THE NEURAL BASIS FOR SYMBOLIC NUMBERS: MULTI-CONSTITUENT NEURAL NETWORKS AND THE CONNECTIVITY

by

Ruizhe Liu

Bachelor in Science, Psychology, East China Normal University, 2009

Master in Science, Psychology, Beijing Normal University, 2012

Submitted to the Graduate Faculty of the

Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2020

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

This dissertation was presented

by

Ruizhe Liu

It was defended on

March 30, 2020

and approved by

Julie Fiez, