantitative Concepts, Reading, and Vocabulary Knowledge Tasks

Portions of the Third Edition of the Woodcock Johnson III Standardized Test (WJ-III) were administered to blind participants in Grade II Braille (using the WJ-III Braille Adaptation) and to sighted participants in visual print (Jaffe, 2009; Jaffe, Henderson, Evans, McClurg, & Etter, 2009).

To measure participants' general math knowledge (e.g., how many square feet are in a square yard), I administered the last 26 questions of the WJ-III Quantitative Concepts test. The experimenter asked the participants questions verbally and participants answered verbally. Some questions required tactile (for blind) or visual (for sighted) graphics.

To measure participants' reading ability, I administered the WJ-III Letter/Word Identification and Word Attack tests in Braille for blind participants and in print for sighted participants. On the Letter/Word Identification test, participants read 60 words aloud (e.g., "scientist"; "bounties") and on the Word-Attack test, participants read 33 non-words aloud (e.g., "lindify"; "knoink"). Scores from these two reading sections were averaged to obtain a reading score for each participant.

To measure participants' vocabulary knowledge, I administered the WJ-III Oral Vocabulary test which consisted of Synonym, Antonym and Analogies subtests. On the Synonym and Antonym tests, participants verbally provided synonyms and antonyms for 24 different words (12 synonyms, 12 antonyms; e.g., provide synonyms for "assist" and "obvious"; provide antonyms for "attract" and "demure"). On the analogies test, participants completed 12 analogies (e.g., run is to fast as walk is to ___). Scores across the three subtests were averaged to obtain one vocabulary score per participant.

Items in each section of the WJ-III were presented in increasing difficulty. On all subtests, participants were allowed to take as much time as needed and did not receive any feedback. Each section was scored by dividing the number of items participants completed correctly by the total number of items tested from that section.

2.3 Results

2.3.1 Precision on auditory approximate number task

I first asked whether there was a difference between the numerical approximation abilities of the congenitally blind versus sighted participants. In overall accuracy, congenitally blind and sighted participants performed similarly: the blind participants averaged 75.41% correct (SD=6.76%) and the sighted participants averaged 79.08% correct (SD=4.80%; unpaired t-test: t(37)=-1.83, p=0.08). Even on trials on which numerosity was incongruent with total sequence duration, both blind and sighted participants successfully identified the more numerous sequence (blind accuracy=63.99%, SD=17.85; sighted accuracy=62.32%, SD=11.55). Furthermore, performance was ratio-dependent on these total duration incongruent trials (blind w=0.33, R^2=0.83; sighted w=0.52, R^2=0.80).

Both blind and sighted participants' data was well fit by the psychophysical model. On average, the model accounted for 71.19% (SD=18.15, min=37.35, max=95.45) of the variation in the accuracy across ratios of blind participants, and 66.37% (SD=24.79, min=11.63, max=96.61) of the variation in the accuracy across ratios of the sighted participants (unpaired t-test: t(37)=0.7, p=0.49).

The Weber fractions, or *w*'s, of the blind participants averaged 0.25 (SD=0.08) and of the sighted participants averaged 0.20 (SD=0.07; unpaired t-test: t(37)=1.81, p=0.08) (Fig. 2.1). Note that the marginal difference in ANS performance between blind and sighted groups disappeared when ROP participants were excluded from analysis (see below).

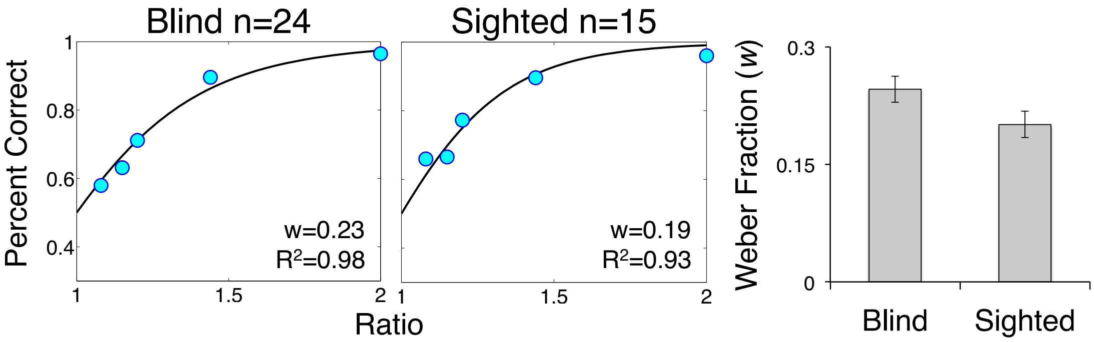


Fig. 2.1 Performance on auditory numerosity discrimination task. Two left graphs: Percent of correct trials across participants for each ratio; best fitting curve for group accuracy from psychophysical model shown with black line and group Weber fraction shown on bottom right of each graph. Right graph: Average Weber fraction across participants in blind and sighted groups (right bar). Error bars represent standard error of the mean.

2.3.2 Relationship of ANS and symbolic math performance

My next question concerned symbolic math performance and its link with ANS precision. I found similar performance across blind and sighted participants on the symbolic subtraction and division tasks. On the subtraction task, blind participants correctly answered 67.39% (SD=25.96) of problems and sighted participants correctly answered 59.77% (SD=24.72) of problems (unpaired t-test: t(37)=0.91, p=0.37; Table 2.3). On the division task, blind participants correctly answered 30.21% (SD=15.63) of problems and sighted participants correctly answered 33.37% (SD=15.93) of problems (unpaired t-test: t(37)=-0.61, p=0.55; Table 2.3).

A key question was whether ANS precision on a numerosity discrimination task is linked to symbolic math ability in both sighted participants (as has been observed in many previous studies) and congenitally blind participants. I found that ANS precision (Weber faction, *w*) was negatively correlated with subtraction performance in both the sighted group (R2=0.29, p=0.04) and the blind group (R2=0.28, p<0.01; Fig 2.2). This correlation did not differ across groups (Fisher z transform test for difference among independent sample correlation coefficients, z=0.06, p=0.95; Fisher, 1921). The correlation between ANS precision and division performance was marginally significant in the blind group (R2=0.16, p=0.051) but was not present in the sighted group (R2=0.13, p=0.18) (Fig 2.2).

To characterize the specificity of the relationship between ANS precision and symbolic math performance, I examined the correlation between ANS precision and performance on the non-math WJ-III tests. Blind and sighted participants performed similarly on control WJ-III subtests, as summarized in Table 2.3. I found that ANS precision was not significantly correlated with the ability to read words and non-words (mean of WJ-III letter/word identification and word attack scores; blind: R2=0.09, p=0.16; sighted: R2=0.05, p=0.41). ANS performance and vocabulary knowledge were marginally correlated in the blind group (mean of WJ-III synonym, antonym and analogy scores; R2=0.14, p=0.07) but were not correlated in the sighted group (R2=0.07, p=0.34). Similarly, ANS precision was correlated with knowledge of math concepts in the blind group (R2=0.17, p=0.05) but not in the sighted group (R2=0.14, p=0.17).

Table 2.3 Summary of results

	Blind			Sighted		
Task	**Mean (SD)**	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**
ANS Task (percent correct)	75.41(6.76)	63.45	92	79.08(4.8)	71.49	84.82
ANS Task (Weber fraction)	0.25(0.08)	0.08	0.4	0.20(0.07)	0.11	0.33
Subtraction Task	67.39(25.96)	13.79	100	59.77(24.72)	10.35	100
Division Task	30.21(15.63)	6.25	65.63	33.37(15.93)	15.63	68.75
Forward Letter Span Task	68.97(15.55)	31.25	93.75	55.42(9.41)	37.50	75.00
Backward Letter Span Task	59.01(16.99)	14.29	85.71	41.90(11.09)	21.43	57.14
Reading Words	89.10(13.98)	36.67	100	93.11(6.48)	75.00	100
Reading Non-words	83.15(19.23)	20.00	100	88.28(11.78)	54.55	96.97
Math Concepts	64.90(13.14)	34.62	88.46	69.90(10.70)	50.00	88.46
Verbal Task: Synonyms	81.60(16.30)	50.00	100	83.33(13.73)	50.00	100
Verbal Task: Antonyms	74.65(17.11)	25.00	100	77.78(13.61)	41.67	91.67
Verbal Task: Analogies	59.29(21.48)	16.67	91.67	75.56(17.10)	41.67	100

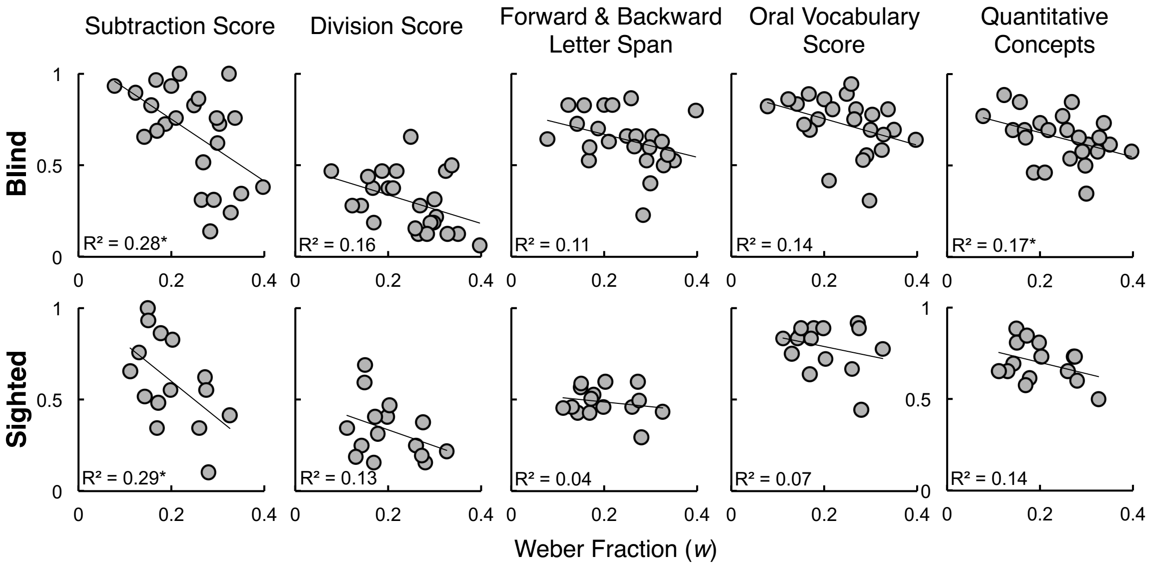


Fig. 2.2 Correlations between ANS precision and math performance. Correlation between individual subjects' Weber fractions and scores for subtraction, division, working memory, oral vocabulary, and quantitative concepts tasks (from left to right). Significant correlations marked with asterisk (p<0.05).

Finally, I asked whether the relationship between ANS precision and math performance was mediated by general working memory abilities. Consistent with previous studies, blind participants performed significantly better then sighted participants on the working memory task (blind: 63.97%, SD=15.50; sighted: 48.66%, SD=8.17; unpaired t-test: t(36)=3.51, p=0.001) (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Crollen et al., 2011; Dormal, Crollen, Baumans, Lepore, & Collignon, 2016; Occelli, Lacey, Stephens, & Sathian, 2016; Raz, Striem, Pundak, Orlov, & Zohary, 2007). Working memory was correlated with subtraction performance in both the blind (R2=0.34, p=0.003) and sighted groups (R2=0.66, p<0.001), to the same extent (Fisher r to z transformation, z=-1.31, p=0.19; Fisher, 1921). The correlation between ANS precision and subtraction performance when controlling for working memory held in the both sighted group (sighted: R2=0.43, p=0.01) and was marginally significant in the blind group (blind: R2=0.14, p=0.09).

Blind participants with retinopathy of prematurity (ROP, n=5) performed slightly worse than non-ROP blind participants despite comparable age and education (ROP mean accuracy=69.70%, SD=4.56, mean w=0.31, SD=0.05; non-ROP mean accuracy=76.91%, SD=6.50; mean w=0.23, SD=0.08). After excluding blind participants with ROP, ANS precision was similar across blind and sighted (unpaired t-tests; accuracy: t(32)=-1.08, p=0.29; Weber fraction: t(32)=1.09, p=0.28). Among blind participants without ROP, ANS precision (*w*) was still significantly correlated with subtraction and division performance (subtraction: R2=0.38, p=0.005; division: R2=0.29, p=0.02), even when controlling for working memory (subtraction: R2=0.35, p=0.01; division: R2=0.27, p=0.03). In this group, ANS precision (*w*) remained uncorrelated with reading ability (R2=0.06, p=0.31) and with vocabulary knowledge (R2=0.16, p=0.09) and remained correlated with knowledge of math concepts (R2=0.23, p=0.04).

2.4 Discussion

2.4.1 Preserved ANS precision in congenital blindness

If visual experience with sets of objects is necessary for the normal development of ANS precision, then congenitally blind individuals should exhibit impaired performance on a numerical approximation task. Contrary to this hypothesis, congenitally blind and sighted individuals demonstrated equal precision when estimating the numerosity of auditory tone sequences. For both groups, performance was well described by the same psychophysical function. These results suggest that vision is not required for typical ANS development.

I also found no evidence for the idea that blind individuals show superior ANS precision on auditory sequential estimation tasks. Thus, blindness does not render the ANS more “auditory” or “sequential,” consistent with the idea that the ANS is a modality-independent system. By contrast, two previous studies reported that blind individuals are more precise on numerical estimation tasks that involve producing sequences of a particular numerical quantity (e.g., produce 35 footsteps or 20 key presses) (Castronovo and Seron, 2007; Castronovo and Delvenne, 2013). There are a number of reasons why our results might differ from these prior investigations. First, our numerical approximation task did not require overt production. Participants listened to two sequences of tones and judged which was more numerous. Unlike production tasks, which are inherently subject-paced, the tones in our current experiment occurred rapidly and were spaced at variable intervals. Furthermore, in the current experiment, participants had a concurrent verbal load during numerical approximation that has previously been shown to prevent counting (Cordes et al., 2001). I adopted these measures because pilot testing revealed that blind participants were better able to count the auditory stimuli than sighted participants, producing nearly perfect performance, independent of numerical ratio. Thus, it is possible that some of the previously reported advantages in numerical estimation among blind individuals result not from changes in ANS precision itself but from differences between blind and sighted groups' ability to rapidly count.

It is worth nothing that one prior study reported slightly better performance among blind individuals in a non-production task, specifically when estimating the numerosity of sequences containing more than 40 auditory tones (Castronovo and Seron, 2007). In the current study I did not test any numerosities above 40. Therefore, it remains possible that blind individuals have increased precision for estimating the numerosity of larger auditory sequences. It is unclear why changes to ANS precision would affect performance with large but not small numbers. One possibility is that performance on larger number sequences is more dependent on working memory abilities, which are enhanced in individuals who are blind (Amedi et al., 2003; Dormal et al., 2016; Occelli et al., 2016; Raz et al., 2007). The available data are thus most consistent with the hypothesis that the ANS is neither specialized for a particular modality nor for a particular input format (sequential versus simultaneous).

If not vision, what kinds of experiences are relevant to ANS development? It may be that experiences estimating numerosities in any modality or format are equivalently suited to drive improvements in ANS precision. According to some theories, numerical processing shares a common mechanism with other magnitude systems (e.g., estimation of temporal duration (Allman, Pelphrey, & Meck, 2012; Bueti & Walsh, 2009; Meck & Church, 1983; Walsh, 2003). If so, numerical estimation could plausibly even be improved by judging these other magnitudes (Allman et al., 2012; Bueti & Walsh, 2009; Walsh, 2003; but see Odic et al., 2013 for an alternative view).

Furthermore, some evidence suggests that educational and cultural experiences can hone the precision of approximate number representations. Members of the indigenous Amazonian Munduruku group have an extremely limited numerical lexicon, little or no mathematical experience, and relatively poor ANS precision (Piazza et al., 2013). However, members of this group who completed at least three years of education and therefore learned number words and simple arithmetic had significantly better ANS precision than those with less exposure to math, even when controlling for age (Piazza et al., 2013). This finding suggests that math education—whether primarily visual or auditory in nature—may sharpen ANS representations (Piazza et al., 2013). Alternatively, the majority of age-related improvement in the precision of the ANS could be intrinsically driven and result from maturation rather than learning. The evidence I present here is most consistent with the hypotheses that ANS precision improves over development regardless of experience, or that experience tunes the ANS, but equally so regardless of the sensory modality and format in which it occurs.

2.4.2 Preserved relationship between ANS and symbolic number abilities in congenital blindness

My second key finding is that individual differences in performance on a numerical approximation task predict performance on a symbolic math task in both sighted and congenitally blind individuals. Thus the relationship between the ANS and symbolic numerical reasoning is preserved even in those who have never experienced number visually, and who arguably are less likely to experience number spatially because of the unique capacity of the visual system to perceive large numbers of objects in parallel (Dakin et al., 2011; Anobile et al., 2014). These results suggest that the link between ANS precision and symbolic math abilities is not mediated by visual abilities. Note, however, that our results do not rule out the possibility that there is an independent relationship between spatial and mathematical abilities. Whether spatial abilities among blind individuals independently predict mathematical performance is an important question to explore in future research. Furthermore, since the current study is, to our knowledge, the first to look at this relationship between ANS precision and mathematics in blindness, it will be important to replicate our findings in future work.

The precise nature of the relationship between the ANS and math remains an open question. According to one hypothesis, children with better ANS precision may quickly learn to map number words to discrete numerical quantities, whereas those with noisier ANS representations may have more trouble forming this mapping (Libertus et al., 2011). Such an advantage in early math education may even lead to those with better ANS precision to pursue and practice math. Consistent with this idea, in the current experiment, I find some evidence that ANS precision is correlated with the knowledge of math facts. Another possibility is that greater ANS precision allows individuals to better evaluate their answers when performing math (Gilmore, McCarthy, & Spelke, 2007; Libertus et al., 2012; Lyons & Beilock, 2011). For example, an individual with poor ANS precision may be less likely or slower to realize that 34-19=25 is implausible. A third possibility is that more experience with math, or better symbolic math abilities, hones the precision of the ANS (Piazza et al., 2013; Shusterman et al., 2016). Of course, some combination of these influences is also possible.

2.4.3 Relationship between numerical and working memory abilities

Consistent with prior studies, I also found that symbolic math performance was correlated with working memory abilities. However, the relationship between the ANS and symbolic math persisted even when working memory performance was factored out. In addition, I replicated previous findings that congenitally blind individuals have superior verbal working memory, relative to sighted individuals, as measured by participants' forward and backward letter spans (Amedi et al., 2003; Dormal et al., 2016; Occelli et al., 2016; Raz et al., 2007). Working memory advantages associated with blindness can be traced back to childhood: blind children between the ages of 7 and 13 are better at remembering lists of pseudo-words than sighted children (Crollen et al., 2011).

There is some evidence that blind children spontaneously rely on working memory-demanding strategies to complete some numerical tasks, such as counting the number of times that particular syllables appear in a series of other syllables (Crollen et al., 2011). Whereas sighted children use their fingers to keep track of syllable numbers, blind children were more likely to count mentally (Crollen et al., 2011). However, I found no evidence for the idea that blind adults were more likely than the sighted to rely on working memory to solve approximate number tasks or solve simple arithmetic equations, as correlations between arithmetic performance, ANS precision, and working memory were equivalent across blind and sighted groups. Finally, although blind subjects had substantially better working memory, their performance on the arithmetic task was equivalent to the sighted.

One possibility is that the particular aspect of working memory that is improved in blindness is not the same component of working memory that is most relevant to solving symbolic math equations—at least not the types of equations I tested here. Blind individuals consistently show enhanced verbal working memory and serial or sequential memory (Amedi et al., 2003; Crollen et al., 2011; Dormal et al., 2016; Occelli et al., 2016; Raz et al., 2007). However, it is unclear whether other aspects of working memory, such as spatial working memory, are improved in blindness.

At least one study directly compared verbal and spatial working memory abilities in blind and sighted individuals and found specific improvements in verbal working memory but not spatial working memory in blindness (Occelli et al., 2016). Thus, it is possible that blind individuals experience improvements in specific aspects of working memory that do not necessarily translate to enhancements in subtraction and division problem solving. By contrast, blind individuals do outperform sighted individuals on multiplication tasks that rely more heavily on verbal memory for arithmetic facts (Dehaene & Cohen, 1997; Dormal et al., 2016).

2.5 Conclusions

In summary, the present findings suggest that the cognitive building blocks of numerical cognition develop independently of visual experience. First, the precision of approximate number representations is indistinguishable across congenitally blind and sighted individuals. Second, congenitally blind and sighted individuals performed similarly on a simple timed arithmetic task. Finally, ANS precision was correlated with symbolic number reasoning in both congenitally blind and sighted individuals. Thus, despite the strong links between numerical processing and visual abilities, I find that the key signatures of numerical cognition are preserved in the total absence of vision. One question that this study leaves open is whether numerical thinking is supported by similar neural mechanisms in congenitally blind and sighted individuals. In the following chapters, I proceed to investigate how the absence of visual experience modifies the neural basis of these numerical abilities.

Chapter 3

Preservation and change in the neural basis of symbolic number processing in blindness

3.1 Introduction

In remaining Chapters of the dissertation, I investigate whether the neural basis of symbolic number processing is modified by the absence of visual experience. In this Chapter, I begin by asking whether, like sighted individuals, congenitally blind individuals recruit a fronto-parietal network during symbolic number processing and whether the IPS is similarly sensitive to the difficulty of math equations across both groups. As discussed in the introduction, representations of symbolic number are hypothesized to build upon the IPS approximate number system that is present earlier in development (for review see Szkudlarek et al. 2017). Thus, if the absence of visual experience affects the development of the approximate number system in the IPS, as outlined in Chapter 1.2, these effects should transfer to the localization of symbolic number reasoning in the IPS. Therefore, the first goal of this study was to investigate whether IPS responses to symbolic number are preserved in congenital blindness.

A second goal of this study was to ask whether fronto-parietal networks recruit parts of the "visual" cortex during numerical processing in congenital blindness. As discussed in Chapter 1.4, the “visual” cortex of congenitally blind individuals responds to non-visual input. Furthermore, there is some evidence that, in the absence of vision, parts of the “visual” cortex are repurposed for language functions (Röder et al., 2002; Bedny et al., 2011; Lane et al., 2015; Kim et al., 2017). One interpretation of this finding is that in the absence of bottom-up visual input, visual cortices become functionally coupled with fronto-parietal and fronto-temporal higher-cognitive networks that typically play a modulatory role in visual processing in sighted individuals. Consistent with this hypothesis, the same “visual” regions that demonstrate sensitivity to language become more synchronized with inferior frontal language regions at rest in congenital blindness (Bedny et al., 2011; Watkins et al., 2012; Deen et al., 2015).

Therefore, a second goal of this study is to test the hypothesis that parts of the visual cortex are repurposed for higher-cognitive functions, possibly via top-down feedback from fronto-parietal networks. I asked whether parts of the “visual” cortex are recruited during numerical processing in congenitally blind but not sighted individuals.

Studying visual cortex responses to symbolic math is an excellent test of this question because, first, it recruits a fronto-parietal network, in particular the IPS, which is known to modulate activity in the visual cortex (Wardak et al., 2004; Rossi et al., 2007, 2009) (see Chapter 1.4.2). Therefore, fronto-parietal number regions may be well positioned to incorporate deafferented visual cortices into their network. Second, symbolic math is functionally distinct from low-level vision. Unlike low-level vision, symbolic math is acquired through years of educational and cultural experience. Thus, any responses to symbolic math that are observed in visual cortex of congenitally blind individuals is unlikely to be caused by shared computations underlying visual and mathematical processing. Finally, we can compare visual cortex responses to symbolic mathematical stimuli to closely matched linguistic stimuli. This tight comparison allows me to distinguish between visual cortex plasticity for number as opposed to language and further ask whether the visual cortex of congenitally blind individuals becomes sub-specialized for distinct higher-cognitive functions.

Congenitally blind and blindfolded sighted adults performed a math task and a language control task while undergoing fMRI. In the math task, participants heard pairs of spoken subtraction equations, each containing an unknown variable x, and decided whether the value of x was the same in the two equations (e.g., $7 - 2 = x$; $6 - 1 = x$). In the language control task, participants heard pairs of spoken sentences and judged whether the meanings of the sentences were the same.

I chose to use subtraction problems for the math task because subtraction requires active quantity manipulation rather than long-term memory retrieval, and has been shown to recruit the IPS more than operations such as addition and multiplication (Kawashima et al., 2004; Kong et al., 2005; Prado et al., 2011). I included two orthogonal math difficulty manipulations. Equation pairs contained either single-digit (easy) or double-digit (difficult) numbers (e.g., $7 - 2 = x$ vs. $27 - 12 = x$), and were either algebraically simple (solving for an unknown difference) or complex (solving for an unknown minuend; e.g., $7 - 2 = x$ vs. $x - 2 = 7$).

No “borrowing” operations were required to solve any of the math equations (e.g., $27 - 12 = x$ does not require “borrowing” but $27 - 19 = x$ does require “borrowing”). Arithmetic problems that are matched in the number of digits take more time to solve if they require “borrowing” or “carry-over” (Deschuyteneer et al., 2005; Imbo and

Vandierendonck, 2007; Knops and Willmes, 2014). It is thought that the difficulty of these problem types stems from increased working memory demands rather than numerical difficulty, per se. For example, performing a separate working memory task while solving arithmetic problems specifically affects response latencies on problems that involve carry over (Ashcraft and Kirk, 2001). Thus, to mitigate the effects of working memory on math difficulty, the difficulty of math problems did not depend on whether or not they involved “borrowing”.

With respect to the IPS number system, I predict that if the development of representations of symbolic number does not require visual experience, the IPS will respond preferentially to mathematical stimuli than linguistic stimuli and show greater responses to more difficult math problems in both congenitally blind and sighted individuals. By contrast, if visual experience plays an important role in the development number representations in the IPS, the functional profile of the IPS during a symbolic math task will be different across congenitally blind and sighted groups.

With respect to visual cortex plasticity, if the “visual” cortex of congenitally blind individuals becomes repurposed for higher-cognitive functions, I predict that parts of the visual cortex will be active during mathematical calculation and show greater responses to more difficult math equations in congenitally blind but not sighted individuals. I further predict that regions of the visual cortex that respond to math in congenital blindness will be anatomically and functionally distinct from language-responsive visual areas, providing evidence for sub-specialization of the visual cortex by multiple distinct higher-cognitive functions.

3.2 Materials and Methods

3.2.1 Participants

Nineteen sighted (9 females, mean age 46 y, SD = 16) and 17 congenitally blind adults (12 females, mean age 47 y, SD = 16) participated (Table 3.1). Thirteen of the blind and nine of the sighted participants contributed resting-state data. No sighted or blind participants had cognitive or neurological disabilities (screened through self-report). All blind participants lost their vision due to pathology at or anterior to the optic chiasm, not due to brain damage, and had at most minimal light perception from birth (never saw colors, shapes, or motion; Table 3.1). Informed consent from participants was obtained in accordance with the Johns Hopkins Medicine Institutional Review Boards. Four additional blind participants were scanned but not included in the final sample because their average accuracy across math and language trials was significantly lower than the group mean (performance outside the 95% confidence interval). Two sighted participants were excluded due to an error in MRI data acquisition.

3.2.2 Behavioral Paradigm

Participants performed auditory math and language-control tasks while undergoing fMRI. Stimuli were presented in American English and were delivered to the participant through MRI compatible headphones. On math trials, participants heard two math equations each containing an unknown variable (e.g. 7-2=x). Equations lasted 3.5 seconds each and were separated by a 2.75 second delay. Participants pressed one of two buttons to indicate whether the value of x in the two equations was the same (4 seconds to respond). Participants were able to respond at any point after the onset of the second math equation or sentence.

The format of language trials was identical to that of math trials except participants heard 2 sentences and indicated whether the meaning of the two sentences was the same. One of the sentences was always in active voice and the other was in passive voice. On “different” trials, who-did-what-to-whom was switched from one sentence to the other while all nouns and verbs remained identical. Half of the language trials had an object relative construction and half had a subject relative construction (two total language conditions). These two language conditions were not compared in this study.

The difficulty of math equations was varied using two orthogonal manipulations (four total math conditions). Half of the equations contained all single-digit numbers (e.g. 7-2=x) and half contained all double-digit numbers (e.g. 27-12=x). Orthogonally, in half of the equations, the unknown variable x was isolated on the right side of the equation (algebraically simple; e.g. 7-2=x), while the other half required manipulation to isolate x (algebraically complex; e.g. x-2=7). Double-digit math equations never required “carry-over” to reach a solution, thus reducing any differences in working memory demands across the double- and single-digit conditions. By contrast, the algebraic complexity manipulation may tax both numerical and working memory processes (Maruyama et al., 2012; Monti et al., 2012).

Each pair of math equations and sentences was presented once throughout the experiment. The experiment was divided into 6 runs each with 24 trials (16 math trials and 8 language trials). Thus, there was a total of 96 unique math trials and 48 unique language trials in the experiment. The 4 math conditions and 2 language conditions (6 total conditions) were counterbalanced in a Latin square design across all 6 runs. A small number of participants completed fewer than 6 runs of the experiment (2 CB, and 7 S completed 5 runs and 2 S completed 4 runs).

Trials on which participants did not respond were excluded from the behavioral and fMRI data analysis (blind: 2.05% of trials, SD = 2.09; sighted: 2.81% of trials, SD = 3.23; t(34) = −0.83, P = 0.41).

Table 3.1. Participant demographic information

Participant	Gender	Age	Cause of Blindness	Light Perception	Education
B1	M	23	LCA	Minimal	Some College
B2	F	33	ROP	Minimal	BA
B3	F	70	ROP	Minimal	High School
B4	M	44	Unknown	None	JD
B5	F	68	ROP	None	MA
B6	F	27	ROP	Minimal	MA
B7	F	65	ROP	None	MA
B8	F	35	LCA	Minimal	MA
B9	M	48	LCA	None	JD
B10	F	40	ROP	None	MA
B11	F	50	LCA	Minimal	MA
B12	F	25	LCA	Minimal	MA
B13	F	63	ROP	None	MA
B14	M	37	CG/Cat	None	MA
B15	M	63	ROP	None	BA
B16	F	61	ROP	None	JD
B17	F	47	ROP	None	BA
Average					
Blind	**12 F**	**47**	**--**	**--**	**BA**
Sighted	**9 F**	**45**	**--**	**--**	**BA**

LCA=Leber's congenital amaurosis; ROP= retinopathy of prematurity; CG=congenital glaucoma; Cat=cataracts; BA=Bachelor of Arts; MA=Master of Arts; JD=Juris Doctor

3.2.3 fMRI Data Acquisition

Whole-brain MRI structural and functional data were collected with a 3T Phillips scanner. T1-weighted anatomical images were collected in 150 1-mm axial slices (1-mm isotropic voxels). Functional BOLD data were acquired in 36 3-mm axial slices (2.4 × 2.4 × 3 mm voxels; repetition time 2 s). The same image-acquisition parameters were used for the task- based and resting-state data. Task-based fMRI data were acquired in six runs. All participants were blindfolded throughout the entire experiment.

3.2.4 fMRI Data Analysis

fMRI Data were analyzed using Freesurfer, FSL, HCP workbench and custom in-house software. Data were motion corrected, high-pass filtered (128 seconds), mapped to the cortical surface using the standard Freesurfer pipeline, spatially smoothed on the surface (6-mm FWHM Gaussian kernel), and prewhitened to remove temporal autocorrelation.

Task-based fMRI data were analyzed using a standard general linear model (GLM). Each of the four math conditions and each of the 2 language conditions were entered as predictors in the GLM after convolving with the canonical hemodynamic response function. First temporal derivatives were also modeled. Trials on which participants failed to respond and time-points with excessive motion (>1.5mm) were modeled with two separate regressors and dropped from analyses (blind: 1.45 drops per run, SD = 1.32; sighted: 1.48 drops per run, SD = 3.06, t(34) = 0.03, P = 0.98).

Within each participant, each run was modeled separately and then combined using a fixed-effects model. Data across participants (within-group and between-group) were analyzed using a random-effects model. I used Monte Carlo simulations as implemented in FSL to correct for multiple comparisons across the whole cortex. For within-group results, on each permutation iteration, voxel values signs across the brain are flipped (e.g. 4.5 to -4.5) for a random subset of subjects and the subsequent group map is thresholded at a cluster-forming threshold ($p<0.01$) (Winkler et al., 2014). The size of largest number of contiguous vertices is then entered into a null distribution and clusters from our true results that lie in the top 5% (alpha of $p<0.05$) of this distribution pass the cluster-correction. The correction procedure for between-group results was similar except group labels were permuted rather than voxel value signs (Winkler et al., 2014).

IPS and visual cortex (rMOG) ROIs were defined in individual subjects using the math > language contrast (orthogonal to the differences between math conditions). ROIs were defined using a leave-one-run-out procedure. For each participant, using all but one run, ROIs were defined as the top 5% of voxels within an IPS and visual cortex search-space with the highest math > language z value. Search space definition was orthogonal to the contrast of interest (differences between math conditions) and orthogonal to subject.

The left and right IPS search spaces were defined using the sighted and congenitally blind groups' average responses for the math > sentences contrast within the anatomical location of the IPS ($P < 0.01$, uncorrected) (Destrieux et al., 2010). rMOG search-spaces were defined using a leave-one-subject-out analysis (on 10 mm smoothed data). I iteratively excluded one subject and defined the rMOG search-space, based on the remaining subjects, as the cluster within visual cortex that showed an interaction between the math > sentences contrast and blind > sighted contrast ($P < 0.001$, uncorrected). This procedure ensures that search-space definition is orthogonal to subject—that is, a given subject did not contribute to the definition of his or her own search space. Before data extraction, the resulting search spaces of all sighted and blind participants were manually trimmed to ensure that they did not extend into the IPS and to avoid irregularly shaped search spaces. Finally, the rVOT search-space was defined by taking the cluster in the right ventral occipito-temporal cortex that responded more language than math in congenitally blind>sighted individuals within anatomically defined occipito-temporal cortex ($p<0.01$, uncorrected) (Destrieux et al., 2010). Data from four additional congenitally blind subjects who are not analyzed in this Chapter were used to defined the rVOT search-space. Data from one congenitally blind participant from Table 3.1 was not used to define the rVOT search space and was not included in the rVOT ROI analysis.

For each ROI, I extracted percentage signal change (PSC) from 2 mm smoothed data during the stimulus portion of the trial (0.25–10 s after trial onset) and averaged PSC across voxels. PSC was computed relative to rest not including the 2 s following the offset of the previous trial. This process was repeated iteratively until every run was excluded from ROI definition. Therefore, ROIs were defined using independent data as well as using a contrast that is orthogonal to the conditions of interest.

3.3 Results

3.3.1 Behavioral results

Accuracy (percentage correct) was analyzed using a 2 × 2 × 2 repeated-measures ANOVA with group (blind vs. sighted) as a between-subjects factor and digit–number (single vs. double-digit) and algebraic complexity (algebraically simple vs. complex) as within-subject factors. Both blind and sighted participants made more errors on trials with double than single-digit problems (main effect of digit–number: $F(1, 34) = 10.25$, $P = 0.003$; group × digit–number interaction: $F(1, 34) = 1.83$, $P = 0.19$; Fig. 3.1). Both groups were also less accurate with algebraically complex than algebraically simple problems (main effect of algebraic complexity: $F (1, 34) = 23.28$, $P < 0.001$; group × algebraic complexity interaction: $F(1, 34) = 0.31$, $P = 0.58$) (Fig. 3.1). There was no effect of group on accuracy (main effect of group: $F(1, 34) = 0.54$, $P = 0.47$) and no other group interactions.

Response times (percentage correct) were analyzed using a 2 × 2 × 2 repeated-measures ANOVA with group (blind vs. sighted) as a between-subjects factor and digit–number (single vs. double- digit) and algebraic complexity (algebraically simple vs. complex) as within-subject factors. Both blind and sighted participants were slower to respond on trials with double-digit problems than single- digit problems (main effect of number of digits: $F(1, 34) = 13.11$, $P=0.001$; group × digit–number interaction: $F(1, 34) = 0.60$, $P = 0.81$). Both groups were also slower to respond on trials with algebraically complex than algebraically simple math problems (main effect of algebraic complexity: $F(1, 34) = 75.37$, $P < 0.001$; group × algebraic complexity interaction: $F(1, 32) = 2.67$, P

= 0.14). There was no effect of group on response times (main effect of group: F(1, 34) = 0.71, P = 0.41) and no other group interactions.

To test whether accuracy was matched across the math and language tasks, I ran a 2 × 2 repeated-measures ANOVA with group (blind vs. sighted) as a between-subject factor and task (math vs. language) as a within-subject factor. Accuracy was similar across the tasks (main effect of task: F(1, 34) = 0.42, P = 0.53). There was a marginal group × task interaction such that blind participants were slightly better on the language task, whereas sighted participants were slightly better on the math task (group × task interaction: F(1, 34) = 3.37, P = 0.08). However, direct comparison of the blind and sighted groups revealed no significant group differences on either task (math: t(34) = −0.74, P = 0.74; language: t(34) = 1.01, P = 0.32) (see Fig. 3.1). Response times across the math and language tasks were analyzed using a separate 2 × 2 repeated-measures ANOVA with group (blind vs. sighted) as a between-subjects factor and task (math vs. language) as a within-subject factor. Blind and sighted participants were slower to respond on math trials than language trials (main effect of task: F(1, 34) = 8.76, P= 0.0061). This effect was larger in the blind group compared to the sighted group. (group × task interaction: F(1, 34) = 17.74, P < 0.001).

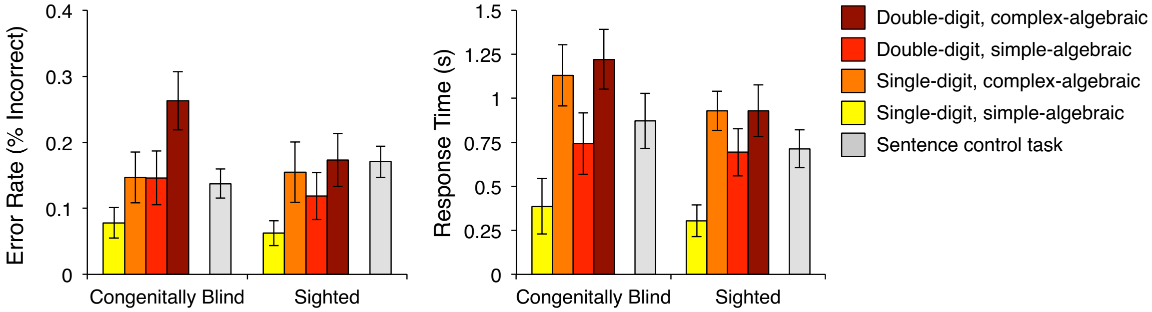


Fig. 3.1 Behavioral performance on math task. Congenitally blind (n = 17) and sighted (n = 19) groups' error rates (Left) and response times (Right) for all conditions in math task and language control task. Response times were measured from the onset of the second stimulus.

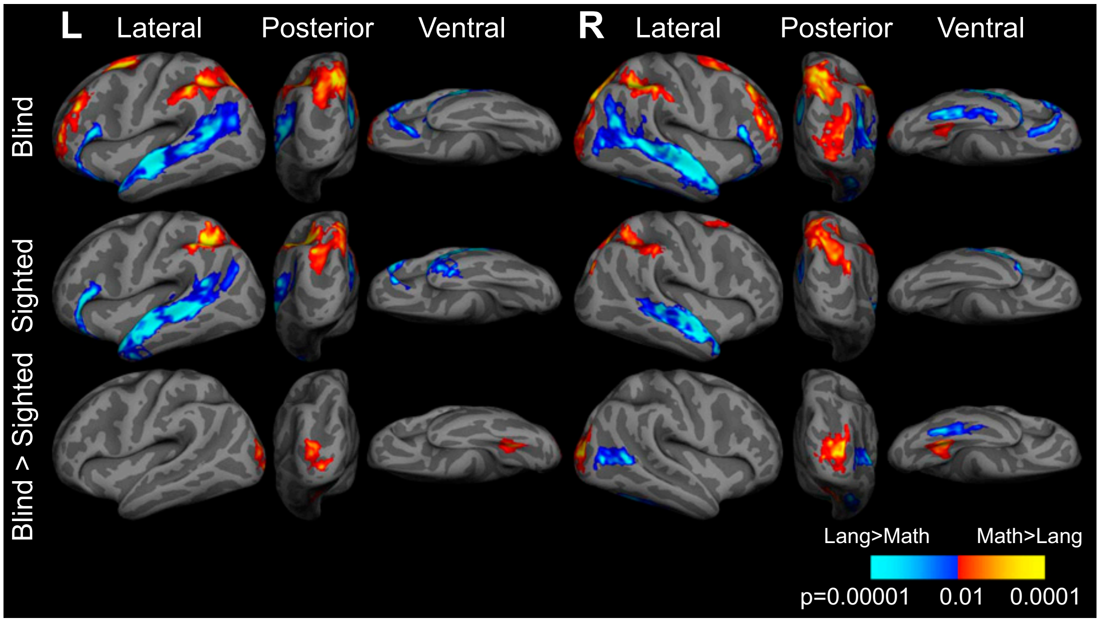


Fig. 3.2 Whole-cortex responses to math and language. Brain regions active for math > language (warm colors) and language > math (cool colors) in blind (n = 17) and sighted (n = 19) individuals (P < 0.05, cluster corrected).

3.3.2 Preserved fronto-parietal responses to number in congenital blindness

In whole-cortex analysis, both congenitally blind and sighted participants activated bilateral IPS more while solving math equations than during sentence comprehension (whole-brain analysis, $P < 0.05$, cluster corrected; Fig. 3.2). A whole-cortex group × task interaction analysis failed to find any regions that responded more to math than language in sighted than blind individuals (group × task interaction, sighted > blind, math > language, $P < 0.05$, cluster corrected).

I next used a region of interest (ROI) analysis to ask whether math difficulty modulated IPS activity in blind and sighted individuals, using a $2 \times 2 \times 2 \times 2$ repeated-measures ANOVA with group (blind vs. sighted) as a between-subjects factor and digit–number (single vs. double-digit), algebraic complexity (algebraically simple vs. complex), and hemisphere (left vs. right) as within-subject factors (Fig. 3.3). Across blind and sighted groups, the IPS was sensitive to digit– number (main effect of digit–number: $F(1, 34) = 46.08$, $P < 0.001$) and algebraic complexity (main effect of algebraic complexity: $F(1, 34) = 18.84$, $P < 0.001$; main effect of group: $F(1, 34) = 0.21$, $P = 0.65$) (Fig. 3.3). Crucially, the factor of group did not interact with digit–number ($F(1, 34) = 1.784$, $P = 0.18$) or algebraic complexity ($F(1, 34) = 0.28$, $P = 0.60$). Thus, I found no difference in IPS sensitivity to math difficulty between the blind and sighted groups.

The left and right IPS of congenitally blind adults responded more to trials with double- digit math equations than single-digit math equations ($F(1, 16) = 36.70$, $P < 0.001$; digit–number × hemisphere interaction: $F(1, 16) = 0.02$, $P = 0.9$) and more to algebraically complex equations than algebraically simpler equations ($F(1, 16) = 8.13$, P

= 0.01; algebraic complexity × hemisphere interaction: F(1, 16) = 1.74, P = 0.21) (Fig. 3.3). A similar pattern was observed in the sighted group (main effect of digit–number: F(1, 18) = 13.85, P = 0.002; main effect of algebraic complexity: F(1, 18) = 11.05, P = 0.004). In the sighted group, the effect of digit–number was more pronounced in the left hemisphere (group × digit–number × hemi- sphere interaction: F(1, 34) = 8.33, P = 0.007). No other group interactions were significant.

3.3.3 Responses to number in visual cortex of congenitally blind adults

In whole- cortex analyses, distinct sub-regions of visual cortex responded to number vs. language in congenitally blind individuals. I observed greater responses to math equations than sentences in the right and left middle occipital gyri (MOG) in congenitally blind compared with sighted participants (group (blind > sighted) × task (math > language) interaction, $P < 0.05$, cluster-corrected) (Fig. 3.2). This effect was more pronounced in the right hemisphere. I also found that neighboring regions in right lateral occipital and ventral occipito-temporal (rVOT) cortices responded more during the language task than the number task in the blind compared with the sighted (group (blind > sighted) × task (language > math) interaction) (Fig. 3.2) (Lane et al., 2015; Kim et al., 2017).

I used an ROI analysis to test for sensitivity to math difficulty in the rMOG of the blind and sighted groups (individual subject rMOG ROIs defined based on math > language contrast using leave- one-run-out analysis) (Fig. 3.3). I ran a 2 × 2 × 2 repeated-measures ANOVA with group (blind vs. sighted) as a between-subjects factor and digit–

number (single vs. double-digit) and algebraic complexity (algebraically simple vs. complex) as within- subject factors. I found a main effect of digit–number and a group × digit–number interaction (main effect of digit–number: $F(1, 34) = 28.08$, $P < 0.001$; group × digit–number interaction: $F(1, 34) = 28.08$, $P < 0.001$). In post-hoc comparisons, I found that the effect of digit–number was significant in the blind group but not the sighted group (main effect of digit–number in blind rMOG: $F(1, 16) = 24.43$, $P < 0.001$; main effect of digit–number in sighted rMOG: $F(1, 18) = 1.80$, $P = 0.20$). Thus, in blind but not sighted individuals, rMOG is sensitive to the number of digits in math equations.

In the same ANOVA I observed a main effect of algebraic complexity ($F(1, 34) = 6.50$, $P = 0.02$) but no algebraic complexity × group interaction ($F(1, 34) = 1.24$, $P = 0.27$). Although the algebraic complexity × group interaction was not significant, the algebraic complexity effect was numerically larger in the blind group (marginal effect of algebraic complexity: $F(1, 16) = 4.20$, $P = 0.06$; digit–number × algebraic complexity interaction: $F (1, 16) = 1.19$, $P = 0.30$) (Fig. 3.3). By contrast, the rMOG of sighted individuals was not sensitive to algebraic complexity (main effect of algebraic complexity: $F(1, 18) = 2.01$, $P = 0.17$; digit–number × algebraic complexity interaction: $F(1, 18) = 0.30$, $P = 0.59$).

I also observed a main effect of group, with larger overall occipital responses in the blind group than the sighted group (main effect of group: $F(1, 34) = 34.53$, $P < 0.001$). No other group interactions were significant.

Finally, I asked whether the right ventral occipito-temporal region of the visual cortex that preferentially responded to language (language>math) in congenitally blind individuals was sensitive to math difficulty (Fig. 3.2). I ran a 2 × 2 × 2 repeated-measures

ANOVA with group (blind vs. sighted) as a between-subjects factor and digit–number (single vs. double-digit) and algebraic complexity (algebraically simple vs. complex) as within- subject factors. Language-responsive rVOT was neither sensitive to the number of digits in math equations nor the algebraic complexity of math equations across congenitally blind and sighted individuals (main effect of digit-number: F(1,33)=0.20, p=0.66; main effect of algebraic complexity: F(1,33)=3.62, p=0.07; digit-number by algebraic complexity interaction: F(1,33)=0.18, p=0.68; Fig. 3.3). Within-group analyses confirmed that the rVOT in both the congenitally blind and sighted groups was not sensitive to mathematical difficulty (main effect of digit-number in blind: F(1,15)=0.00, p=0.99; main effect of algebraic complexity in blind: F(1,15)=1.69, p=0.21; main effect of digit-number in sighted: F(1,18)=0.29, p=0.60; main effect of algebraic complexity in sighted: F(1,18)=2.19, p=0.16).

ROI analyses confirmed that the rVOT, unlike math-responsive rMOG, responds preferentially during sentence comprehension compared to math calculation (2 x 2 repeated measures ANOVA with task as within-subjects factor and group as between subjects factor; main effect of task: F(1,33)=67.40, p<0.001; task by group interaction: F(1,33)=11.64, p=0.002). Although selectivity for linguistic stimuli was stronger in the rVOT of congenitally blind individuals compared to sighted individuals, this effect was present in the rVOT of both groups (blind: t(15)=8.95, p<0.001; sighted: t(18)=3.26, p=0.004).

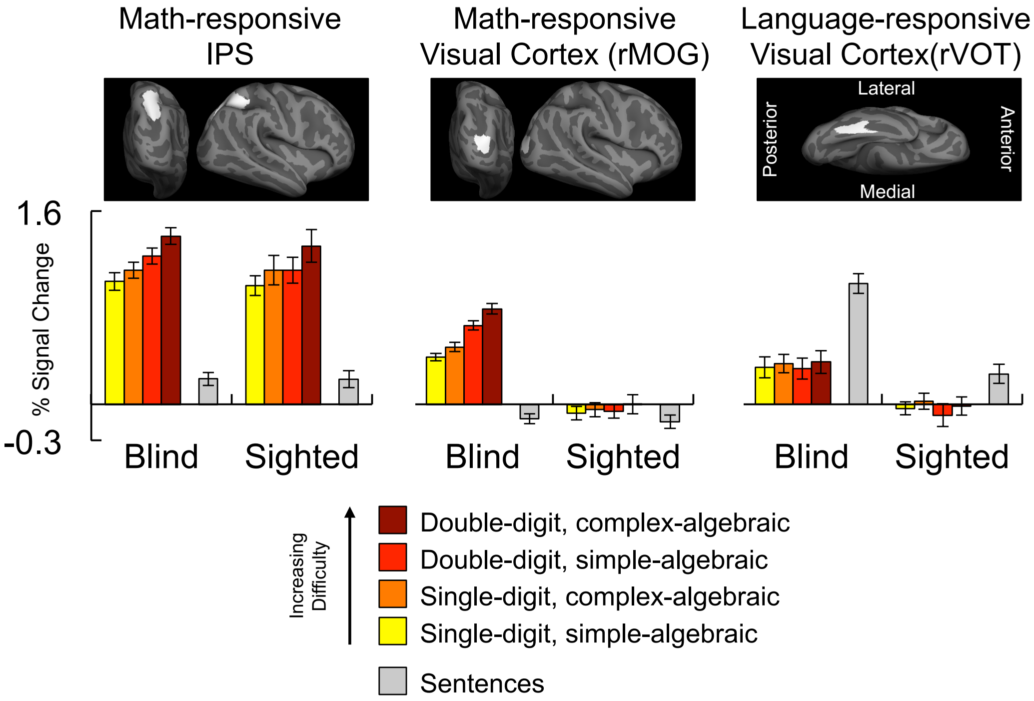


Fig. 3.3 Responses to math difficulty in IPS and math- and language-responsive “visual” cortex. Responses to math difficulty in IPS (Left), math-responsive visual cortex (rMOG; middle) and language-responsive visual cortex (rVOT; right) regions of interest in blind (n = 17 for IPS and rMOG, n=16 for rVOT, see Methods) and sighted (n = 19) individuals (error bars represent SEM). Percentage of signal change relative to rest was extracted from individual-subject ROIs defined within IPS and rVOT search-space and average rMOG search-space, shown at the top. IPS results are averaged across left and right hemispheres.

3.4 Discussion

3.4.1 IPS Number representations develop independent of visual experience

Previous studies show that the IPS is active when adults solve math equations and estimate non-symbolic quantities (Menon et al., 2000; Piazza et al., 2007a). This IPS sensitivity to number is present by 4-years of age, prior to formal math training (Cantlon et al., 2006, 2009; Lussier and Cantlon, 2016). Yet the effect of experience on the neural basis of number processing has remained largely unknown. Here I shed light on the role of early visual experience in the emergence of IPS number representations. I report that the functional profile of the IPS in numerical processing is preserved in individuals who are blind from birth, demonstrating that visual experience with numerical sets is not necessary for the typical development of IPS number responses.

The resilience of number representations in blindness is noteworthy in light of the links between number and visuo-spatial processing. In adults, individual differences in both non-symbolic and symbolic number performance correlate with individual differences in visual discriminations involving area, density, and orientation (Lourenco et al., 2012; Tibber et al., 2012). Children who are better at mentally rotating visual objects perform better on math tasks (Reuhkala, 2001). Numerical estimation and visuo-spatial functions, like orienting visual attention, are supported by neighboring regions of parietal cortex (Culham and Kanwisher, 2001; Simon et al., 2002; Hubbard et al., 2005). Sighted individuals recruit overlapping regions in the IPS when making judgments about numerical quantity, as well as other visual magnitudes, such as luminance, line length, and physical size (Cohen Kadosh et al., 2005; Kaufmann et al., 2005, 2006, Tudusciuc and Nieder, 2007, 2009). Despite these links between numerical and visual processing, I find that IPS representations of number develop independently of visual experience with sets.

3.4.2 Visual cortex of congenitally blind adults is recruited into number-processing network

Although I found that visual experience is not required for IPS representations of number, blindness does change the neural basis of numerical cognition in a surprising way. I found that in blind individuals, a subset of early visual cortices is active while solving math equations, and this activity scales with mathematical difficulty. This functional profile was specific to math-responsive regions of “visual” cortex, as a language-responsive “visual” region (rVOT) showed no sensitivity to mathematical difficulty in congenital blindness.

Much evidence has documented responses to auditory and tactile stimuli in visual cortices of congenitally blind individuals (Röder et al., 2002; Sadato et al., 2002; Amedi et al., 2003; Bedny et al., 2011; Watkins et al., 2013; Lane et al., 2015). The mechanisms and the scope of functional reorganization in cross-modal plasticity remain debated (Pascual-Leone et al., 2005). On the one hand, some examples of visual cortex plasticity preserve aspects of the original visual functions. Visual motion responsive area MT+ responds to auditory motion in blindness (Poirier et al., 2005), and parts of visual cortex typically involved in visuo-spatial localization are active when blind individuals localize sounds (Collignon et al., 2011). On the other hand, visual cortices of blind individuals are also active during high-level language tasks such as remembering words and understanding sentences (Röder et al., 2002; Sadato et al., 2002; Amedi et al., 2003; Bedny et al., 2011; Lane et al., 2015). Here I find that these visual cortex responses to language coexist with but are distinct from responses to number. Our results thus suggest that previously observed plasticity for language is part of a broader pattern whereby the visual system of blind individuals takes on higher-cognitive functions.

The responses to math that I observed in the occipital cortices of blind individuals overlap with early visual areas that, in sighted individuals, contain retinotopic maps, support visual functions such as motion detection, shape representation, and visuospatial attention (Tootell et al., 1997; Grill-Spector et al., 1998; Martínez et al., 1999; Vinberg and Grill-Spector, 2008). Unlike these visual functions, mathematics is symbolic and depends on cultural experience. The present results thus show that plasticity need not preserve the "typical" functions of cortex, and that the same cortical circuit can participate in widely different cognitive functions depending on experience (Amedi et al., 2003; Bedny et al., 2011).

A full test of this idea will require investigating the representational content of number-responsive visual regions in blindness. It is not yet known whether, like the IPS, number-responsive visual regions participate in non-symbolic number processing (e.g., numerical approximation), and whether math-responsive "visual" cortex develops population codes to represent approximate quantities (Piazza et al., 2007a; Eger et al., 2009). It will also be important to determine whether number-responsive visual cortices are functionally relevant to numerical behavior. For example, studies using TMS suggest that visual cortices are functionally relevant for Braille reading, verb generation, and tactile discrimination (Cohen et al., 1997; Amedi et al., 2004; Merabet et al., 2004). In the present study, I observed a relationship between numerical performance and neural activity in number-responsive visual cortex of blind individuals, suggesting that visual cortex plasticity may play a role in modulating behavior. The functional relevance of the visual cortex for numerical cognition should be directly tested using techniques such as TMS.

Finally, this work raises questions regarding the timing of radical cortical plasticity. I hypothesize that such extreme functional repurposing--from vision to symbolic number--is restricted to a sensitive period during development. Previous work has shown that congenital and late blindness lead to different patterns of plasticity (Bedny et al., 2012b). An intriguing possibility, then, is that cortex is cognitively pluripotent only in early development. If so, the functions of visual cortices in late blind individuals may resemble the original functions of visual cortices in the sighted. Testing these predictions will further inform our understanding of how biology and experience shape the neural basis of thought.

3.5 Conclusions

In Chapter 3, I established two important observations about the neural basis of numerical thinking in blindness. First, the fronto-parietal number system is preserved in blindness, as measured by a symbolic number task. Second, blind individuals recruit parts of the “visual” cortex during symbolic math calculation and these areas are both anatomically and functionally distinct from “visual” areas that respond to language. In

Chapters 4 and 5 I address two questions about the “visual” cortex plasticity observed in this Chapter. First, to more directly test whether functional repurposing of visual cortices for higher-cognitive functions is related to connectivity with fronto-parietal networks, I ask whether number- and language-responsive “visual” cortices show dissociable patterns of functional connectivity with fronto-parietal networks. Second, in Chapter 5, I ask whether the visual cortex is capable of such dramatic functional repurposing even in adulthood or whether plasticity for higher-cognitive functions follows a sensitive period of development. Finally, in Chapter 6, I ask whether “visual” areas that respond to symbolic number also develop a more fine-grained population code to represent non-symbolic, approximate numerosity. In this final chapter, I also return to the question of whether fronto-parietal networks that represent approximate number information in sighted individuals develop such representations in the absence of vision.

3.6 Supplementary Material

Supplementary Table 3.1 Brain regions more active for math than sentences

Brain Region	*x*	*y*	*z*	**Peak *t***	**mm^2**	$P_{cluster}$
Math > Sentences						
Blind						
Left superior parietal lobule	-17	-70	45	8.25	3268.82	0.0002
Left precuneus	-6	-72	50	7.95		
Left supramarginal gyrus	-54	-39	47	6.82		
Left postcentral sulcus	-35	-44	42	6.36		
Left intraparietal sulcus	-28	-64	43	5.87		
Left superior parietal lobule	-15	-58	60	5.47		
Left middle frontal gyrus	-39	50	9	7.71	1376.01	0.008
Left transverse frontopolar gyri and sulci	-21	59	-3	6.78		
Left middle frontal gyrus	-45	31	29	6.56		
Left superior frontal sulcus	-22	3	50	7.96	932.94	0.0172
Left superior precentral sulcus	-34	-8	46	4.1		
Left pericallosal sulcus	-2	-30	27	6.47	792.97	0.021
Left marginal branch of cingulate sulcus	-11	-41	45	5.93		
Left middle-anterior cingulate gyrus and sulcus	-8	5	48	5.9	487.78	0.0426
Left superior frontal gyrus	-7	31	31	5.58		
Right intraparietal sulcus	24	-60	50	7.89	1585.75	0.0084
Right precuneus	5	-61	56	7.82		
Right superior occipital gyrus	23	-75	44	7.09		
Right superior parietal lobule	24	-59	61	5.87		
Right middle occipital sulcus	33	-82	9	6.4	1206.92	0.012

Right middle occipital gyrus	40	-83	22	5.76		
Right occipital pole	24	-98	8	5.52		
Right superior occipital sulcus	26	-83	16	5.29		
Right inferior frontal sulcus	43	33	20	7.27	1124.94	0.0128
Right middle frontal gyrus	38	27	39	7.12		
Right superior frontal sulcus	26	34	34	5.25		
Right supramarginal gyrus	59	-25	36	4.79		
Right middle frontal sulcus	27	49	3	4.57		
Right middle frontal gyrus	35	4	55	8.39	829.84	0.018
Right superior frontal gyrus	23	3	66	5.45		
Right posterior cingulate gyrus and sulcus	3	3	34	8.35	517.48	0.0316
Right pericallosal sulcus	5	-15	30	4.04		
Right marginal branch of cingulate sulcus	7	-41	44	6.89	439.95	0.0418
Right medial occipito-temporal sulcus	32	-43	-15	5.84	393.22	0.0488
Sighted						
Left intraparietal sulcus	-34	-46	42	7.9	2574.59	0.0016
Left angular gyrus	-29	-69	41	7.62		
Left superior parietal lobule	-13	-61	61	5.99		
Left marginal branch of cingulate sulcus	-16	-37	41	10.86	1014.38	0.0086
Left posterior-dorsal cingulate gyrus	-3	-25	33	4.75		
Left pericallosal sulcus	-2	-28	27	4.11		
Right marginal branch of cingulate sulcus	13	-28	38	7.48	2090.13	0.0014
Right superior parietal lobule	16	-75	45	5.99		
Right middle occipital gyrus	40	-80	30	5.98		
Right superior parietal lobule	17	-63	63	5.93		
Right precuneus	8	-54	59	5.23		
Right intraparietal sulcus	36	-46	36	5.96	907.48	0.008

Right supramarginal gyrus	58	-36	44	4.96		
Right superior precentral sulcus	31	-4	46	4.92	432.29	0.0402
Right superior frontal gyrus	18	14	62	4.61		
Blind > Sighted						
Left middle occipital sulcus	-25	-95	1	5.08	508.99	0.0282
Left medial occipito-temporal sulcus	-29	-55	-12	4.84	399.62	0.0474
Right middle occipital sulcus	33	-82	9	6.38	962.39	0.0064
Right superior occipital sulcus	27	-84	15	5.19		
Right occipital pole	24	-98	8	5.08		
Right medial occipito-temporal sulcus	32	-45	-14	5.56	574.51	0.0194

Peaks of brain regions active more for math than language ($p<0.05$, cluster-corrected; $p<0.01$ cluster forming threshold; 10mm minimum distance between peaks). Coordinates reported in MNI space. Peak *t*: t-values corresponding to local maxima; mm2: area occupied by cluster on cortical surface; $P_{cluster}$: p-value for entire cluster.

Chapter 4

Region-specific increases in fronto-occipital resting-state synchrony mirror functional sub-specialization of visual cortex for higher cognitive functions

4.1 Introduction

In Chapter 3, I find that, in congenitally blind but not sighted individuals, a dorsal occipital (“visual”) region, specifically the right middle occipital gyrus (rMOG), is recruited during math calculation and is sensitive to the difficulty of math equations. This finding suggests that parts of the “visual” cortex are repurposed for higher-cognitive functions in congenital blindness and, in doing so, support the hypothesis that cortical areas are functionally flexible at birth and that experience plays a major role in the development of cortical function. However, the prior study did not directly test the hypothesized link between connectivity and function. As noted in the introduction, according to the pluripotency hypothesis, the function of a cortical area is heavily influenced by the input it receives during development. This input is jointly constrained by the connectivity of a cortical area and the experience of the individual. The evidence presented in Chapter 3 shows that experience plays a role in the development of cortical function, but does connectivity do so as well? How would we test this prediction?

Previous studies using diffusion tractography imaging (DTI) in humans and chemical tracers in animals have shown that intraparietal regions and dorsal occipital cortices are indeed anatomically connected (Blatt et al., 1990; Nakamura et al., 2001; Uddin et al., 2010a; Greenberg et al., 2012). One hypothesis might be that these occipito-parietal anatomical connections are enhanced in congenital blindness. However, anatomical connectivity need not be modified to support functional repurposing of visual cortices in congenital blindness. Instead, merely removing competing bottom-up input from the lateral geniculate nucleus (LGN) may be sufficient to spark functional coupling between visual cortices and higher-cognitive networks, without necessarily increasing the anatomical connectivity between "visual" cortices and fronto-parietal networks.

Indeed, studies of anatomical connectivity in congenital blindness do not find increases in anatomical connectivity between the "visual" cortex and fronto-parietal networks (Shimony et al., 2006; Liu et al., 2007; Yu et al., 2008). Rather, modifications in structural connectivity are observed in the partial atrophy of the lateral geniculate pathway and fewer connections among visual cortex areas (Noppeney et al., 2005; Noppeney, 2007). By contrast, functional connectivity between the visual cortex and fronto-parietal networks does increase in congenital and early blindness (Liu et al., 2007, 2017b; Striem-Amit et al., 2012; Watkins et al., 2012; Wang et al., 2014; Deen et al., 2015; Hasson et al., 2016). I return to this finding below, but first I briefly discuss how functional connectivity is measured and what biological factors it is thought to reflect.

Measures of resting-state functional connectivity are obtained by correlating the activity among different cortical regions while participants are awake and resting in the scanner (i.e. in the absence of a task). These correlations reflect a complex combination of anatomical and functional factors (Fox and Raichle, 2007; Damoiseaux and Greicius, 2009; Greicius et al., 2009; Honey et al., 2009; Raichle, 2010; Hutchison et al., 2013). Cortical regions that have strong long-range anatomical connections tend to have stronger functional connectivity, however, as regions can be synchronized through intermediary areas, these anatomical connections need not be direct (Damoiseaux and Greicius, 2009; Greicius et al., 2009; Honey et al., 2009). Critically, resting-state connectivity reflects the functional coupling between cortical regions above and beyond the strength of anatomical connectivity. A number of studies show that training and practice with specific tasks can shape the degree of synchronization across task-relevant cortical areas, suggesting that spontaneous fluctuations in brain activity are influenced by experience (Lewis et al., 2009; Ma et al., 2011; Taubert et al., 2011; Mackey et al., 2013).

Studies of blindness further support the hypothesis that functional connectivity can be altered by life-time experience, without changing anatomical connectivity. As stated earlier, a number of studies find increased resting-state functional connectivity between fronto-parietal regions and visual cortices in congenital blindness (Liu et al., 2007, 2017b; Striem-Amit et al., 2012; Watkins et al., 2012; Wang et al., 2014; Deen et al., 2015; Hasson et al., 2016). Consistent with functional repurposing for language functions, some “visual” regions become more correlated with inferior frontal language areas in congenital blindness and these same “visual” regions develop sensitivity to language in congenital blindness (Bedny et al., 2011; Watkins et al., 2012; Deen et al., 2015). These studies suggest that the functional reorganization of the visual cortex may be accomplished, in part, by up-regulating its functional interactions with fronto-parietal and fronto-temporal systems.

This hypothesis predicts that parts of the “visual” cortex that are recruited during numerical processing will show increased resting-state functional connectivity with fronto-parietal number networks, analogous to the enhanced resting-state synchrony observed between inferior frontal language areas and language responsive “visual” cortex (Bedny et al., 2011; Watkins et al., 2012; Deen et al., 2015). Furthermore, the proposed mechanism visual cortex plasticity predicts that the sub-specialization of visual cortices for numerical as opposed to linguistic processing will be related to specialized patterns of resting-state functional connectivity with higher-cognitive networks.

In order to test these hypotheses, I asked whether the sub-specialization of visual cortices for math and language functions systematically aligns with their functional connectivity patterns with math- and language-responsive fronto-parietal networks. First, I asked if math-responsive IPS exhibits a higher degree of resting-state functional connectivity with the math-responsive visual region identified in Chapter 3, the right middle occipital gyrus (rMOG), compared to language-responsive ventral occipito-temporal cortex (rVOT). Next, to address the possibility that activity in the IPS is more correlated with that of the rMOG than rVOT simply due to its proximity to the rMOG, I also tested whether the rMOG is more correlated with math-responsive dorsolateral prefrontal cortex (rDLPFC) than a similarly distant language-responsive inferior frontal region (inferior frontal cortex, rIFC). Furthermore, to determine whether the sub-specialization of the visual cortex is related to connectivity with distinct higher-cognitive networks, I asked if the resting-state functional connectivity patterns of math- and language-responsive visual cortices show a double dissociation with respect to math- and language-responsive prefrontal cortices.

4.2 Materials & Methods

4.2.1 Participants

Forty-three blind-folded sighted (mean age=34.12 years, SD=14.33, min=18.88, max=63.19; 25 female) and 25 (mean age=46.63, SD=16.91, min=18.81, max=72.98; 18 female) congenitally blind individuals contributed resting-state data.

4.2.2 MRI Data Acquisition

Participants contributed one to four 8-minute runs of resting-state data across different testing sessions. Participants were instructed to relax and remain awake. All other data acquisition parameters were identical to those described in Chapter 3.

4.2.3 Resting-state functional connectivity analysis

Resting-state data were analyzed using CONN v.17 Functional Connectivity Toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Functional data were linearly detrended by including a linear regressor in the general linear model to remove low-frequency drift. Data were despiked by applying a hyperbolic tangent “squashing” function to data from every time point. Data were band-pass filtered (0.008-0.1 Hz) and signal from white mater and cerebrospinal fluid were regressed out. Functional data were smoothed 23 diffusion steps (corresponding to ~6mm smoothing in volume) (Hagler et al., 2006).

ROI-to-ROI resting-state functional connectivity analyses were conducted in the right hemisphere, since task-based effects were right-lateralized. Search-spaces were defined across groups and group-specific (congenitally blind and sighted) ROIs were defined within these search-spaces. To avoid biasing search-space definition to the group with the larger sample size, I used data from the first 13 congenitally blind and first 13 sighted participants to define search-spaces. Note that 13 adult-onset blind participants also contributed data to the ROI definition. Data from adult-onset blind individuals will be discussed in Chapter 5. This subsample of 39 participants was entered into a single random-effects model to find prefrontal math (math>language) and language (language>math) responsive areas common across groups ($p<0.01$, uncorrected). Within these broad regions, math- and language-responsive prefrontal ROI's were defined separately for each group (using all participants for that group) by taking the top 250 vertices with the greatest response to the math>language and language>math contrast, respectively (Fig. 4.1). Math-responsive IPS ROI's were defined for each group by taking the top 250 vertices with the greatest math>language effect within anatomically defined IPS search-space (Destrieux et al. 2010; Fig. 4.1).

Math- and language-responsive ROIs in the visual cortex could only be defined in the congenitally blind group and thus CB ROIs were used for both groups. A cluster in dorsal occipital cortex that responded to the math>language contrast in CB>S served as the math-responsive visual cortex ROI ($p<0.01$, uncorrected; Fig. 4.1). A cluster in ventral occipito-temporal cortex (within occipital lobe mask) that responded to the language>math contrast in CB>S served as the language-responsive visual cortex ROI ($p<0.01$, uncorrected; Fig. 4.1).

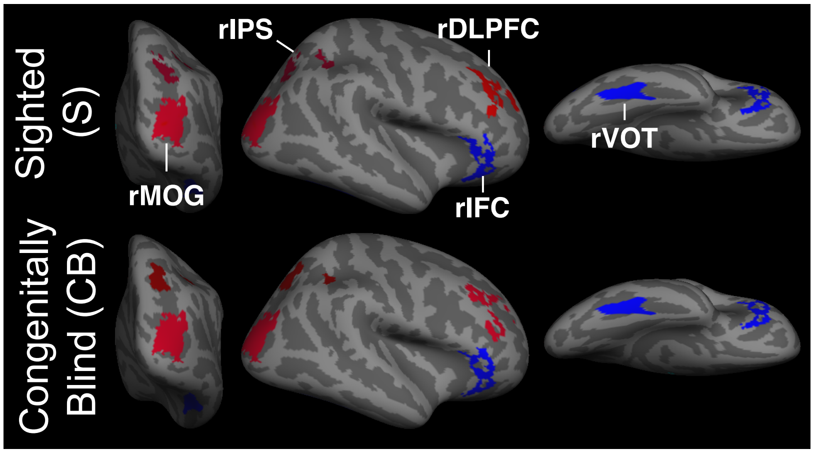


Fig. 4.1 Regions of interest (ROIs) for resting-state analysis. Red ROIs are math-responsive (defined with math>sentences contrast) and blue ROIs are language – responsive (defined with sentences> math contrast).

4.3 Results

First, I asked whether fronto-occipital resting-state synchrony increases in general in congenital blindness. Indeed, in congenital blindness, visual cortices become more correlated at rest with parietal and prefrontal cortices: math-responsive rMOG and language-responsive rVOT were more correlated with the rIPS, rDLPFC and rIFG in the congenitally blind as opposed to sighted (main effect of group (CB vs. S) connectivity of visual cortex to rIPS: $F(1,65)=24.49$, $p<0.001$; main effect of group connectivity of visual cortex to prefrontal cortices (rDLPFC and rIFG): $F(1,65)=16.11$, $p<0.001$; Fig. 4.2 & 4.3).

Furthermore, I found that increases in functional connectivity among congenitally blind individuals are network-specific. Math-responsive rMOG but not language responsive rVOT shows elevated resting-state correlations with math-responsive rIPS (seed (rMOG vs. rVOT) by group (CB vs. S) interaction: F(1,65)=5.32, p=0.02; Fig. 4.2). Similarly, while math-responsive visual cortex (rMOG) becomes more correlated with math-responsive portions of prefrontal cortex (rDLPFC), language-responsive visual cortex (VOT) becomes more correlated with inferior frontal language areas (seed (rMOG vs. rVOT) by ROI (rDLFPC vs. rIFC) by group (CB vs. S) interaction: F(1,65)=12.39, p=0.001; Fig. 4.3).

Although the specialization of functional connectivity is stronger in the congenitally blind group, within-group analyses showed that, both for the congenitally blind and for the sighted, within-network correlations (math visual cortex to math prefrontal cortex) are higher than between network correlations (math visual cortex to language prefrontal cortex) (seed by ROI interaction in CB group: F(1,23)=23.41, p<0.001; and sighted group: F(1,42)=6.57, p=0.01).

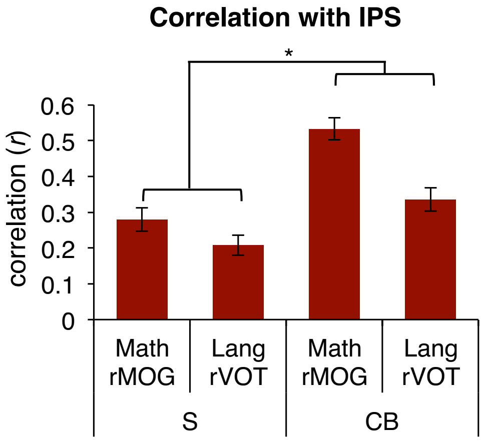


Fig. 4.2 Resting-state functional connectivity between "visual" cortex and IPS. Functional connectivity of math-responsive visual cortex (rMOG) and language-responsive visual cortex (rVOT) with math-responsive IPS.

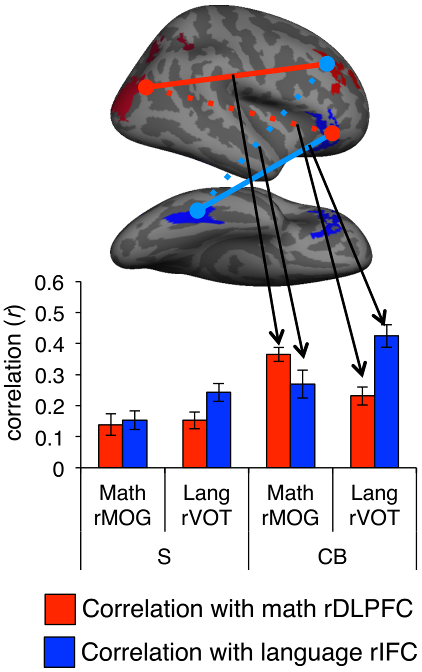


Fig. 4.3 Resting-state functional connectivity between "visual" cortex and prefrontal cortex. Schematic for predicted connectivity patterns shown on inflated surface above. Higher resting-state correlations are predicted between regions connected by solid lines and lower correlations are predicted between regions connected by dashed lines. Bar graph shows actual correlation values between math-responsive visual cortex (rMOG) and language-responsive visual cortex (rVOT) with math-responsive rDLPFC (red) and language-responsive rIFC (blue).

4.4 Discussion

I found that, in resting-state data, number-responsive occipital areas of congenitally blind individuals were correlated with the fronto-parietal number network, whereas language-responsive visual areas were correlated with the language network.

Specifically, activity in math-responsive intraparietal sulcus (rIPS) was more correlated with that of math-responsive visual cortex (rMOG) than that of language-responsive visual cortex (rVOT). This pattern is likely related to the functional similarity between the rMOG and the rIPS rather than their physical proximity because the rMOG also showed selective increases in resting-state synchrony with math-responsive rDLPFC compared to similarly distant language-responsive rIFC. By contrast, language-responsive visual cortex (rVOT) showed the opposite pattern, with activity more correlated with that of language-responsive rIFC than math-responsive rDLPFC.

These results indicate that dissociations in resting-state functional connectivity across visual cortices relate to dissociations in task-based response profiles of visual cortices of blind individuals. More generally, these results suggest that, in congenital blindness, if the baseline spontaneous activity of a "visual" area is preferentially synchronized with a specific higher-cognitive network, it also demonstrates a similar response profile as that network during a task.

These results are consistent with findings that visual cortex repurposing for language functions in congenital blindness goes hand in hand with increased resting-state synchrony with inferior frontal language regions (Bedny et al., 2011; Watkins et al., 2012; Deen et al., 2015). For example, sentence-responsive lateral occipital cortex of congenitally blind individuals is more correlated with the inferior frontal gyrus at rest in congenitally blind compared to sighted individuals (Bedny et al., 2011; Deen et al., 2015). Independent component analyses reveal that occipital cortices are incorporated into the canonical resting-state language in individuals who are congenitally blind due to anophthalmia (Watkins et al., 2012). Similarly, central V1 shows increased resting-state correlations with the inferior frontal gyrus in congenitally blind compared to sighted individuals (Striem-Amit et al., 2015). Consistent with the connectivity hypothesis, during language tasks, V1 responds more to sentences than backwards speech and shows sensitivity to grammar in congenitally blind but not sighted individuals (Bedny et al., 2012b; Lane et al., 2015).

Here, I find that the previously observed relationships between resting-state functional connectivity and functional repurposing is not exclusive to language-related visual cortex plasticity. I find that, in congenital blindness, regions across the visual cortex become selectivity coupled with distinct higher-cognitive networks at rest. Furthermore, the task-evoked responses of visual cortices reflect that of the higher-cognitive network with which it is coupled during rest. These results point to increased functional connectivity with fronto-parietal networks as a potential mechanism by which visual cortices are repurposed for multiple distinct higher-cognitive functions in congenital blindness.

A key open question concerns the developmental origins of these functional connectivity biases across visual cortices in congenital blindness. Why does the rMOG become selectively coupled with the fronto-parietal number network while the rVOT becomes synchronized with inferior frontal language regions at rest? Dissociations in the resting-state functional connectivity patterns across visual cortices could emerge from intrinsic biases in anatomical connectivity across the visual cortex. According to this idea, in sighted and blind infants alike, there is stronger anatomical connectivity between the rMOG region of visual cortex and the fronto-parietal number network on the one hand, and the rVOT region of the visual cortex and the fronto-temporal language network on the other. In the sighted, this anatomical pattern may give rise to some region-specific fronto-occipital synchrony but does not lead to the specialization for number and language in the visual cortex, because non-visual inputs are dwarfed by bottom-up inputs from the visual pathway. By contrast, in congenital blindness, this anatomical bias leads both to selective increases in functional synchronization at rest and to recruitment of these different "visual" areas during language and number tasks respectively.

Indeed, in the current study, I find that the rMOG and rVOT of sighted individuals show a small but similar dissociation in functional connectivity with number and language networks as congenitally blind individuals. This is despite the fact that the visual cortices of sighted individuals do not become sub-specialized for math and language. This result suggests different "visual" regions may have intrinsic biases in functional connectivity with different higher-cognitive networks, perhaps as a result of innately specified anatomical tracts. Predisposed biases may become enhanced in the absence of competing bottom-up visual input in congenital blindness.

Although there is, at present, no direct anatomical connectivity evidence for the above hypothesis in blindness, anatomical biases have been shown to determine the localization of visual functions in sighted individuals. For example, in sighted children, the visual word form area (VWFA) has strong anatomical connectivity with fronto-temporal language networks even before literacy (Dehaene et al., 2015). Furthermore, the location of these anatomical connections within the ventral occipito-temporal cortex predicts individual differences in the future location of letter and word responses in the ventral stream (Saygin et al. 2016). Notably, in congenital blindness, the VWFA is one of the "visual" areas that becomes responsive to high level linguistic content (i.e. grammar)

(Lane et al., 2015; Kim et al., 2017). Such evidence provides general support for the idea that anatomical connectivity predicts resting-state synchrony and task-based responses. Whether it does so in the specialization of visual cortex for number as opposed to language remains to be tested. Future work should use diffusion tractography imaging (DTI) to directly compare structural connectivity of math- and language-responsive visual areas between sighted and congenitally blind individuals.

4.5 Conclusions

To summarize, I find that, in congenital blindness, parts of the “visual” cortex that are recruited during numerical processing are preferentially functionally coupled with the fronto-parietal number network even in the absence of a task. Furthermore, the sub-specialization of visual cortices for different higher-cognitive functions is related to biases in functional connectivity with higher-cognitive fronto-parietal networks. These results point enhanced functional coupling between visual cortices and higher-cognitive networks as a potential mechanism by which “visual” cortex is repurposed for higher-cognitive functions.

In the following chapter (Chapter 5), I ask whether the human cortex is capable of dramatic functional repurposing even later in development or whether the the observed visual cortex plasticity for numerical functions is circumscribed to a sensitive period in development. I asked whether the rMOG is recruited for numerical processing and shows sensitivity to mathematical difficulty in individuals who became blind in adulthood. Furthermore, I investigate whether the up-regulation of functional connectivity between “visual” cortices and fronto-parietal networks is similarly restricted to a sensitive period in development by conducting the resting-state functional connectivity analyses described in this Chapter in individuals who became blind in adulthood.

Chapter 5

Repurposing of visual cortex for number is restricted to sensitive periods in development

5.1 Introduction

In Chapters 3 and 4, I present evidence that the "visual" cortex can be repurposed for multiple higher-cognitive functions if vision is absent since birth and that the sub-specialization of visual cortex relates to functional connectivity of visual regions with higher-cognitive networks. Consistent with the pluripotency hypothesis, this pattern of plasticity suggests that the visual system can be taken over by cortical networks that have strong connectivity to visual cortices, irrespective of the cognitive differences between the functions of these networks and the visual cortices (Bedny et al., 2011). More generally, these results illustrate that the human cortex is extremely flexible and capable of supporting a wide range of functions, from low-level vision to high-level language and math, both of which require years of cultural and educational experience to develop.

A key question concerns the limits on such cortical flexibility. Does human cortex retain the ability to support a wide range of cognitive functions throughout the lifespan? Alternatively, is such drastic functional repurposing uniquely possible during sensitive periods of development?

It is generally established that plasticity in the developing brain is enhanced relative to the mature brain. The most well studied example of this phenomenon comes from monocular visual deprivation. When one eye does not receive typical input during a critical period in development, visual cortex neurons that would normally respond to the deprived eye are overtaken by input from the dominant or “good” eye (Hubel and Wiesel, 1970). Analogously in humans, dense cataracts in one eye during the first years of life but not afterwards cause impairments in visual acuity, even after the cataract is removed (Banks et al., 1975; Lewis and Maurer, 2005). Recent research in the mouse model has uncovered local-circuit neurophysiological mechanisms that regulate sensitive period plasticity and distinguish it from other forms of learning. Sensitive period opening and closure involves shifts in the excitatory/inhibitory balance and the closure of sensitive periods coincides with formation of perineuronal nets, which dampens synaptic plasticity (Pizzorusso, 2002; Hensch, 2005; Bavelier *et al.*, 2010). Thus, local circuit plasticity during sensitive periods is mediated by specific neurophysiological mechanisms.

Whether the capacity of cortex to take on novel cognitive functions similarly depends on sensitive period plasticity remains unknown. As noted above, some functional plasticity is possible, even in adulthood (Merzenich et al., 1983, 1984; Kaas, 1991). For example, amputation of a limb causes neighboring cortical representations of intact body parts to expand into deafferented somatosensory cortices (Calford and Tweedale, 1988; Pascual-Leone et al., 1996, 2005; Borsook et al., 1998; Röricht et al., 1999). This activation appears to be functionally relevant as TMS to the newly deafferented arm region of somatosensory cortex induces sensations in the face and biceps (Pascual-Leone et al., 1996; Röricht et al., 1999). Arguably, however, the functional plasticity observed in amputation is relatively subtle, as compared to that seen in blindness or deafness. Is more dramatic functional repurposing of cortex circumscribed to sensitive periods of development?

Some evidence for the idea that visual cortices assume different functions in congenital and adult-onset blindness comes from studies of auditory motion and spatial perception. Dorsal visual areas that preferentially respond to sound localization in congenital blindness do not show such cross-modal recruitment in adult-onset blindness (Haxby et al., 1991; Goodale and Milner, 1992; Voss et al., 2006; Collignon et al., 2013a). Visual motion processing area, MT, only shows enhanced auditory motion processing in individuals who lose their vision early in life, but not later in life (Jiang et al., 2016). Such evidence suggests that the capacity of cortex to take on novel functions in adulthood is restricted.

However, studies of higher-cognitive plasticity in visual cortex of adult-onset blind individuals have thus far yielded mixed results. Consistent with the idea of sensitive periods, one study reported that V1 responds more to sentences than non-verbal sounds only in those who are congenitally blind (Bedny et al., 2012b). On the other hand, even in adult-onset blindness, visual cortices appear to be active during higher-cognitive tasks, such as Braille reading, phonological judgments of spoken words and sentence comprehension, although it is not clear what such activity reflects (Cohen et al., 1999; Burton and McLaren, 2006; Burton et al., 2011). A recent study also found that resting-state activity of visual cortices becomes synchronized with that of Broca's area in adult-onset blindness (Sabbah et al., 2016).

None of previous studies, however, directly address the question of whether visual cortices are sensitive to higher-cognitive information in adult-onset blindness. The most compelling evidence for visual cortex involvement in higher-cognitive functions in congenital blindness comes from studies that manipulate fine-grained higher-cognitive information, such as the grammatical complexity of sentences and difficulty of math equations (Röder et al., 2002; Bedny et al., 2011; Lane et al., 2015; Kanjlia et al., 2016). By contrast, all prior work with adult-onset blind individuals has compared higher-cognitive tasks to a resting baseline or low-level perceptual control condition, making it difficult to determine what cognitive processes visual cortex activity truly reflects in the adult-onset blind population (Cohen et al., 1999; Burton and McLaren, 2006; Burton et al., 2011). If the extreme cognitive flexibility of cortex is restricted to a sensitive period, visual cortices of adult-onset blind individuals should not respond to manipulations of higher-cognitive information.

A further open question concerns whether cognitive repurposing, as measured by task-based responses, follows a similar developmental time-course as changes in resting-state connectivity. As noted above, in congenital blindness, resting-state activity in visual cortices becomes synchronized with that of fronto-parietal higher-cognitive networks. These resting-state changes are region and network-specific. “Visual” regions that are active during mathematical processing show correlated activity with fronto-parietal number networks, even at rest, whereas those that respond to grammatical and semantic information during language tasks are correlated with Broca’s area (Bedny et al., 2009; Kanjlia et al., 2016). It is not known whether such region-specific increases in functional connectivity of visual cortex follow a sensitive period and, if so, whether this sensitive period aligns with that of task-based responses. Answering this question could provide general insights into the relationship between task-based and resting-state connectivity measures.

In the current study, I addressed these open questions by comparing task-based activation and resting-state functional connectivity across adult-onset blind (blind after 17-years-of-age), congenitally blind and blindfolded sighted participants. Since the goal of this Chapter is to investigate the limits of functional reorganization in the human cortex, I studied the visual cortex plasticity in individuals who became blind after puberty (i.e. in adulthood). Furthermore, non-congenital blindness is often progressive and can onset as early as at birth before individuals become completely blind in adulthood. Thus, the participant pool was restricted to individuals whose blindness onset was either clearly defined or at least acquired progressively within adulthood.

First, adult-onset blind participants completed the symbolic math experiment described in Chapter 3. I asked whether visual cortices of adult-onset blind individuals show regional specialization for math as opposed to language and whether they show load dependent responses during higher-cognitive tasks--in particular, during symbolic mathematical reasoning. Second, I used the resting-state functional connectivity analysis described in Chapter 3 to test whether adult-onset blind individuals show similar region-specific increases in functional connectivity between visual cortices and fronto-parietal networks.

This study improves upon prior work in a number of respects. First, prior studies often confound cognitive effects with general cross-modal responses by comparing activity during cognitive tasks to to rest or to low-level controls. Here, I test plasticity for math by comparing math calculation to a closely-matched language control task. Second, rather than comparing the magnitude and extent of visual cortex responses to one contrast across groups, this experiment allows us to assess whether the visual cortex of adult-onset blind individuals shows a qualitatively similar functional profile as that of congenitally blind individuals. Third, prior studies often compare congenitally blind individuals to late-blind individuals with a wider range of blindness onsets. If the capacity for functional reorganization of the visual cortex changes gradually over development, prior studies may be averaging over different capacities to reorganize. Here, I work with a more clearly defined adult-onset blind group to evaluate the plastic potential of the adult cortex. Finally, I improve on the smaller sample sizes of prior studies by collecting data from a sizeable set of 13 adult-onset blind individuals.

5.2 Materials and Methods

5.2.1 Participants

Nineteen blind-folded sighted (age=21.45-75.49 years, mean=45.61, SD=16.03; 9 female), 13 adult-onset blind (age=34.74-74.72, mean=57.18, SD=11.77; 3 female) and 20 congenitally blind (age=19.34-70.12, mean age=46.08 years, SD=16.80; 15 female) participants contributed data to the current study (Table 5.1). Seven additional participants were scanned but excluded from all analyses because overall accuracy on the math and language tasks fell below 60% (5 congenitally blind) or because of incomplete coverage of the occipital lobe (2 sighted).

All blind participants had at most minimal light perception at the time of the experiment and had lost their vision due to pathology at or anterior to the optic chiasm and not due to brain damage. All participants reported having no cognitive or neurological disabilities. Participants with adult-onset blindness became blind (reached their current level of vision) after the age of 17 (mean=40.85, SD=17.36, min=17, max=70) and were blind for an average of 16.11 years after reaching their current level of vision (SD=8.99, min=4.72, max=31.35) (Table 5.1).

Forty-three blind-folded sighted (mean age=34.12 years, SD=14.33, min=18.88, max=63.19; 25 female), 12 adult-onset blind (mean age=56.79, SD=12.21, min=34.74, max=74.75; 2 female) and 25 (mean age=46.63, SD=16.91, min=18.81, max=72.98; 18 female) congenitally blind individuals contributed resting-state data. A subset of participants who contributed resting-state data also participated in the task-based fMRI experiment (indicated with asterisk in Table 5.1).

Task data from all 19 sighted participants and 16 congenitally blind participants as well as resting-state data from all sighted and congenitally blind participants are reported in Chapters 3 and 4, respectively.

Table 5.1 Participant demographic information

Participant	**M/F**	**Age**	**Cause of Blindness**	**Light Perception**	**Education**	**Age Functional Vision Loss Began**	**Age Could No Longer Read Written Print**	**Age Reached Current Level of Vision**	**Blindness Duration (after reaching current level of vision)**
AB1	F	62	Autoimmune	None	AA	37	55	57	5
AB2*†	M	46	Trauma	Minimal	PhD	22	22	22	24
AB3*†	M	48	DR	None	BA	17	17	17	31
AB4*†	M	54	RP	Minimal	BA	33	34	35	19
AB5*†	M	35	RP	Minimal	MA	19	19	19	31
AB6*	F	50	Trauma	None	JD	17	21	25	10
AB7*†	F	68	Glaucoma	Minimal	BA	48	49	49	19
AB8*†	M	70	DR	None	HS	45	47	47	20
AB9*	M	65	RP	Minimal	MA	28	57	59	6
AB10*	M	69	Glaucoma	None	PhD	49	55	59	10
AB11*	M	75	RP	Minimal	BS	32	62	70	5
AB12*	M	51	ONN	None	BA	21	32	34	17
AB13*†	M	52	Glaucoma	None	HS	38	38	38	14
CB1	M	23	LCA	Minimal	SC	0	0	0	23
CB2*	F	33	ROP	Minimal	BA	0	0	0	33
CB3*	F	70	ROP	Minimal	HS	0	0	0	70
CB4*	M	43	Unknown	None	JD	0	0	0	43
CB5	F	68	ROP	None	MA	0	0	0	68
CB6*	F	27	ROP	Minimal	MA	0	0	0	27
CB7*	F	65	ROP	None	MA	0	0	0	65
CB8	F	35	LCA	Minimal	MA	0	0	0	35
CB9*	M	48	LCA	None	JD	0	0	0	48
CB10*	F	40	ROP	None	MA	0	0	0	40
CB11*	F	49	LCA	Minimal	MA	0	0	0	49
CB12*	F	25	LCA	Minimal	MA	0	0	0	25
CB13*	F	63	ROP	None	MA	0	0	0	63
CB14*	M	63	ROP	None	BA	0	0	0	63
CB15*	F	61	ROP	None	JD	0	0	0	61
CB16*	F	47	ROP	None	BA	0	0	0	47
CB17*	F	68	ROP	None	BA	0	0	0	68
CB18*	F	29	LCA	Minimal	BA	0	0	0	29
CB19*	M	47	Unknown	Minimal	BA	0	0	0	47
CB20*	F	19	LCA	Minimal	SC	0	0	0	19
Average of Participants in Math Task (LB and CB listed individually above)									
Sighted	**n=19** **9 F**	**45**	**--**	**--**	**BA**	**--**	**--**	**--**	**--**
Late Blind	**n=13** **3 F**	**58**	**--**	**--**	**BA**	**31**	**39**	**41**	**16**
Congenitally Blind	**n=20** **12 F**	**46**	**--**	**--**	**BA**	**0**	**0**	**0**	**46**
Average of Participants in Resting-State									
Sighted	**n=43** **25F**	**34**	**--**	**--**	**--**	**--**	**--**	**--**	**--**
Late Blind	**n=12** **2F**	**57**	**--**	**--**		**25**	**32**	**33**	**21**
Congenitally Blind	**n=25** **18 F**	**47**	**--**	**--**		**0**	**0**	**0**	**45**

*Indicates that participant contributed resting-state data; †Indicates that participant included in correlations with duration of blindness (see Methods); DR=Diabetic Retinopathy; LCA=Leber Congenital Amaurosis; ONN=Optic Nerve Neuropathy; RP=Retinitis Pigmentosa; ROP=Retinopathy of Prematurity; AA=Associates Degree; BA=Bachelor of Arts; MA=Master of Arts; HS=High School; JD=Juris Doctor; SC=Some College;

5.2.2 Behavioral Task

The behavioral task was identical to that described in Chapter 3.

5.2.3 MRI Data Acquisition

MRI data acquisition parameters were identical to that described in Chapter 3.

5.2.4 fMRI Data Analysis

fMRI preprocessing, within- and between-subject analyses, and correction for multiple comparison steps were identical to those described in Chapter 3.

Math-responsive regions of interest (ROIs) in the intraparietal sulcus (IPS) were defined within an anatomical IPS search-space, using a leave-one-run-out procedure. Using all but one run, ROIs were defined by taking the top 20 vertices within the search-space with the greatest math>language effect (Destrieux et al., 2010). Percent signal change (PSC) for all four math conditions and the language condition was then extracted from the left out run using finite impulse response modeling (Lindquist et al., 2009). This procedure was repeated iteratively until PSC was extracted from every run and the results were averaged across the iterations.

I then looked for an effect of digit-number and algebraic complexity, which are orthogonal to the math>sentence contrast used for ROI definition. I also tested selectivity for math over language by comparing the math and sentence conditions (note that independent data were used to define math>sentence ROIs). Under the null hypothesis, the vertices that show the math>sentence effect in the runs used to define the ROI are random, and would not be expected to show the effect in held out run. Results of parametric tests comparing math and sentence conditions were confirmed with non-parametric tests (Mann-Whitney U test and Wilcoxon signed rank test).

Within the visual cortex, I looked at activity in math-responsive rMOG, which has previously been observed to respond to numerical information in congenitally blind individuals (Kanjlia et al., 2016). Math-responsive ROIs in the visual cortex were defined as follows: for each congenitally blind and sighted subject, a search-space was created by taking the rMOG cluster that responded to the math>language contrast in CB>S ($p<0.0001$, uncorrected). Each congenitally blind and sighted participant did not contribute to the creation of his or her own search-space. Each congenitally blind and sighted participant was "left out," iteratively, and his or her search-space was created based on functional data from the remaining subjects. Since search-space definition procedure was independent of the adult-onset blind group, the same search-space was used for all adult-onset blind subjects (all CB>S, math>language, $p<0.0001$, uncorrected). Functional ROIs were then defined within the search-space in every subject using the leave-one-run-out procedure described above. Additionally, I looked at responses in V1 because this is the first cortical stage of visual processing (Van Essen et al., 2012). The functional reorganization of this region is of particular interest and has been investigated in many prior studies of sensitive periods in visual cortex plasticity (Cohen et al., 1999; Bedny et al., 2012b; Collignon et al., 2013b).

Paired t-tests were used to compare means within a group and unpaired t-tests were used when comparing means across groups. All t-tests were two-tailed.

Correlations with duration of blindness were conducted including only adult-onset blind participants who lost their vision abruptly (within 2 years, n=7; see Table 5.1) because blindness duration is less clearly defined when vision is lost progressively.

5.2.5 Resting-state functional connectivity analysis

Resting-state analyses were identical to those described in Chapter 4.

5.3 Results

5.3.1 Behavioral Results

In adult-onset blind participants, accuracy and response times were similar across math and sentence conditions (accuracy: t(12)=0.58, p=0.57; response times: t(12)=1.02, p=0.33) (Fig. 5.1). As previously reported for congenitally blind and sighted individuals (Kanjlia et al., 2016), adult-onset blind individuals were faster and more accurate on trials with single-digit than double-digit math equations (digit-number by algebraic complexity repeated measures ANOVA; main effect of digit-number on accuracy: F(1,12)=9.88, p=0.008; main effect of digit-number on response times: F(1,12)=9.00, p=0.01) (Fig. 5.1). Similarly, adult-onset blind individuals were faster more accurate on trials with algebraically simple math problems than algebraically complex problems (main effect of algebraic complexity on accuracy: F(1,12)=21.41,p=0.001; main effect of algebraic complexity on response times: F(1,12)= 15.82, p=0.002).

The adult-onset blind group was less accurate than the congenitally blind and sighted group across the math and language tasks (task by group repeated measures ANOVA: main effect of group (AB vs CB): F(1,31)=6.96, p=0.01; main effect of group (AB vs. S): F(1,30)=5.37, p=0.03). The adult-onset blind group was slightly less accurate than the sighted group on math trials (t(30)=2.1, p=0.04) and less accurate on sentence trials relative to both of the other groups (AB vs. CB: t(31)=3.60, p=0.001; AB vs. S: t(30)=2.03, p=0.051). Adult-onset blind individuals were marginally slower to respond on sentence trials compared to the congenitally blind group (AB vs. CB: t(31)=-2.00, p=0.06) and slower on math trials compared to the sighted group (AB vs. S: t(30)=-2.30, p=0.03). All other comparisons were not significant (p>0.05; Table 5.2).

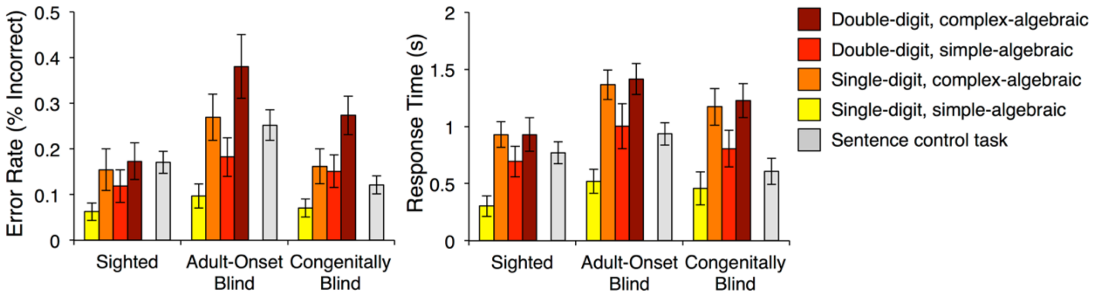


Fig. 5.1 Behavioral performance on math task. Error rates (left) and response times (relative to offset of second stimulus; right) for all conditions in math task (warm colors) and language control task (grey). Error bars show standard error of the mean.

Table 5.2 Summary of behavioral results

	Accuracy		Response Time	
	AB vs. CB	AB vs. S	AB vs. CB	AB vs. S
Effect of Digit-Number	F(1,31)=0.002, p=0.96	F(1,30)=2.37, p=0.13	F(1,31)=1.35, p=0.25	F(1,30)=0.66, p=0.42
Effect of Algebraic Complexity	F(1,31)=3.01, p=0.09	F(1,30)=6.51, p=0.02	F(1,31)=0.28, p=0.60	F(1,30)=5.12, p=0.03
Effect of Task	F(1,31)=2.57, p=0.12	F(1,30)=0.31, p=0.59	F(1,31)=1.27, p=0.27	F(1,30)=1.46, p=0.24
Math	t(31)=1.41, p=0.17	t(30)=2.1, p=0.04	t(31)=-1.85, p=0.07	t(30)=1.67, p=0.11
Sentences	t(31)=3.60, p=0.001	t(30)=2.03, p=0.051	t(31)=-2.54, p=0.02	t(30)=0.87, p=0.39

5.3.2 Similar fronto-parietal responses in adult-onset blind, congenitally blind and sighted groups

In whole-cortex analyses, all three groups showed similar responses in fronto-parietal cortices for the math>language contrast (p<0.05, cluster-corrected, Fig. 5.2). ROI analyses show that, like the IPS of congenitally blind and sighted individuals, the IPS of adult-onset blind individuals responded more to the math than the language task (AB group, hemisphere by task repeated-measures ANOVA; main effect of task (math vs. language): F(1,12)=187.91, p<0.001; hemisphere by task interaction: F(1,12)=14.71, p=0.002; Table 5.3) and showed the same sensitivity to digit-number (hemisphere by digit-number by algebraic complexity repeated-measures ANOVA; main effect of digit-number in AB group: F(1,12)=14.38, p=0.003; digit-number by group (AB vs. S) interaction: F(1,30)=0.95, p=0.34; digit-number by group (AB vs. CB) interaction: F(1,31)=0.002, p=0.96; Table 5.3). The adult-onset blind group did not show an effect of algebraic complexity in the IPS (AB group: F(1,12)=0.20, p=0.66). The effect of algebraic complexity was not different across adult-onset blind and congenitally blind groups but was slightly larger in the sighted group compared to the adult-onset blind group (algebraic complexity by group (AB vs. CB) interaction: F(1,31)=0.84, p=0.37; algebraic complexity by group (AB vs. S) interaction: F(1,30)=3.18, p=0.09).

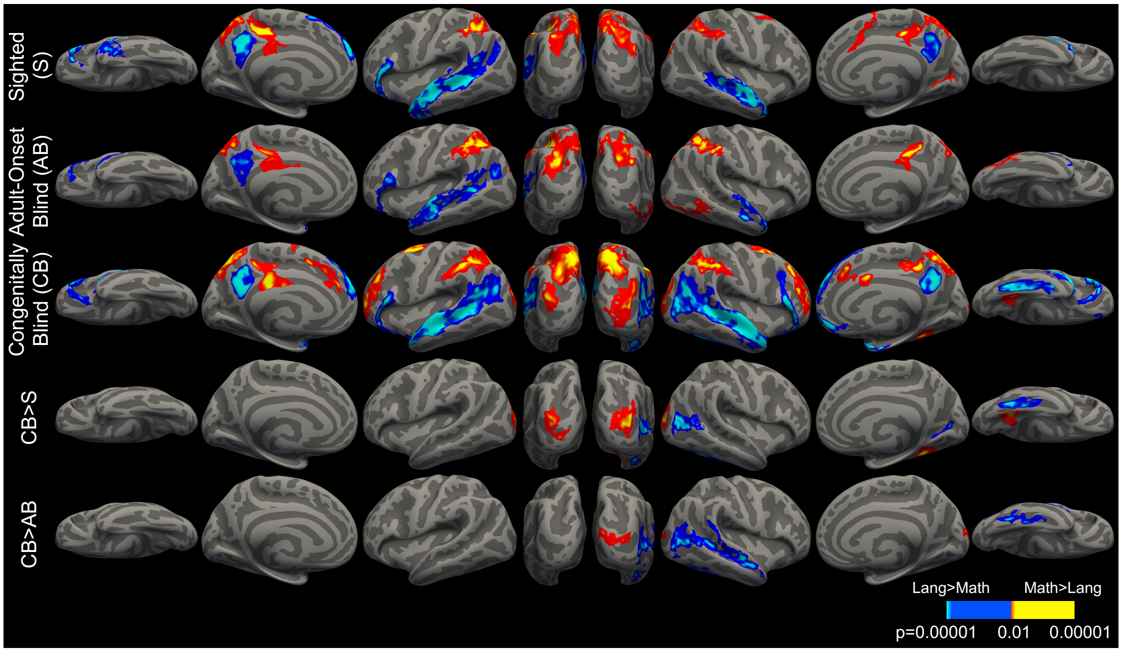


Fig. 5.2 Whole-cortex responses to math and language. Brain regions active for math > language (warm colors) and language > math (cool colors) ($p < 0.05$, cluster corrected).

<u>5.3.3 Different visual cortex sensitivity to higher-cognitive functions in congenitally blind as opposed to adult-onset blind and sighted groups</u>

Relative to the sighted, congenitally blind but not adult-onset blind participants activated several regions within “visual” cortex during math calculation versus sentence comprehension and vice versa: in whole-cortex analyses**,** the rMOG was more active for math than language while the rVOT and right lateral occipital cortex (rLO) were more active for language than math (Fig. 5.2). Although some visual cortex activity was observed in the within-group analysis of the adult-onset blind group, this activity was focused around the location of the so-called visual number-form area (VNFA), which has previously been shown to respond to numerical tasks in sighted individuals and was also observed in the sighted group at a reduced statistical threshold in the present study (Abboud et al., 2015). Direct comparison of congenitally blind and adult-onset blind participants revealed greater rMOG activity in the congenitally blind for the math>language contrast and greater right rLO activity in the congenitally blind for language>math contrast (Fig. 5.2, CB>AB, math>language, $p<0.05$, cluster-corrected).

In ROI analyses, overall response to all math and language conditions in rMOG was greater in both congenitally and adult-onset blind groups compared to the sighted group (CB vs. S: $t(37)=6.30$, $p<0.001$; AB vs. S: $t(30)=4.73$, $p<0.001$; Fig. 5.3). rMOG response to all stimuli was marginally higher in the congenitally blind group than the adult-onset blind group ($t(31)=1.94$, $p=0.06$). Selectivity for mathematical stimuli over sentence stimuli was also significantly larger in congenitally blind as compared to the adult-onset blind group (CB vs. AB; task by group interaction: $F(1,31)=10.72$, $p=0.003$). However, the rMOG showed a larger response to mathematical stimuli over sentence stimuli in adult-onset blind individuals as well (math vs. language, AB: $t(12)=2.28$, $p=0.04$; CB: $t(19)=5.5$, $p<0.001$). There was no difference in rMOG selectivity for math over language stimuli across adult-onset blind and sighted individuals (AB vs. S; task by group interaction: $F(1,30)=1.27$, $p=0.27$).

Similarly, the effect of digit-number was larger in the congenitally blind than the adult-onset blind group (digit-number by group interaction: $F(1,31)=9.58$, $p=0.004$). There was a marginal difference in the algebraic complexity effect across congenitally blind and adult-onset blind groups (algebraic complexity by group interaction: $F(1,31)=3.28$, $p=0.08$). The rMOG of the adult-onset blind was not different from that of the sighted in its sensitivity to either math difficulty manipulation (digit-number by group interaction: $F(1,30)=2.88$, $p=0.10$; algebraic complexity by group interaction: $F(1,30)=0.004$, $p=0.95$). Within the adult-onset blind group, the rMOG did not show sensitivity to either digit-number or algebraic complexity (AB group, digit-number by algebraic complexity ANOVA; main effect of digit-number: $F(1,12)=2.90$, $p=0.12$; main effect of algebraic complexity: $F(1,12)=0.06$, $p=0.82$; Table 5.3).

In V1, selectivity for mathematical stimuli over sentence stimuli was stronger in the congenitally blind than the adult-onset blind group and marginally larger in the sighted than the adult-onset blind group (hemisphere by task by group repeated measures ANOVA: task by group (CB vs. AB) interaction: $F(1,31)=18.87$, $p<0.001$; task by group (AB vs. S) interaction: $F(1,30)=3.43$, $p=0.07$; Fig. 5.3; Table 5.3). The effect of digit-number was larger in the congenitally blind than the adult-onset blind group (hemisphere by digit-number by algebraic complexity by group repeated measures ANOVA: digit-number by group (CB vs. AB) interaction: $F(1,31)=4.18$, $p=0.05$). Interestingly, the sighted group showed a significant effect of algebraic complexity in V1 (main effect of algebraic complexity: $F(1,18)=10.67$, $p=0.004$; main effect of digit-number: $F(1,18)=1.70$, $p=0.21$). By contrast, adult-onset blind individuals show no sensitivity to digit-number or algebraic complexity (main effect of digit-number: $F(1,12)=1.16$, p=0.30; main effect of algebraic complexity: F(1,12)=0.90, p=0.36; algebraic complexity by group (S vs. AB) interaction: F(1,30)=2.58, p=0.12).

Notably, selectivity for math (% signal change for mathematical stimuli - language stimuli) in the rMOG and V1 was not predicted by duration of blindness among adult-onset blind participants with abrupt vision loss (see Methods & Materials) and was not predicted by age among congenitally blind participants (AB rMOG: R2=0.02, p=0.79; AB V1: R2=0.17, p=0.36; CB rMOG: R2=0.05, p=0.34; CB V1: R2=0.00, p=0.91). Similarly, there was no correlation between blindness duration and the size of the math difficulty effect (% signal change for hardest math condition – easiest math condition) in either the rMOG or V1 of the AB or CB (AB rMOG: R2=0.46, p=0.09; AB V1: R2=0.08, p=0.53; CB rMOG: R2=0.01, p=0.76; CB V1: R2=0.03, p=0.45).

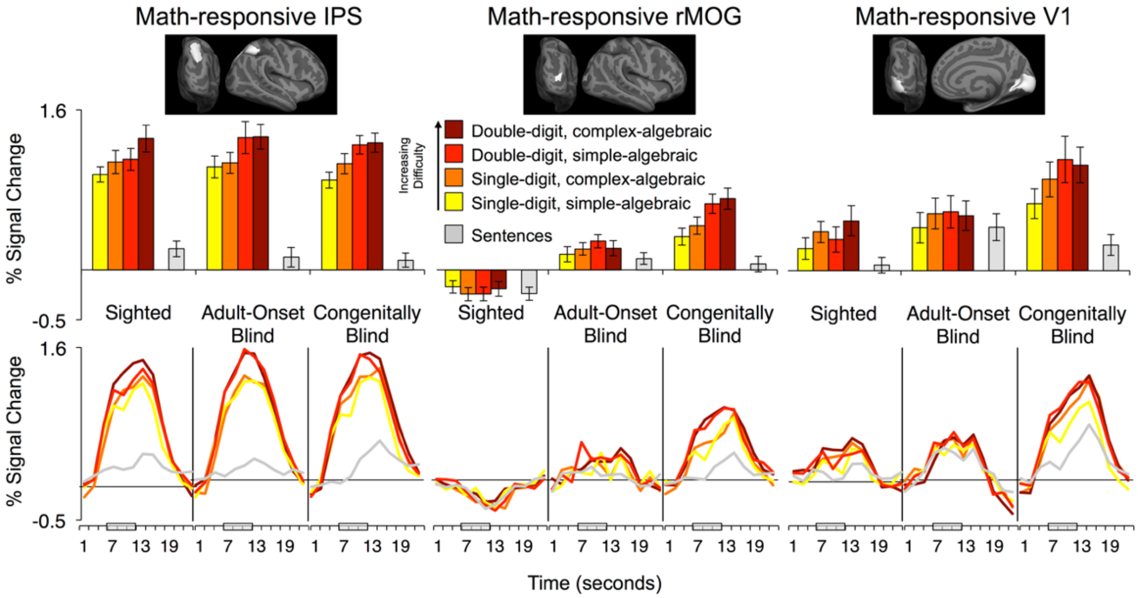


Fig. 5.3 Math and language activity in IPS, rMOG and V1 ROIs. Responses to math equations by difficulty in math-responsive IPS (left), math-responsive rMOG (middle) and math-responsive V1 (right). Percent signal change relative to rest was extracted from individual-subject ROIs defined within IPS, rMOG and V1 search-spaces. Adult-onset blind search-spaces displayed at the top. IPS and V1 results are averaged across left and right hemispheres. Error bars represent standard error of the mean.

Table 5.3. Results of ROI analysis for math task

		AB Group	AB vs. CB	AB vs. S	S
IPS	Effect of Digit	F(1,12)=14.38, p=0.003	F(1,31)=0.002, p=0.96	F(1,30)=0.95, p=0.34	--
	Effect of Alg. Comp.	(1,12)=0.20, p=0.66	F(1,31)=0.84, p=0.37	F(1,30)=3.18, p=0.09	--
	Effect of Task	F(1,12)=187.91, p<0.001	F(1,31)=0.13, p=0.72	F(1,30)=1.63, p=0.21	--
rMOG	Effect of Digit	F(1,12)=2.90, p=0.12	F(1,31)=9.58, p=0.004	F(1,30)=2.88, p=0.10	--
	Effect of Alg. Comp.	F(1,12)=0.06, p=0.82	F(1,31)=3.28, p=0.08	F(1,30)=0.004, p=0.95	--
	Effect of Task	t(12)=2.28, p=0.04	F(1,31)=10.72, p=0.003	F(1,30)=1.27, p=0.27	--
rV1	Effect of Digit	F(1,12)=1.16, p=0.30	F(1,31)=4.18, p=0.05	F(1,30)=0.09, p=0.77	F(1,18)=1.70, p=0.21
	Effect of Alg. Comp.	F(1,12)=0.90, p=0.36	F(1,31)=0.17, p=0.69	F(1,30)=2.58, p=0.12	F(1,18)=10.67, p=0.004
	Effect of Task	t(12)=2.72, p=0.13	F(1,31)=18.87, p<0.001	F(1,30)=3.43, p=0.07	F(1,18)=14.59, p=0.001

5.3.4 Functional connectivity between "visual" cortices and fronto-parietal cortices in adult-onset blindness

Among the adult-onset blind group, resting-state functional connectivity of visual cortices show an intermediate pattern between that of the sighted and congenitally blind groups discussed in Chapter 4 (Fig. 5.4).

Overall magnitude of correlation between visual cortices and the rIPS and visual cortices and prefrontal cortices was marginally lower in the adult-onset blind group, compared to the congenitally blind and was not different from the sighted (connectivity with rIPS, seed (rMOG vs. rVOT) by group (AB vs. CB) repeated measures ANOVA, main effect of group: F(1,34)=6.14, p=0.02; connectivity with prefrontal cortices, seed (rMOG vs. rVOT) by ROI (rDLPFC vs. rIFC) by group (AB vs. CB) repeated measures ANOVA, main effect of group: F(1,34)=3.25, p=0.08; connectivity with rIPS, seed by group (AB vs. S) ANOVA, main effect of group: F(1,53)=1.68, p=0.20; connectivity with prefrontal cortices, seed by ROI by group (AB vs. S); main effect of group: F(1,53)=1.15, p=0.29; Fig. 5.4, Table 5.4).

Resting-state correlations of visual cortices among the adult-onset blind group show clear network selectivity: activity of math-responsive visual cortex (rMOG) is more correlated with math-responsive parietal (rIPS) and prefrontal (rDLPFC), whereas activity of language-responsive visual cortex (rVOT) is more correlated with language-responsive inferior frontal cortex (rIFC) (within adult-onset blind group; connectivity with rIPS, effect of seed (rMOG vs. rVOT): t(11)=3.52, p=0.005; connectivity with prefrontal cortices, seed (rMOG vs. rVOT) by ROI (rDLPFC vs. rIFC) interaction: F(1,11)=7.81, p=0.02; Fig. 5.4, Table 5.4).

Selectivity of functional connectivity across number and language networks in adult-onset blindness did not differ from either the congenitally-blind or sighted groups (connectivity with rIPS, seed (rMOG vs. rVOT) by group (AB vs. CB) interaction: F(1,34)=0.17, p=0.68; connectivity with prefrontal cortices, seed by ROI (rDLPFC vs. rIFC) by group (AB vs. CB) interaction: F(1,34)=1.28, p=0.27; connectivity with rIPS, seed by group (AB vs. S) interaction: F(1,53)=2.00, p=0.16; connectivity with prefrontal cortices, seed by ROI by group (AB vs. S) interaction: F(1,53)=2.40, p=0.13; Fig. 5.4, Table 5.4).

Notably, among adult-onset blind individuals with abrupt vision loss (see Methods), resting-state functional connectivity between rMOG and rIPS but not rPFC was significantly correlated with blindness duration since reaching one’s current level of vision (rIPS: R2=0.72, p=0.02; rPFC: R2=0.14, p=0.42).

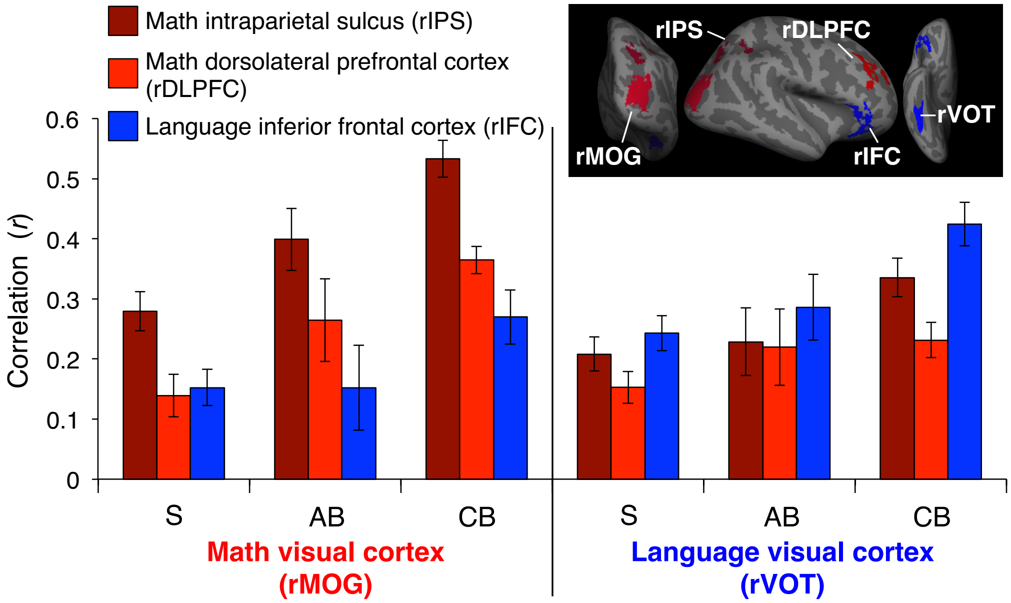


Fig. 5.4 Resting-State functional connectivity between occipital and fronto-parietal networks. Resting-state correlations between math-responsive (left) and language-responsive (right) visual cortices and fronto-parietal math network (red) and inferior frontal language region (blue). ROIs for sighted group shown above (see Supplementary Fig. 5.1 for congenitally blind and adult-onset blind group ROIs). Error bars show standard error of the mean.

Table 5.4. Results of resting-state functional connectivity seed-to-ROI analysis

		AB vs S	AB vs CB	CB vs S	AB Group	CB Group	S Group
Correlation with rIPS ROI	Main effect of seed (rMOG vs rVOT)	F(1,53)=2.00, p=0.16	F(1,34)=0.17, p=0.68	F(1,65)=5.32, p=0.02	t(11)=3.52, p=0.005	t(23)=5.00, p<0.001	t(42)=2.08, p=0.04
	Main effect of group across seed (rMOG vs rVOT)	F(1,53)=1.68, p=0.20	F(1,34)=6.14, p=0.02	F(1,65)=24.49, p<0.001	N/A	N/A	N/A
Correlation with Math DLFPC and Lang rIFC ROIs	Seed by ROI interaction	F(1,53)=2.40, p=0.13	F(1,34)=1.28, p=0.27	F(1,65)=12.39, p=0.001	F(1,11)=7.81, p=0.02	F(1,23)=23.41, p<0.001	F(1,42)=6.57, p=0.01
	Main effect of group across seed (rMOG vs rVOT)	F(1,53)=1.15, p=0.29	F(1,34)=3.25, p=0.08	F(1,65)=16.11, p<0.001	N/A	N/A	N/A

5.4 Discussion

5.4.1 Sensitive period for cognitive repurposing in visual cortex

I find that the capacity of cortex to take on novel cognitive functions narrows over the course of development. In congenital blindness, different visual cortex regions become specialized for numerical as opposed to linguistic processing and BOLD signal in these regions increases with cognitive load (Bedny et al., 2011; Lane et al., 2015; Kanjlia et al., 2016). A dorsal occipital area (rMOG) is more responsive to math equations than sentences and activity increases with the difficulty of math equations in congenitally blind but not sighted participants (Kanjlia et al., 2016). By contrast, regions in ventral occipito-temporal cortex (VOT) and lateral occipital cortex (LOC) are more responsive to sentences (Bedny et al., 2011; Lane et al., 2015; Kim et al., 2017).

Here I report that this type of cognitive repurposing is qualitatively different in individuals who lose their vision as adults. In adult-onset blindness (blind at age 17 or later), there is less regional specialization within visual cortex (i.e. for numerical and linguistic processing). Instead, the "visual" cortex shows an above rest response across cognitive tasks and conditions. Crucially, relative to the congenitally blind, visual cortices of adult-onset blind participants show less sensitivity to mathematical difficulty (i.e. cognitive load). This is despite the fact that, in adult-onset and congenitally blind participants alike, the overall amount of visual cortex activity during auditory tasks is elevated relative to rest, as are resting-state correlations of visual cortex with fronto-parietal networks (Bedny et al., 2012b; Collignon et al., 2013b).

Differences in the functional profile of visual cortex cross the adult-onset and congenitally blind groups do not appear to be related to the blindness duration, since neither the selectivity of the visual cortex for math equations nor its response to equation-difficulty increased with blindness duration among the adult-onset or congenitally blind participants. As with any null result it remains possible that an effect of blindness duration does exist in the population and was not detected in the current study, perhaps due to insufficient power. However, the present results suggest that any putative effect of blindness duration coexists with a more robust effect of age of blindness onset.

Why might the recruitment of visual cortex for higher-cognitive functions be limited to a sensitive period during development? One possibility is that cognitive specialization of cortex requires circuit-internal structural changes that are uniquely possible during sensitive periods in development. As noted in the introduction, studies in animals suggest that dendritic spine formation, spine elimination and axon retraction are enhanced during sensitive periods (Hensch, 2004; Hensch, 2005; Hensch, 2005; Maurer and Hensch, 2012). Sensitive period closure coincides with formation of molecular "brakes," such as perineuronal nets, which dampen plasticity (Pizzorusso, 2002; Bavelier et al., 2010). Enhanced levels of structural flexibility in visual cortex during sensitive periods may enable it to acquire non-visual cognitive functions in those who are blind from birth and early blind. According to this hypothesis, cognitive repurposing of visual cortex depends on sensitive period neurophysiology, which declines over the first few years of life in humans (Maurer and Hensch, 2012). Alternatively, establishing one set of representations (e.g. visual) could block cortex from representing other content (e.g. number). If so, repurposing of visual cortex is only possible in individuals who are "visually naïve."

In support of the structural flexibility hypothesis, previous studies provide some evidence for gradual decline in cross-modal responses with age of blindness onset. For example, the amount of visual cortex activity in early blind individuals during Braille and spoken language tasks is intermediate between that of congenitally and adult-onset blind individuals (Cohen et al., 1999; Sadato et al., 2002; Burton et al., 2003). However, these studies compare non-visual tasks to rest and the current data suggest that responses to higher-cognitive information in visual cortex have a different developmental time-course than responses to non-visual stimulation in general. Future work should ask whether the capacity of visual cortex to specialize for *specific* cognitive operations declines gradually over childhood or abruptly after birth.

A further question raised by the current findings concerns the cognitive and behavioral significance of visual cortex activity in adult-onset blindness. As noted in the introduction, sensory cortices can assume new, behaviorally relevant functions even in adulthood. Amputation of a limb causes deafferented somatosensory cortices to respond to body parts represented by neighboring regions and there is some evidence that these responses are behaviorally relevant (Pascual-Leone et al., 1996; Röricht et al., 1999). However, in such cases, functional repurposing occurs within a modality. Whether adult cortex can repurpose across modalities remains an open question.

In the current study, visual cortex activity during auditory tasks may not be cognitively or behaviorally relevant in adult-onset blindness. Consistent with this possibility, even though visual cortices of congenitally and adult-onset blind individuals are active during Braille reading tasks, TMS to the visual cortex impairs Braille reading only in those who are congenitally blind (Cohen et al., 1999). Alternatively, the visual cortex of adult-onset blind individuals may take on non-visual cognitive functions that are different from those it takes on in congenital blindness, perhaps functions that are easier for mature cortex to acquire. Under this view, adult cortex can repurpose but only within a narrow cognitive range.

It is worth noting that although cognitive repurposing of visual cortex in the adult-onset blind group is greatly reduced relative to congenitally blind individuals, the visual cortex nevertheless does change its function to some ways even in adult-onset blindness relative to the sighted. First, as noted above rMOG showed higher activity during an auditory task in general (relative to rest) in AB relative to the sighted. Second, in the rMOG there was a small but significant preference for math over language stimuli in the adult-onset blind group but not in the sighted group. This effect was weaker than what was found in the congenitally blind group. Importantly, unlike in the congenitally blind group, there was no effect of cognitive load. Together these results suggest that blindness in adulthood does, in fact, change the function of the visual cortex, but not in the same way or to the same degree as blindness at birth. Thus although there appears to be a sensitive period for cortex to assume a specific new cognitive function, there is still potential for some types of reorganization even in adult cortex.

Exactly what defines the cognitive potential of cortex in adulthood and what distinguishes it from the cognitive range of developing cortex remains an open question for future research. Notably, even though the present findings suggest that the cognitive range of adult cortex is naturally restricted, pharmacological and even targeted behavioral interventions (e.g. sensory deprivation or environmental enrichment), can "reopen" sensitive periods (Putignano et al., 2007; Baroncelli et al., 2010; Bavelier et al., 2010; Maya Vetencourt et al., 2011; Spolidoro et al., 2011). Therefore the existence of such windows of sensitivity is better viewed as a time of greatest neurocognitive flexibly, rather than as a unique and immutable window for change.

5.4.2 Functional connectivity of visual cortices changes, even in adult-onset blindness

Although I find that the visual cortices of adult-onset blind individuals do not take on the same cognitive functions as those of congenitally blind individuals, blindness in adulthood still changes the functional properties of visual cortex: resting-state correlations between visual cortices and the fronto-parietal number network increase.

These findings are consistent with a recent study that found increased resting-state correlations between visual cortices and Broca's area in individuals who became totally blind after the age of 21 due to retinitis pigmentosa compared to sighted individuals (Sabbah et al., 2016). Interestingly, the same study found a similar increase in functional fronto-occipital connectivity even in the case of partial vision loss (Sabbah et al., 2016). Together these findings suggest that functional connectivity of visual cortex remains modifiable into adulthood.

It is worth noting, however, that we and others have found that resting-state correlations between visual cortex and higher-cognitive networks are lower in those who are adult-onset as compared to congenitally blind (Bedny et al., 2010; Butt et al., 2013). In this respect the adult-onset blind group is intermediate between what is observed in congenital blindness and in the blindfolded sighted group. Therefore, the flexibility of the adult brain, even in the case of functional connectivity, is not quite as extensive as that of the juvenile brain.

Importantly, in adult-onset blind individuals, visual cortices not only demonstrate increased resting-state correlations with fronto-parietal networks overall, but exhibit region-specific increases with different fronto-parietal functional networks, similar to what is found in congenital blindness (Kanjlia et al., 2016). In particular, visual areas that respond to math equations in the congenitally blind group are correlated with the fronto-parietal number network in the adult-onset blind group. By contrast, those that respond to language in congenital blindness are correlated with inferior frontal language areas in the adult-onset blind group. This pattern is surprising, given that adult-onset blind individuals do not show sub-specialization of the visual cortex for math and language processing in task-based data.

These data provide further evidence for the hypothesis presented in Chapter 4 suggesting that vision loss “unmasks” the functional consequences of intrinsic differences in the anatomical connectivity among visual areas (Pascual-Leone et al., 2005; Wang et al., 2015). According to this hypothesis, in blind and sighted individuals alike, visual regions that have stronger resting-state correlations with the fronto-parietal number network have stronger anatomical connectivity with this network, whereas visual areas that correlate with inferior frontal language areas are anatomically connected with the language network. In the sighted, non-visual inputs are dwarfed by bottom-up inputs from the visual pathway, thus blocking synchronization with higher-cognitive networks. Blindness at any age unmasks the latent effects of these anatomical biases and leads to region-specific increases in resting-state correlations with fronto-parietal networks. Anatomical connectivity dissociations may thus precede and enable the cognitive repurposing observed in congenital blindness. This hypothesis could be tested directly in future work, using diffusion tractography imaging (DTI) to compare structural connectivity between math- and language-responsive visual areas in both sighted and blind individuals (Pascual-Leone et al., 2005; Wang et al., 2015).

In this regard, the present results provide an illustration of the potential dissociations between long-range functional connectivity patterns and local circuit functional properties. An ever-increasing number of studies demonstrates that, in general, a cortical region’s connectivity profile is predictive of its functional specialization as measured by task-based fMRI. A prime example comes from studies of the visual word form area (VWFA), which shows strong connectivity with the fronto-temporal language network among sighted and blind individuals alike, even before literacy (Dehaene et al., 2015; Saygin et al., 2016). Similarly, there is evidence that connectivity patterns in the ventral stream predict which regions are specialized for scene as opposed to face recognition, above and beyond anatomical location (Tavor et al., 2014; Osher et al., 2016; Saygin et al., 2016). The present results uncover an important caveat to this general pattern. They suggest that long-range inputs are necessary but not sufficient for functional specialization. Long-range functional connectivity enables relevant information to reach cortical circuits during development. However, if such information arrives after the sensitive period has closed, specialization fails to occur despite the existence of relevant long-range connections.

5.5 Conclusions

In summary, I find that the visual cortices of adult-onset and congenitally blind adults show different capacities to take on higher-cognitive functions. However, blindness at any age causes visual cortices to become synchronized with multiple different higher-cognitive fronto-parietal networks in a region-specific manner. These results suggest that resting-state functional connectivity maybe a prerequisite but not sufficient on its own for functional repurposing. When competing bottom-up visual input is removed, occipital regions may become more coupled with fronto-parietal networks at rest. However, it appears that this coupling is only associated with similarities in task-evoked activity if it occurs early in development. These findings suggest that the capacity of cortex to take on novel functions is restricted to sensitive periods in development, possibly due to local cortical constraints.

5.6 Supplementary Material

Supplementary Table 5.1 Brain regions more active for math than sentences

Brain regions active for math > language	***x***	***y***	***z***	**Peak *t***	**mm2**	**Pcluster**
Adult-Onset Blind Group						
Left postcentral sulcus	40	-40	37	13.56	3247.83	0.0008
Left intraparietal sulcus and transverse parietal sulci	31	-65	34	10.53		
Left precuneus	7	-65	50	9.05		
Left marginal branch of the cingulate sulcus	7	-33	43	6.84	671.49	0.043
Right intraparietal sulcus and transverse parietal sulci	29	-51	44	12.67	2274.23	0.0002
Right supramarginal gyrus	56	-41	42	10.78		
Right middle occipital gyrus	35	-79	34	9.01		
Right superior occipital sulcus and transverse occipital sulcus	28	-64	29	7.5		
Right superior parietal lobule	17	-68	54	7.09		
Right inferior temporal sulcus	55	-53	-4	5.98	590.13	0.033
Right inferior occipital gyrus and sulcus	45	-82	-9	5.08		
Right marginal branch of the cingulate sulcus	7	-38	43	11.66	579.53	0.0332
Congenitally Blind Group						
Left superior parietal lobule	-17	-70	45	9.62	4297.49	0.0002
Left supramarginal gyrus	-52	-39	47	7.96		
Left middle occipital gyrus	-38	-88	16	6.25		
Left middle frontal gyrus	-39	50	9	8.39	1703.1	0.003

Left middle frontal gyrus	-44	31	30	6.46		
Left fronto-marginal gyrus and sulcus	-23	56	-7	5.02		
Left superior frontal sulcus	-21	7	50	9.51	1127.99	0.0086
Left posterior-dorsal part of the cingulate gyrus	-6	-30	29	6.88	871.01	0.016
Left marginal branch of the cingulate sulcus	-11	-41	45	6.46		
Left middle-anterior part of the cingulate gyrus and sulcus	-8	8	45	6.4	642.01	0.0286
Left anterior part of the cingulate gyrus and sulcus	-9	35	26	6.32		
Right sulcus intermedius primus	43	-44	36	10.3	3551.84	0.002
Right intraparietal sulcus and transverse parietal sulci	19	-63	53	9.07		
Right marginal branch of the cingulate sulcus	7	-41	44	7.95		
Right middle frontal gyrus	38	27	39	7.36	1591.46	0.0068
Right inferior frontal sulcus	43	33	20	7.12		
Right middle frontal sulcus	30	50	0	5.89		
Right middle occipital sulcus and lunatus sulcus	33	-82	9	6.83	1204.35	0.0092
Right superior frontal sulcus	28	6	51	8.29	925.6	0.0138
Right middle-posterior part of the cingulate gyrus and sulcus	3	3	34	7.45	570.11	0.0342
Right superior frontal gyrus	6	23	43	6.62		
Right medial occipito-temporal sulcus and lingual sulcus	31	-45	-14	6.04	455.74	0.0476

Sighted Group						
Left intraparietal sulcus and transverse parietal sulci	33	-43	44	7.86	2594.9	0.0012
Left angular gyrus	33	-65	45	7.41		
Left superior parietal lobule	10	-61	64	6.03		
Left precuneuS	14	-75	46	5.94		
Left marginal branch of the cingulate sulcus	16	-39	42	10.96	1043.9	0.0072
Right marginal branch of the cingulate sulcus	13	-28	38	7.7	2172.41	0.0008
Right intraparietal sulcus and transverse parietal sulci	22	-63	43	6.34		
Right middle occipital gyrus	40	-80	30	5.99		
Right intraparietal sulcus and transverse parietal sulci	36	-46	36	5.99	941.89	0.0074
Right supramarginal gyrus	58	-36	44	5.02		
Right calcarine sulcus	12	-75	6	4.18	457	0.0366
Right calcarine sulcus	25	-55	1	3.9		
Right superior frontal gyrus	7	0	59	5.13	450.49	0.037
Right superior part of the precentral sulcus	31	-4	46	4.94	431.03	0.0406
Right superior frontal gyrus	18	14	62	4.66		
Congenitally Blind Group > Adult-Onset Blind Group						
Right superior occipital gyrus	14	-92	15	4.67	483.51	0.046
Right middle occipital gyrus	30	-89	12	4.53		
Congenitally Blind Group > Sighted Group						

Left middle occipital gyrus	-34	-88	14	4.98	528.72	0.0312
Left middle occipital sulcus and lunatus sulcus	-25	-95	1	4.78		
Right middle occipital sulcus and lunatus sulcus	33	-82	9	6.52	807.7	0.011
Right medial occipito-temporal sulcus and lingual sulcus	32	-45	-14	5.43	548.72	0.027

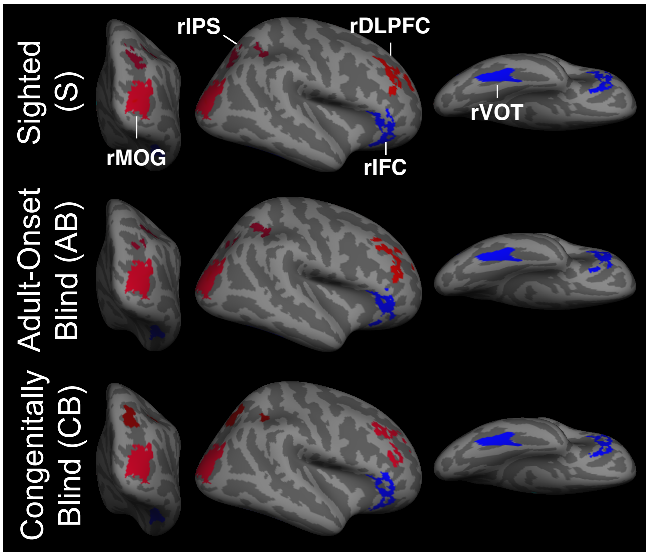
Brain regions active for language > math	***x***	***y***	***z***	**Peak *t***	**mm2**	**Pcluster**
Adult-Onset Blind Group						
Left superior temporal gyrus	-61	-15	3	11.81	3684.03	0.0002
Left planum polare of the superior temporal gyrus	-47	7	-17	11.14		
Left superior temporal sulcus	-51	-49	5	9.74		
Left superior temporal sulcus	-54	-19	-15	8.88		
Left superior temporal sulcus	-41	-63	19	7.08		
Left opercular part of the inferior frontal gyrus	-52	25	17	7.36	835.81	0.0242
Left orbital sulci	-38	31	-13	6.54		
Left precuneus	-5	-61	31	7.28	781.82	0.0268
Right superior temporal sulcus	57	-9	-20	9.98	1576.82	0.0014
Right lateral aspect of the superior temporal gyrus	48	15	-21	9.88		
Right lateral aspect of the superior temporal gyrus	64	-5	-4	7.88		
Congenitally Blind Group						

Left lateral aspect of the superior temporal gyrus	-61	-14	-5	13.01	4536.4	0.0002
Left superior temporal sulcus	-53	-39	3	9.03		
Left lateral aspect of the superior temporal gyrus	-46	16	-26	8.68		
Left triangular part of the inferior frontal gyrus	-55	23	12	8.52	1166.59	0.0108
Left orbital part of the inferior frontal gyrus	-47	32	-14	7.08		
Left orbital gyri	-31	18	-22	5.57		
Left superior frontal gyrus	-9	61	25	7.66	876.66	0.016
Left subparietal sulcus	-10	-55	26	9.64	799.73	0.019
Right lateral aspect of the superior temporal gyrus	65	-10	0	12.51	5884.37	0.0002
Right superior temporal sulcus	49	-13	-15	12.07		
Right planum polare of the superior temporal gyrus	39	9	-27	9.7		
Right superior temporal sulcus	51	-60	19	9.41		
Right superior temporal sulcus	45	-40	3	8.55		
Right parahippocampal gyrus	25	-7	-30	8.01		
Right anterior occipital sulcus and preoccipital notch	45	-69	10	7.09		
Right triangular part of the inferior frontal gyrus	56	24	18	8.87	1309.03	0.0092
Right triangular part of the inferior frontal gyrus	52	32	-4	7.72		
Right superior frontal gyrus	10	56	32	7.64	978.34	0.0152
Right superior frontal gyrus	10	15	65	5.6		

Right lateral occipito-temporal gyrus (fusiform gyrus)	38	-48	-22	8.69	891.01	0.017
Right anterior transverse collateral sulcus	41	-8	-35	6.59		
Right subparietal sulcus	8	-56	36	9.01	635.66	0.0278
Right straight gyrus	6	54	-13	8.58	633.27	0.0282
Sighted Group						
Left lateral aspect of the superior temporal gyrus	-50	13	-21	12.91	4568.42	0.0002
Left superior temporal sulcus	-54	-46	0	10.68		
Left lateral aspect of the superior temporal gyrus	-57	-15	-8	9.85		
Left superior temporal sulcus	-44	-67	26	5.01		
Left horizontal ramus of the anterior segment of the lateral sulcus	-44	31	-3	9.91	950.64	0.0112
Left superior frontal gyrus	-6	55	32	10.72	902.06	0.0132
Left superior frontal gyrus	-8	12	66	6.37		
Left subparietal sulcus	-12	-51	36	8.66	811.73	0.0154
Right lateral aspect of the superior temporal gyrus	47	13	-20	10.68	3109.97	0.0002
Right lateral aspect of the superior temporal gyrus	62	-6	-7	9.61		
Right superior temporal sulcus	52	-33	1	8.97		
Right middle temporal gyrus	61	-35	-6	7.18		
Right precuneus	5	-58	31	6.23	642.25	0.018
Congenitally Blind Group > Adult-Onset Blind Group						
Right superior temporal sulcus	51	-6	-17	6.01	2604.86	0.0002

Right lateral occipito-temporal sulcus	42	-52	-17	5.52	518.55	0.0436
Congenitally Blind Group > Sighted Group						
Right anterior occipital sulcus and preoccipital notch	46	-68	8	5.96	689.95	0.016
Right lateral occipito-temporal sulcus	42	-50	-18	6.14	533.68	0.0316
Right calcarine sulcus	17	-74	9	5	477.16	0.0386

Peaks of brain regions active more for math than language ($p < 0.05$, cluster corrected; $p < 0.01$ cluster-forming threshold; 20 mm minimum distance between peaks). Coordinates reported in MNI space. Peak t: t values corresponding to local maxima; mm2: area occupied by cluster on cortical surface; Pcluster: P value for entire cluster



Supplementary Fig. 5.1 Regions of interest (ROIs) for resting-state analysis. Red ROIs are math-responsive (defined with math>sentences contrast) and blue ROIs are language –responsive (defined with sentences> math contrast)

Chapter 6

The neural basis of approximate number in congenital blindness

6.1 Introduction

In the preceding chapters, I showed that fronto-parietal responses to symbolic number develop independently of visual experience. In both congenitally blind and sighted groups, the IPS was selectively active during math calculation more so than sentence processing and was sensitive to the difficulty of math equations. However, the absence of visual experience modified the neural basis of symbolic number processing by incorporating dorsal occipital cortices (right middle occipital gyrus, rMOG) into the fronto-parietal number network. In congenitally blind but not sighted individuals, symbolic number processing evoked the same response profile in the rMOG as it did in the IPS. These findings raise two outstanding questions. First, is visual experience critical for the development of *approximate* number representations in the IPS? Second, is math-responsive rMOG likewise sensitive to approximate quantities?

Although the preceding chapters find that the fronto-parietal cortices show typical functional responses to symbolic number in blind individuals, whether they similarly show preserved coding of approximate number remains an open question. Furthermore, even if the IPS develops representations of approximate number in the absence of visual experience, it is possible that the precision of these representations is different across congenitally blind and sighted individuals. Although the results from Chapter 1 suggest that the precision of approximate number representations develops independently of visual experience, it is possible that the neural instantiation of these representations in the IPS is affected by visual experience.

As mentioned earlier, different quantities elicit partially overlapping patterns of activity within the IPS, with more overlap for more similar quantities (Piazza et al., 2004, 2007a; Eger et al., 2009). For example, fMRI priming studies in humans show that IPS activity declines following repeated presentations of similar visual quantities and recovers after a new quantity is presented, suggesting that distinct quantities are represented by non-overlapping neuronal populations (Piazza et al., 2004, 2007a). Recovery in IPS activity is greater for novel quantities that differ from the adaptation quantity by a larger ratio, indicating that representations of more dissimilar quantities have less neural overlap. If the precision of approximate number representations is honed by visual experience, representations of specific quantities may be less distinguishable from patterns of IPS activity of congenitally blind individuals relative to sighted individuals.

Thus, to test the prediction that visual experience contributes to the development and precision of IPS population codes for approximate numerosity, I will use a different analysis of fMRI data that is more sensitive to fine-grained differences between representations within a broad cognitive domain: multivariate pattern analysis (MVPA). This method allows us to test whether neural populations in a cortical area distinguish between different categories of stimuli within a cognitive domain. It does so by testing whether different categories (e.g. different quantities) evoke unique spatial patterns of activity within a cortical area, such that a model could learn to reliably predict the category of stimulus a participant saw or heard based on the pattern of activity in a cortical area (Norman et al., 2006).

A second goal of the current study was to investigate whether number-responsive “visual” cortex likewise develops a population code for representing approximate numerosities. In sighted individuals, representations of approximate and symbolic number are co-localized to fronto-parietal networks, possibly because the approximate number system serves as a foundation for the development of symbolic number representations (Chapter 1.1). Thus, whether representations of symbolic and approximate number become co-localized in the “visual” cortex of congenitally blind individuals is an interesting open question. Here I asked whether number-responsive rMOG possesses more fine-grained representations of approximate number by asking whether it codes for quantities in a manner similar to the IPS.

On each trial, subjects heard a sample sequence of either 4, 8, 16 or 32 beeps and decided whether a subsequent test sequence had more or less beeps than the sample sequence. I then provide labeled neural patterns associated with two numerosities (e.g. 4 and 8) to a machine learning classifier. In the training phase, the classifier learns to discriminate between these two categories of neural patterns. In the testing phase, the classifier is given new, unlabeled neural patterns and is asked to identify their corresponding numerosities. This procedure is repeated for every pair of numerosities and classification accuracy is averaged across all pairs of numerosities. If the spatial pattern of activity in the IPS does, indeed, encode the two numerosities the classifier should be able to discriminate between their neural patterns with high accuracy. By contrast, if neural patterns in the IPS do not code for numerosities, the discrimination performance of the classifier will be at chance (50%).

Additionally, I asked whether quantity representations in the IPS of congenitally blind individuals become more discriminable as the ratio between quantities increases. To determine whether the IPS represents quantities with similar precision in both congenitally blind and sighted individuals, I tested whether ratio had a similar effect on the machine learning classifier's ability to discriminate between two quantities across the two groups. If the precision of approximate number representations is similar across congenitally blind and sighted participants, classification accuracy should increase with ratio at the same rate. By contrast, if visual experience is necessary for improving the precision of IPS quantity representations, ratio may have a smaller effect on classification accuracy in congenitally blind compared to sighted individuals.

Finally, I asked if regions of the "visual" cortex that showed sensitivity to symbolic number also develop population coding for approximate quantities in congenital blindness.

6.2 Materials and Methods

6.2.1 Participants

Sixteen congenitally blind (mean age 49 years, SD=16, min=29, max=73) and 18 sighted control participants (mean age 38 years, SD=15, min=19, max=63) contributed data to the final sample. Three additional participants were tested but excluded from the final sample because further screening revealed that the participant had a history of some vision (1 blind) or because they fell asleep during the experiment (2 sighted). Blind participants had at most minimal light perception and their blindness was due to pathology of the eyes or optic nerve, not due to brain damage. All participants reported having no cognitive or neurological disorders.

6.2.2 Behavioral Paradigm

Participants completed an auditory approximate number comparison task that was adapted from a visual approximate number comparison task designed by Eger et al. (2009). On each trial, participants heard a tap to indicate the trial was starting followed by a sample sequence of 4, 8, 16 or 32 beeps. After a 6-second delay they heard a second, test sequence of beeps whose numerosity differed from the first by a ratio of 2 (e.g. sample sequence: 8 beeps, test sequence: 4 or 16 beeps). After a second tap (to indicate the end of the second stimulus), participants had 4 seconds to indicate whether the second sequence was more or less numerous than the first by pressing one of two buttons (left button = less numerous, right button = more numerous). Each trial was followed by a 6-second rest period.

To ensure that numerosity was not being decoded on the basis of low-level stimulus features, sample sequences were matched across numerosities either on 1) total sequence duration or 2) individual element duration. In the total duration matched condition, all sample sequences for every numerosity was 3 seconds long, with larger sequence (e.g. 32) played faster than smaller sequences (e.g. 4). In the element duration matched condition, each beep in the sequence played for ~0.2 seconds (with some jitter), thus matching on pace but not overall duration.

To discourage participants from using the duration of the sequences as a cue to numerosity, the duration of test sequences was either congruent or incongruent with respect to the ratio between the sample and test sequence. On congruent trials, test sequences that were more numerous than sample sequences also played twice as long and those that were less numerous were twice as short (e.g. sample sequence: 8 beeps, 3 seconds; test sequence: 16 beeps, 6 seconds) and vice versa on incongruent trials.

Each of the 8 sample conditions (4 numerosities x 2 match conditions) appeared on 4 trials per run (32 total trials per run). The 8 sample conditions were arranged in a Latin Square design such that each condition followed and preceded every other condition an equal number of times over the course of the experiment.

Both blind and sighted participants were blind-folded for the entire experiment. All participants completed all 8 runs of the experiment.

6.2.3 MRI Data Acquisition

MRI data acquisition parameters were identical to those described in Chapter 3.

6.2.4 fMRI Data Analysis

6.2.4.1 Univariate Analysis

MRI surface reconstruction and preprocessing steps were identical to those described in Chapter 3.

fMRI data were analyzed using a general linear model, which included eight regressors of interest—one for each sample condition (4 numerosities x 2 match conditions) that modeled the first stimulus and delay periods together. Beta maps for each of the 8 regressors of interest for each run were used for MVPA. The response period as well as the instruction taps (prior to first stimulus and prior to second stimulus) were modeled separately and were not included in any of the reported analyses. Trials in which the participant failed to respond were also modeled separately and excluded from all analyses.

6.2.4.2 Multivariate Pattern Analysis

I used MVPA to ask whether the following four regions of interest (ROIs) contained a spatial code for auditory quantities: right IPS, left IPS, the right middle occipital gyrus within visual cortex (rMOG) and early auditory cortex (A1). Group-specific IPS ROIs were defined based on a math equations>sentences contrast from a separate published dataset ($p<0.01$, uncorrected for sighted and $p<0.001$, uncorrected for congenitally blind) (see Chapter 3 and Kanjlia et al., 2016 for details). Briefly, in that experiments participants heard pairs of math equations with a variable X and had to decide whether the value of X was the same or different in the two equations. In the control condition, they judged whether a pair of sentences (passive and active) had the same meaning. The math>sentences contrast in this experiment identified bilateral IPS ROIs in both sighted and blind individuals. Additionally, in the blind group only, responses to math were observed in the rMOG of the "visual" cortex. These ROIs were used in the current study.

A math-responsive visual cortex ROI (rMOG) was defined as the cluster within right visual cortex that responded more to math equations than sentences in congenitally blind>sighted individuals (right middle occipital gyrus, rMOG; $p<0.001$, uncorrected). To ask whether the auditory cortex was sensitive to numerosity, I used a previously published auditory cortex ROI that includes anatomically defined posteromedial, middle and anterolateral Heschel's gyrus (Norman-Haignere et al. 2013).

MVPA was conducted using the pyMVPA toolbox (Hanke et al., 2009). I used MVPA to decode numerosity (6 total comparisons: 4 vs. 8, 4 vs. 16, 4 vs. 32, 8 vs. 16, 8 vs. 32, 16 vs. 32) based on patterns of activity with each ROI using a leave-one-run-out cross-validation procedure. For a given pair of numerosities (e.g. 4 vs. 8), a linear support vector machine (SVM) was trained on 28 beta vectors (2 numerosities x 2 match conditions x 7 runs) within an ROI and then tested on 4 unlabeled ROI patterns from the left-out run. This process was repeated iteratively until every run was left out and classification accuracy was averaged over cross-validation folds. To evaluate overall classification performance, I averaged over all numerosities.

I further asked whether regions that code for numerosity demonstrate a known signature of the approximate number system: ratio-dependent numerosity coding.

Quantities that differ by a small ratio are known to be harder to distinguish behaviorally and also activate more overlapping neuronal population codes (Feigenson et al., 2004; Piazza et al., 2004, 2007a; Nieder, 2013; Viswanathan and Nieder, 2013). Thus, we predict more overlapping patterns (i.e. lower classification accuracy) for quantities that differ by smaller ratios than larger ratios in regions that possess quantities. Therefore, I compared classification performances across pairs of different ratios, collapsing over pairs of numbers that differ by the same ratio (e.g. 4 vs. 8 and 8 vs. 16 are both ratio 2). Ratio effects were statistically tested using a univariate general linear model (GLM) in R with ratio as a continuous predictor and hemisphere and group as categorical factors.

Next, I compared the degree to which numerosity decoding was driven by numerical as opposed to non-numerical, low-level stimulus features across ROIs. Numerosity is more confounded with overall amount of sound on trials that were matched on individual beep duration than those matched on overall duration. Therefore, I compared classification accuracy for element-duration and total-duration matched quantities separately to test the hypothesis that auditory cortex (A1) is more sensitive to total amount of sound rather than quantity per se, while the IPS is sensitive to numerosity, even when overall amount of sound is controlled. The same test was also conducted within the “visual” rMOG ROI.

Finally, a searchlight analysis was used to look for networks that code quantities across the entire brain. For each participant and pair of numerosities, MVPA was conducted within searchlight regions of 10mm radius across the cortical surface. Classification accuracy across all 6 quantity pairs was then averaged within each searchlight. Classification accuracy cortical surface maps were logit-transformed and statistically compared across participants within a group and across groups using random-effects GLM analyses. Searchlight results were corrected for multiple comparisons using the permutation-based cluster-correction method described in Chapter 3.

6.3 Results

6.3.1 Behavioral Results

Behaviorally, both sighted and congenitally blind groups performed well above chance and did not perform differently from each other (sighted: 86.65%, SD=2.18; congenitally blind: 86.35%, SD=2.84; t(32)=-0.08, p=0.93).

6.3.2 Similar ratio dependent sensitivity in IPS of sighted and blind

Within the left and right IPS of the sighted group, auditory quantities (i.e. 4, 8, 16 and 32) were discriminated above chance (left 56.25% (SD=1.63), one-sample t-test t(19)=4.02, p=0.001; right IPS 57.63% (SD=1.39) one-sample t-test t(19)=5.70, p<0.001; paired t-test between hemispheres: t(19)=1.18, p=0.25; Fig. 6.1). There was also an effect of numerical ratio on decoding performance (main effect of ratio: F(1,97)=18.27, p<0.001; main effect of hemisphere: F(1,97)=1.33, p=0.25; ratio by hemisphere interaction: F(1,97)=0.71, p=0.40; Fig. 6.1).

Similarly, in the congenitally blind group, left and right math-responsive IPS coded for auditory quantities with 60.45% (2.11) and 64.10% (SD=1.88) accuracy, respectively (left: t(15)=4.96, p<0.001; right: t(15)=7.50, p<0.001). Analogous to the sighted group, numerosities that differed by a larger ratio were discriminated with higher accuracy (main effect of ratio: F(1,77)=10.72, p=0.002; ratio by hemisphere interaction: F(1,77)=2.37, p=0.13). Overall decoding accuracy was greater in the right IPS than the left IPS of the congenitally blind group (main effect of hemisphere: F(1,77)=7.38, p=0.01).

Overall decoding accuracy was better in the IPS of congenitally blind than sighted individuals (hemisphere by group repeated measures ANOVA; main effect of group: F(1,34)=5.86, p=0.02; Fig. 6.1). The effect of ratio did not differ across groups (main effect of ratio: F(1,174)=28.95, p<0.001; ratio by group interaction: F(1,174)=0.42, p=0.52; main effect of hemisphere: F(1,174)=6.81, p=0.01).

6.3.3 Math-responsive visual cortex (rMOG) shows effect of ratio on decoding accuracy in congenitally bind group

I previously found right-lateralized visual cortex (right middle occipital gyrus, rMOG) recruitment during math calculation in congenitally blind but not sighted individuals (Chapter 3, Kanjlia et al. 2016). Here I find that non-symbolic auditory numerosities can be decoded in the rMOG of the blind and sighted (blind rMOG quantity decoding 56.06% (SD=1.38, one-sample t-test; t(15)=4.40, p=0.001; sighted 53.59%, SD=2.57, t(19)=2.42, p=0.03) (Fig. 6.1). Although decoding was slightly better in the blind group, the group difference in overall classification accuracy was not significant (CB vs. S: t(34)=1.19, p=0.24).

However, only the rMOG of congenitally blind individuals showed ratio-dependent discrimination (main effect of ratio in CB: F(1,31)=20.6, p<0.001; sighted (F(1,39)=0.21, p=0.65, Fig. 6.1). Direct comparison of congenitally blind and sighted individuals revealed that the effect of ratio was significantly greater in the congenitally blind group (ratio by group interaction: F(1,83)=9.59, p=0.003).

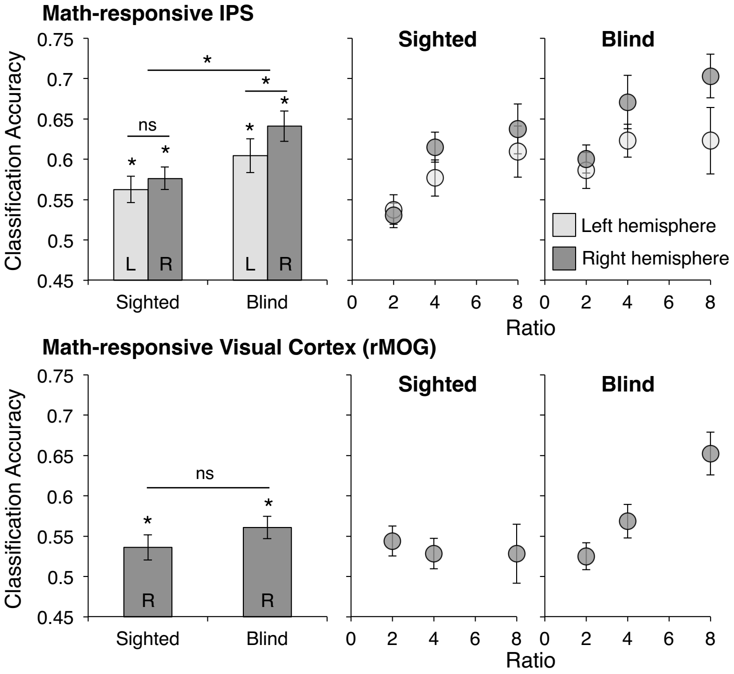


Fig. 6.1 Classification accuracy in IPS and rMOG ROIs. Linear support vector machine accuracy for classifying neural patterns in the left and right IPS (top panel) and rMOG (bottom panel). Classification accuracy is averaged across all numerosity pairs in bar graphs and is averaged across all numerosity pairs of the same ratio in the scatter plots.

6.3.4 Greater effect of low-level auditory features on decoding within A1 than IPS or "visual" rMOG

Apart from the IPS and rMOG, auditory quantities were also discriminable in auditory cortex (A1) of congenitally blind (66.90%, SD=1.43) and sighted adults (66.54%, SD=1.38; between group t-test: t(34)=1.06, p=0.30; Fig. 6.3).

To test whether decoding was driven by low-level features (i.e. overall amount of sound) more so in auditory cortex (A1) than in the IPS or rMOG, I compared decoding performance across element-matched and total duration-matched conditions. In the element-matched condition, quantities with greater numerical distances also differed from each other in overall amount of sound. By contrast, this was not true in the total duration-matched sequences. I therefore reasoned that cortical areas that were more sensitive to overall amount of sound than numerical quantity per se would show better decoding performance for the element-matched than the total duration- matched conditions.

Consistent with the idea that decoding in A1 was driven more by overall amount of sound--the difference in decoding accuracy between element-matched and total duration-matched lists was more pronounced in A1 than in IPS in both the sighted and blind groups (hemisphere by match-condition by ROI (A1 vs. IPS) repeated-measures ANOVA; ROI by match-condition interaction in sighted group: F(1,19)=45.44, p<0.001; blind group: F(1,15)=21.11, p<0.001) (Fig. 6.2). Analogously, in both groups, the difference between element-matched and duration matched lists was more pronounced in A1 than rMOG (match-condition by ROI (rA1 vs. rMOG) repeated-measures ANOVA;

ROI by match-condition interaction in blind group: F(1,15)=18.25, p=0.001; ROI by match-condition interaction in sighted group: F(1,15)=42.59, p<0.001).

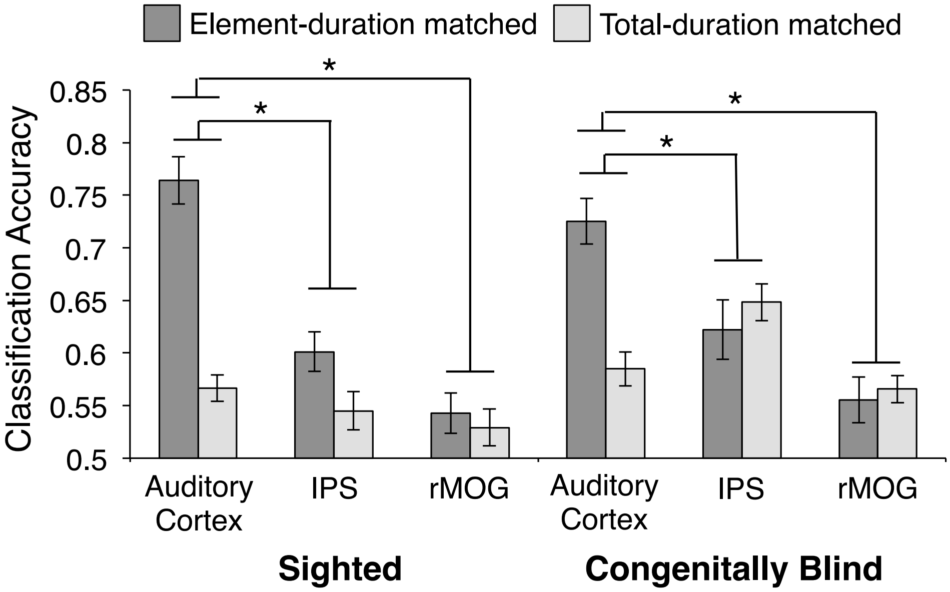


Fig. 6.2 Classification accuracy by match condition. Linear SVM discrimination performance for stimuli that were matched in either element duration or total duration across auditory cortex, IPS and rMOG ROIs. Classification accuracy is averaged across left and right hemispheres for auditory cortex and IPS ROIs.

6.3.5 Searchlight analyses reveal auditory quantity decoding in fronto-parietal number network

Searchlight analyses revealed successful decoding of auditory quantities in a right-lateral fronto-parietal network in both sighted and congenitally blind individuals

(Fig. 6.3). In congenitally blind individuals, numerosity decoding extended posteriorly along dorsal occipital cortex (rMOG) as well as lateral occipito-temporal cortex, in the vicinity of the visual number form area (VNFA) (Shum et al., 2013). However, direct comparison of searchlight results across congenitally blind and sighted groups did not yield significant between group differences.

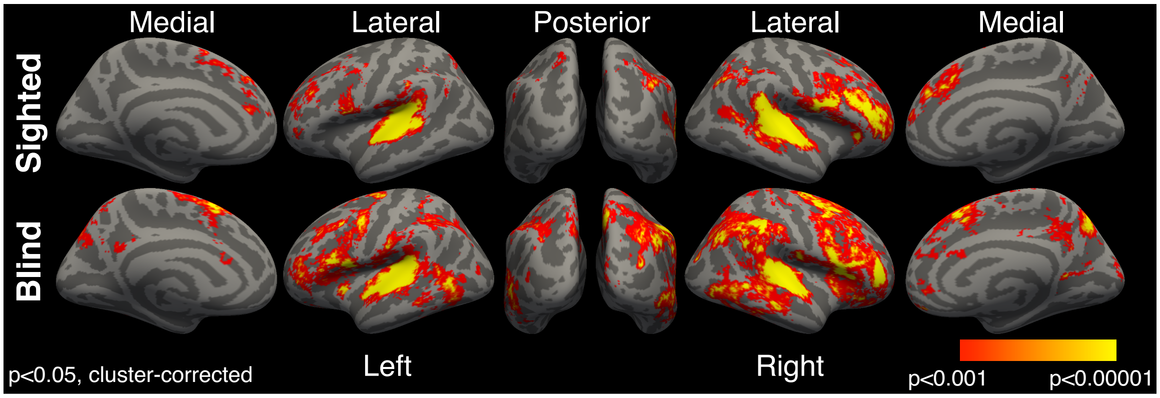


Fig. 6.3 Numerosity classification performance across entire cortex. Multivariate pattern classification analyses conducted in searchlight ROIs with 10mm radius across entire cortex. Whole-cortex searchlight results are cluster-corrected with $p<0.01$ cluster-forming threshold and alpha of $p<0.05$. Results are shown with $p<0.001$ voxel-wise threshold.

6.4 Discussion

6.4.1 Representations of number in the IPS are modality independent

Previous studies with sighted individuals have found that spatial patterns of activity within the IPS discriminate between different numerical quantities. That is, when sighted participants view sets of visual objects (e.g. dots), the pattern of activity within the IPS reflects the number of the objects viewed (Eger et al., 2009). Here I report that the IPS of sighted individuals also codes for auditory quantities. When sighted participants listen to sequences of tones, the numerosity of the tones can be decoded from spatial activity patterns within the IPS. This finding replicates the results one previous fMRI study, which found that activity patterns in the IPS can be used to discriminate between auditory sequences of different quantities (Cavdaroglu et al., 2015).

As in previous work, I found that numerosity could also be decoded from activity patterns in primary auditory cortex, A1 (Cavdaroglu et al., 2015). However, relative to the IPS, decoding in A1 was more influenced by low-level properties of the stimulus (i.e. overall amount of sound). The present results from sighted participants go one step beyond previous findings by showing that coding of auditory numerosities in the IPS is ratio-dependent. I find that quantities that are more similar to each other (differ by a smaller ratio) evoke more overlapping spatial patterns of activity within the IPS than quantities that differ by a larger ratio. This ratio-dependence of the IPS population code mirrors the ratio-dependence of behavioral discrimination and neural responses to number reported in previous work (Piazza et al., 2007a; Odic et al., 2013; Tokita et al., 2013).

The present results thus suggest that the IPS contains modality-independent representations of number. Consistent with this idea, electrophysiological recordings from the IPS of monkeys find overlap between auditory and visual representations of number at the level of individual neurons (Nieder, 2012). That is, some neurons in the IPS are tuned to a specific number of events in a sequence, regardless of whether the events occur visually or auditorily (Nieder, 2012). However, there is also evidence that the IPS additionally has specialized representations for auditorily or visually perceived numerical information. Single unit recordings from neurons in the IPS show that while some neurons are tuned to the same numerical magnitude across presentation formats, the majority are modality specific (Nieder, 2012). Thus the best summary of the available evidence is that humans develop both modality-independent and modality-specific representations of number but all of these representations share a neuroanatomically similar location in the IPS.

6.4.2 IPS representations of number developmentally independent of visual experience

A further key finding of the current study is that representations of number in the IPS develop independent of visual experience. All of the functional signatures of IPS number responses were similar across individuals who are blind from birth and sighted individuals. As in the sighted, in congenitally blind individuals I observed ratio-dependent numerosity coding in the IPS that was less sensitive to low-level auditory features than A1. These findings are consistent with prior evidence that individuals who are congenitally blind recruit the IPS during symbolic number reasoning (Kanjlia et al., 2016; Amalric et al., 2017; Crollen et al., 2018).

The present results extend these findings by showing that the IPS of congenitally blind individuals also develops typical sensitivity to non-symbolic number. If anything, decoding of number in the IPS was somewhat more accurate in the congenitally blind as compared to the sighted group. Thus, visual experience is not necessary for the development of approximate number representations in the IPS. These findings are consistent with behavioral studies showing preserved signatures of numerical reasoning in congenital blindness. Congenitally blind and sighted individuals show similar overall performance when estimating the quantity of tones, footsteps or finger taps, and show similar ratio-dependent performance on these tasks (Castronovo and Seron, 2007; Castronovo and Delvenne, 2013; Kanjlia et al., 2018a). Together these findings support the hypothesis that the IPS number system develops largely independently of vision.

One question that remains unanswered in the present study is whether the IPS number system becomes more "tuned" to sequential auditory quantities as opposed to visual sets in individuals who are blind. As discussed previously, IPS neurons that code for the numerosity of sets in monkeys are sometimes modality- and format-specific. For example, some IPS number neurons respond when 4 items are presented visually but not when they are presented auditorily (Nieder, 2012). Similarly, some neurons respond preferentially when 4 items are presented concurrently but not when they are presented sequentially (Nieder et al., 2006). One possibility is that the IPS number system may become more specialized for processing the numerosity of sequential auditory sets in congenitally blind relative to sighted individuals.

Consistent with this possibility, I found somewhat better decoding of numerosity for auditory sequences in the IPS of congenitally blind as compared to sighted individuals. Alternatively, sequential auditory number processing may be similar across both groups while the ability to process simultaneously presented visual sets fails to develop in congenital blindness. One way to test this question would be to examine visual quantity estimation among individuals who suffer from transient early vision loss. Absence of vision early in life, due to transient cataracts, permanently affects high-level visual functions, such as face and motion perception in adulthood (Maurer et al., 2005; Grady et al., 2014; Maurer, 2017). If the approximate number system in the IPS contains modality- and/or format-specific subsystems that are tuned by perceptual experience, sight-recovery participants may be impaired in simultaneous visual estimation. However, even if such "tuning" does occur, the overall "numerical" function of the IPS is nevertheless preserved.

Whether or not the IPS becomes especially good at processing auditory numerical sequences in blindness, its role numerical processing as well as the precision with which it represents numerical information is preserved in blindness. One interpretation of this robustness to large-scale changes in sensory experience is that the capacity of the IPS to represent quantity has evolutionary precursors. Consistent with this idea, the ability to approximate number emerges early in development in humans and is shared with various species, including non-human primates, rats, birds and fish (Meck and Church, 1983; Roberts et al., 2000; Cantlon and Brannon, 2006; Agrillo et al., 2008; Izard et al., 2009). Homologous areas of the brain support numerical processing in non-human primates (Nieder, 2013; Viswanathan and Nieder, 2013). These findings suggest that the seeds of numerical reasoning are present in our evolutionary heritage. This could partly explain why the number system is resilient to atypical sensory experiences such as blindness.

An alternative possibility is that representations of approximate number are honed by experience but experience in any modality is equally effective in doing so. Whether accumulated perceptual experience with object or event sets hones the approximate number system is at present not known. Behavioral studies show that the acuity of approximate number representations improves over the course of development, including over the first months of life and into adulthood (Halberda and Feigenson, 2008; Libertus and Brannon, 2010). Whether these changes result from maturation or from the accumulation of experience with numerical sets, or both is not known.

One kind of experience that is known to change representations of number is language and education. Acquiring an exact, symbolic number system enables humans to precisely count the number of items in a set and understand that the last number in their count sequence represents the exact cardinality of the set (Frank et al., 2008). Symbolic numbers also allow humans to encode and remember the cardinality of a set, manipulate it in the absence of a physical reference and perform countless mathematical operations over it (Gelman and Gallistel, 2004; Gordon, 2004; Frank et al., 2008). Thus, humans with no counting system, such as members of the Amazonian Piraha tribe, fail to represent the exact cardinality of a set in contexts where numerate individuals do so automatically (Gordon, 2004; Frank et al., 2008). For example, when shown a set of 5 spools of thread and asked to provide the same number of items after a short delay, individuals without number words sometimes produce sets of 3, 4, or 6 and produce more errors for larger quantities (Gordon, 2004; Frank et al., 2008). Acquisition of number words and mathematical education further improves precision on approximate number tasks (Pica et al., 2004; Piazza et al., 2013). Humans who possess a limited vocabulary for numbers show lower precision on approximate number tasks and this precision improves when number words are acquired through years of education (Pica et al., 2004; Piazza et al., 2013).

Several studies suggest that representations of symbolic number, like those of the approximate number system, are shared among sighted and congenitally blind individuals. As I have shown in Chapter 3, in sighted and congenitally blind individuals alike, the IPS is recruited during symbolic number reasoning and is similarly sensitive to the difficulty of math equations (Kanjlia et al., 2016; Amalric et al., 2017; Crollen et al., 2018). Furthermore, in Chapter 2 I find that, like sighted individuals, people who are congenitally blind show similar behavioral correlations between numerical approximation and symbolic math performance across individuals (Kanjlia et al., 2018a). Together with the current findings, these data suggests that IPS representations of approximate number develop independent of visual experience and are able to serve as a foundation for the construction of symbolic number representations in those who are sighted and those who are blind.

6.4.3 Math-responsive visual cortices code for non-symbolic quantities in congenital blindness

In addition to the IPS, parts of the "visual" cortex, in particular the right middle occipital gyrus (rMOG), shows ratio-dependent coding of numerosity in congenitally blind but not sighted individuals. Furthermore, like the IPS, the rMOG was less sensitive to low-level auditory features than early auditory cortex (A1).

The present findings are consistent with prior evidence that the rMOG acquires responses to symbolic number in blindness (Kanjlia et al., 2016; Amalric et al., 2017; Crollen et al., 2018). Like the IPS, the rMOG of blind individuals responds preferentially during math calculation compared to sentence comprehension and activity increases with the difficulty math equations (Kanjlia et al., 2016). Furthermore, even during rest, activity in the rMOG is more synchronized with IPS activity in congenitally blind compared to sighted individuals. Together with the present evidence, these findings suggest that IPS representations of number expand into deafferented visual cortices in congenital blindness. These findings further demonstrate that cognitive functions that are co-localized in other cortical systems show co-localization in the "visual" cortex of congenitally blind individuals. That is, just as the IPS responds to both symbolic and non-symbolic numerical information both in the sighted and in the blind, the rMOG shows sensitivity to both symbolic and non-symbolic number in blindness.

Prior studies suggest that, in sighted individuals, this rMOG region is retinotopically organized and performs mid-level visual functions such as motion and object processing (Tootell et al., 1997; Larsson and Heeger, 2006; Kolster et al., 2010; Van Essen et al., 2012). Furthermore, in blind-folded sighted individuals, this region does not show an above baseline response to auditory numerical stimuli (Kanjlia et al., 2016). Interestingly, in the current study, I find that numerosity can be decoded from activity in the rMOG of sighted individuals, although the effect was not ratio-dependent.

These results are consistent with the idea that plasticity in blindness builds upon pre-existing connectivity patterns that are common to the sighted and blind. According to this hypothesis, the visual cortex has pre-existing regional biases in functional connectivity with fronto-parietal circuits in sighted and blind individuals alike. In sighted individuals, this top-down input from fronto-parietal networks is outweighed by bottom-up visual input but in congenital blindness, these top-down inputs have an opportunity to repurpose the visual regions with which they communicate.

This hypothesis is consistent with the results presented in Chapter 4 in which I find that, relative to a ventral visual area, the rMOG of sighted individuals shows higher resting-state synchrony with math-responsive IPS (Kanjlia et al., 2018b). It is possible that this communication produces some number-related responses in the rMOG of sighted individuals, such as the numerosity-specific patterns observed in the current study. However, when bottom-up visual input is completely removed these network-specific fronto-occipital connectivity biases are enhanced and predict reorganization of the visual cortex (Bedny et al., 2011; Kanjlia et al., 2016, 2018b; Crollen et al., 2018). Thus, despite a common pre-existing "blue-print," early experience alters the functional properties of cortex, engendering ratio-dependent number coding in parts of cortex that do not typically represent this information. In this regard, the results are consistent with accumulating evidence that in blindness "visual" cortices are colonized by top-down projections from higher-cognitive networks, such as the IPS (Kanjlia et al., 2016; Bedny, 2017).

What is the relationship between IPS and rMOG representations of number? One possibility is that, in congenital blindness, numerical processing becomes distributed over two regions rather than isolated to the IPS. In this case, the rMOG may be necessary for numerical processing but may not necessarily impart any behavioral benefit to congenitally blind individuals. A second possibility is that recruitment of additional cortical regions lends advantages to cognitive processing. Finally, it remains possible that the rMOG does not causally contribute to numerical cognitive processes. The possibility that rMOG activity is entirely epiphenomenal seems less likely since the rMOG possesses a relatively fine-grained population code for approximate numerosities. Furthermore, there is evidence that "visual" cortex activity behaviorally relevant to some higher-cognitive tasks in blindness (Amedi et al., 2004; Merabet et al., 2004). In future work it will be important to test whether the rMOG is functionally relevant to numerical performance in blindness using techniques such as TMS.

Irrespective of the functional relevance of the rMOG to number tasks, the current study suggests that visual experience alters the neural basis of numerical processing in a surprising way. On the one hand, IPS number representations are highly resilient to dramatic changes in visual experience. On the other hand, "visual" areas that did not evolve for numerical processing, nevertheless acquire responses to numerical information. Why is it that the "visual" cortex appears highly flexible, while parts of the IPS are constrained to processing number? One possibility is that blindness is a relevant type of experience for the visual system but irrelevant to the development of the IPS number system. According to this view, the "visual" cortex was constrained by evolution to expect visual experience, in part by its strong connectivity with the lateral geniculate nucleus. When this experience does not occur, "visual" areas take on the functional profiles of their next strongest source of input. By contrast, the IPS number system was built to receive numerically-relevant information from multiple modalities and this information arrives without substantial change in blindness. I discuss this hypothesis in more detail in the General Conclusions (Chapter 7).

6.5 Conclusions

In summary, these results suggest that representations of number in the IPS are resilient to dramatic changes in sensory input. These findings suggest that in sighted and blind individuals alike, IPS representations of number are not tied to a specific modality. In contrast to this resilience, completely removing typical input to an area, such as visual input in blindness, enables dramatic plasticity. Deafferented visual cortex, specifically the right middle occipital gyrus, develops sensitivity to symbolic number as well as a numerosity code in congenitally blind individuals. This Chapter concludes the empirical investigations into the cognitive and neural basis of numerical thinking in blindness. The findings from the preceding chapters are summarized in the General Conclusions (Chapter 7). Furthermore, in General Conclusions, I provide a potential synthesis for our findings of resilience of the IPS number system, on the one hand, and dramatic plasticity of the visual cortex for numerical processing on the other.

Chapter 7

General Conclusions

The goal of this dissertation was to investigate how visual experience contributes to the development of numerical thinking and its neural basis. Vision is an important source of information about numerical sets because is the only modality through which we can perceive large sets of objects simultaneously. Yet, despite this, I find that the behavioral and neural signatures of numerical reasoning are preserved in total congenital blindness.

First, I find that congenitally blind and sighted individuals are able to discriminate between approximate quantities with similar accuracy and the precision of approximate number representations is indistinguishable across blind and sighted groups. I further find that, in both congenitally blind and sighted individuals, the precision of approximate number representations was correlated with symbolic math performance. This finding rules out the possibility that the relationship between representations of approximate and symbolic number is mediated by a shared dependence on vision. Instead, these results support the hypothesis that representations of approximate number play a direct role in development of symbolic number representations (Starr et al., 2013; Szkudlarek et al., 2017).

With respect to the neural basis of numerical thinking, I find that the canonical fronto-parietal number network is preserved in individuals who have never had any visual experience. Like sighted individuals, congenitally blind individuals recruit a fronto-parietal network, in particular the intraparietal sulcus (IPS), more so during symbolic math calculation than during a matched sentence comprehension task. Across congenitally blind and sighted groups, the IPS showed similar sensitivity to the number of digits in math equations and the algebraic complexity of math equations.

I further find that representations of approximate number in the IPS develop independent of visual experience. Neural population codes within the IPS distinguish between quantities of auditory events. That is, the spatial pattern of activity in the IPS reflects the number of items participants heard in a set. Furthermore, as predicted by behavioral ratio-dependent signatures of quantity discrimination, auditory quantities that differ by smaller ratios elicit more overlapping spatial patterns of activity in the IPS.

Together, these findings demonstrate that both the cognitive and neural basis of numerical thinking is resilient to dramatic changes in sensory experience and that they develop independent of vision. This could be either because experience in any modality is sufficient for establishing and tuning representations of number in the IPS or these representations have strong evolutionary precursors and therefore require minimal experience for typical development.

Although fronto-parietal responses to number were preserved in congenital blindness, I did find that the neural basis of numerical thinking was modified by the absence of vision in a significant way. Unlike sighted individuals, congenitally blind individuals recruit parts of the “visual” cortex during symbolic math calculation. Previous studies have shown that parts of the “visual” cortex are recruited during language processing in blindness. Here I find that responses to number are anatomically distinct from responses to language in the “visual” cortex of congenitally blind individuals.

Furthermore, sub-specialization of the “visual” cortex for numerical and language processing aligns with the long-range functional connectivity patterns of “visual” cortices—math-responsive visual regions are more synchronized with math-responsive than language-responsive prefrontal cortices at rest and vice versa for language-responsive visual regions. These results point to increased functional coupling with higher-cognitive fronto-parietal networks as a potential mechanism for the takeover of visual cortices by higher-cognitive functions. According to this hypothesis, top-down inputs from higher-cognitive networks are strengthened in the absence of bottom-up visual input, potentially allowing deafferented visual cortices to acquire the cognitive functions of higher-cognitive areas with which they communicate.

Crucially, math-responsive “visual” cortex (rMOG) demonstrated a similar functional profile as the IPS during symbolic math calculation, showing more activity in response to more difficult math equations. Furthermore, the part of the visual cortex that showed sensitivity to symbolic math also developed population codes for representing approximate number. Like the IPS, math-responsive visual cortex shows a ratio-dependent code for numerosity in congenitally blind but not sighted individuals. Thus parts of “visual” cortex take on the full functional profile of math responsive fronto-parietal areas. These results suggest that parts of the visual cortex are incorporated into the fronto-parietal number network in congenital blindness.

Critically, I find that this extreme functional reorganization follows a sensitive period in development. The rMOG does not develop sensitivity to mathematical difficulty in individuals who lose their vision in adulthood. Instead, the rMOG shows general cross-modal responses to auditory stimuli without any modulation by cognitive load. Interestingly, although the visual cortex of adult-onset blind individuals does not become sub-specialized for math and language, the “visual” regions that show such responses in the congenitally blind group (rMOG for math and rVOT for language) still show selective increases in resting-state synchrony with canonical math and language networks, respectively, even in the adult-onset blind group. I therefore hypothesize that resting functional connectivity dissociations between number- and language-responsive “visual” areas arise from anatomical connectivity biases across visual cortices. I predict that such biases are common across sighted and blind individuals alike. Congenital blindness unmasks these biases and enables them to cause repurposing for number and language in the “visual” cortex.

The absence of higher-cognitive repurposing of “visual” cortices in adult-onset blind individuals illustrates how the intrinsic neurophysiology of a cortical region can constrain functional specialization despite the presence of relevant input. Although “visual” cortices become functionally coupled with higher-cognitive networks at rest in adult-onset blindness, these “visual” regions are unable to become functionally repurposed for higher-cognitive functions. Since long-range functional-connectivity with fronto-parietal networks appears to be in place in adult-onset blindness, it is likely that functional repurposing is constrained by local circuits. Indeed, several studies have identified the how neurophysiological changes over development render the cortex particularly susceptible to the effects of experience during sensitive periods (Hensch, 2003, 2004, 2005b; Bavelier et al., 2010). For example, sensitive periods in development are characterized by a shifts in the excitatory/inhibitory balance of cortical tissue and sensitive period closure coincides with the formation of perineuronal nets, which stabilize neuronal connections (Hensch, 2003, 2004, 2005b; Bavelier et al., 2010). Thus, findings from late-blindness demonstrate that functional input to a cortical area will interact with the neurophysiology of local circuits during the process of functional specialization.

More generally, the discovery of number representations in the visual cortex of congenitally blind individuals suggests that the human cortex is cognitive pluripotent at birth and is capable of taking on a wide gamut of functions, from low-level vision to high-level language and mathematics. Rather than being intrinsically constrained to perform specific cognitive operations, cortical areas appear to be highly flexible, with functional specialization being driven by the input the area receives during development. In conclusion, the neural basis of numerical thinking is both preserved and undergoes modification in the absence of vision.

Together the present findings raise an interesting question. Why is it that some neurocognitive systems, like the IPS number system, appear to be impervious to atypical visual experiences while others, such as the “visual” cortex, can and do change their function so dramatically? I hypothesize that that this pattern of preservation and plasticity is predicted by the mechanisms by which evolution constrains functional specialization of cortical areas. By virtue of their microcircuitry, cortical areas are highly flexible and powerful learning devices, capable of taking on a wide range of functions. However, evolution predisposes cortical areas to perform specific functions, in large part by constraining input to an area through biased connectivity patterns. These two properties of cortical systems, intrinsic flexibility and capacity for learning on the one hand and pre-specified input on the other, contributes to the ability of human cortex to both be highly specialized and highly flexible.

Higher-cognitive systems, such as the IPS number system, were designed by evolution to expect input related to a particular cognitive domain (i.e. numerical information) from multiple modalities by having anatomical connectivity with many sources of sensory input. According to this hypothesis, the IPS receives information that is relevant for numerical processing from diverse sources of input. This feature enables higher-cognitive systems to develop normally if input from one modality is unavailable.

The number system is not unique in this respect. For example, the theory of mind network supports the ability to think about the mental state of others and therefore plays a critical role in social cognition (Saxe and Kanwisher, 2003; Saxe and Wexler, 2005). Although vision provides highly informative cues about the mental state of others (e.g. facial expressions, eye gaze, etc.), analogous information can also be gleaned through non-visual modalities and through language (e.g. verbal reports of people's internal mental states and emotions). Indeed, like the IPS number system, the development of the neural basis of the theory of mind network does not appear to be affected by the absence of visual experience, as it is preserved in individuals who have had no vision since birth (Bedny et al., 2009). Similar patterns of preservation have been observed for neural representations of events and objects in congenitally blind individuals (Bedny et al., 2012a; Peelen et al., 2014). Thus, the fact that higher-cognitive systems typically receive content-relevant input from multiple different modalities enables them to to be resilient to atypical sensory experiences. Said differently, from the perspective of higher-cognitive systems, the experience of a blind individual is perfectly typical because they are still receiving information about number, mental states, objects and events.

By contrast, cortical areas with more modality-specific functions, such as early visual cortex, have evolved to expect one dominant source of sensory input. For example, the visual cortex evolved to expect visual input by virtue of having strong anatomical connectivity with the lateral geniculate nucleus (LGN), or visual thalamus, at birth. In typical development (i.e. sighted individuals), input from the LGN shapes the development of edge, color, shape and motion representations in “visual” cortex. When bottom-up visual input is not received in blindness, “visual” areas cannot assume their typical functions because the mechanism by which they become specialized (i.e. input from the LGN) is missing. Instead, deafferented visual cortices assume a function that is determined by the next greatest source of input, such as higher-cognitive systems that typically provide top-down input into the visual cortex.

To summarize the proposed mechanism of preservation and plasticity of the neural basis of numerical thinking, cortical modules are highly flexible by virtue of their microcircuitry, and cortical representations are shaped by input, as determined by connectivity. Under this account, both the IPS and visual cortex are functionally pluripotent. However, on the one hand, the IPS receives multiple sources of numerical information, allowing it to develop numerical representations in the absence of input from one modality. Conversely, visual cortices, whose functions are inextricably linked to visual input, are capable of dramatic functional repurposing in the absence of this dominant source of input.

Although above I argue for the functional flexibility of cortical modules, there are still important local constraints on the cognitive capacity of cortex, even at birth. Cortical tissue is not homogenous across the brain. In seminal work, Broadmann identified how the cytoarchitecture of neural tissue varies across the cortex and was able to parcellate the entire cortex on the basis of these cytoarchitectural features. Furthermore, transitions in cytoarchitecture align with transitions in function, suggesting that the intrinsic physiology of a cortical area influences its functional role. For example, primary visual cortex, V1, is characterized by a thick input layer (layer IV) due to the large amount of bottom-up visual input it receives from the LGN. Studies that combine fMRI and post-mortem histological techniques find that cortical function aligns with underlying cytoarchitectonics at a finer scale (Gomez et al., 2017; Weiner et al., 2017). For example, within a small patch of category-selective ventral visual cortex, face- and place-selective regions overlap with distinct cytoarchitectonic areas (Gomez et al., 2017; Weiner et al., 2017). Although, note that these areas also have a characteristic connectivity fingerprint (Saygin et al., 2011, 2016; Osher et al., 2016).

Thus, although cortical modules flexibly operate over the input they receive through connectivity, the observed relationships between structure and function suggests that local microcircuitry of the module still influences how well it can perform specific cognitive functions. Therefore, I hypothesize that the cognitive domain over which a cortical area operates is determined by input, but how well it does so is shaped partly by its intrinsic microcircuitry.

The interplay between functional flexibility and connectivity on the one hand and local circuit properties on the other is beautifully illustrated in a series of “rewiring” studies by Mriganka Sur (Sur et al., 1988; Sharma et al., 2000; von Melchner et al., 2000; Sur and Rubenstein, 2005). Sur “rewired” retinal (visual) inputs to the auditory thalamus (medial geniculate nucleus) in ferrets before their visual system was fully developed. Remarkably, the auditory cortex of these ferrets developed ocular dominance columns and orientation selectivity (Sur et al., 1988; Sharma et al., 2000; von Melchner et al., 2000; Sur and Rubenstein, 2005). This finding illustrates the extreme functional flexibility of cortex and how powerfully input instructs the cortical development (Sur et al., 1988; Sharma et al., 2000; von Melchner et al., 2000; Sur and Rubenstein, 2005).

However, with respect to the role of the intrinsic physiology, subsequent studies revealed that the visual representations that emerged in “rewired” auditory cortex were less organized than the visual cortex of typically developing control ferrets (Sharma et al., 2000). For example, “auditory” cortex neurons were sharply tuned to specific orientations but the periodicity of orientation maps was lower in primary auditory cortex (A1) compared to typically developing primary visual cortex (V1) (Sharma et al., 2000). Thus, although input is a powerful driving force in cortical development, the intrinsic physiology of a cortical area can limit how well specific functions are implemented in cortical tissue.

With respect to the findings of this dissertation, one open question is whether, like the rewired auditory cortex of ferrets, the intrinsic cytoarchitecture of “visual” cortices preclude it from developing fine-grained representations that are found in canonical higher-cognitive networks. Contrary to this idea, in Chapter 6, I find that number-responsive “visual” regions actually develop a population code for approximate numerosity just like the IPS. This finding is one of the few demonstrations that “visual” cortices are not only active during higher-cognitive tasks but that they are capable of developing structured higher-cognitive representations. These results suggest that similar higher-cognitive representations can be implemented in two different types of neural tissue (Bedny, 2017). One intriguing question is whether the visual cortex is able to support some fine-grained representational content but not others. For instance, do language-responsive "visual" cortices develop structured representations of semantic categories? Future work should further probe the representational content of repurposed "visual" cortices to determine whether there are any limitations to the higher-cognitive representations that "visual" cortices can support.

If not the representational content, the local cytoarchitecture of visual cortices may limit the behavioral relevance of "visual" cortex recruitment for higher-cognitive tasks such as numerical and linguistic processing. Perhaps reorganized "visual" cortices can process higher-cognitive input, but this processing is unable to make a behavioral contribution. Contrary to this idea, there is evidence that cross-modal responses in the "visual" cortex of congenitally blind individuals are behaviorally relevant. Temporarily disrupting activity in the visual cortex with Transcranial Magnetic Stimulation (TMS) causes blind individuals to make more mistakes when generating semantically related verbs to given nouns and when reading Braille (Amedi et al., 2004; Merabet et al., 2004). However, whether visual cortices are functionally involved in numerical processing, in particular, in congenital blindness is an open question that future studies should pursue using TMS.

Another way to determine whether "visual" cortex recruitment for higher-cognitive functions has behavioral implications is by asking if it confers any benefit to cognitive processing. I find that, on average, congenitally blind individuals' performance on numerical tasks is no better than that of sighted individuals (Chapter 2). However, math abilities are heavily influenced by cultural and educational experiences. Therefore, different educational experiences with math across congenitally blind and sighted groups may mask any potential benefit that could be conferred by the addition of the rMOG to the number-network.

Indeed, congenitally blind individuals have been reported to perform better on some cognitive tasks compared to sighted individuals. For example, congenitally blind individuals demonstrate superior verbal memory, language processing, sound localization and executive function abilities (Lessard et al., 1998; Raz et al., 2007). Consistent with these results, I find better working memory performance in congenitally blind individuals compared to sighted individuals in Chapter 2. These results are consistent with the possibility that recruitment of additional "visual" cortices imparts some benefit in congenitally blindness.

The mechanisms by which cognitive processing might be enhanced by the recruitment of additional cortical territory are not known. One possibility is that processing efficiency is increased when "visual" cortices are incorporated into a neurocognitive network. Alternatively, it is possible that blind individuals are simply more practiced with a specific set of skills. It will be important for future studies to investigate whether the superior cognitive abilities observed in blindness stem from practice, the recruitment of additional "visual" cortices during cognitive processing, or a combination of both.

One way to disentangle these potential sources of improvement is by asking whether benefits in performance are attenuated following the application of TMS to the relevant “visual” cortices of blind individuals. If blind individuals continue to outperform sighted individuals on specific cognitive tasks after TMS to the “visual” cortex, it would suggest that behavioral enhancements do not result from the recruitment of additional cortical territory but may rather stem from practice and improvement of canonical cognitive networks. By contrast, if enhancements in performance are reduced after TMS to “visual” cortices, it would suggest that “visual” cortices are functionally relevant to behavior and may even contribute to the superior cognitive abilities observed in congenital blindness. Another interesting possibility to consider is that “visual” cortices bolster processing of higher-cognitive networks into which they are incorporated. According to this idea, repurposed visual cortices of blind individuals may not be the source of enhanced cognitive representations themselves but may improve processing in other higher-cognitive networks. Thus, preservation of the IPS number system and plasticity of the “visual” cortex may not be isolated courses of cortical development but may interact and have complex neural and behavioral implications in congenital blindness.

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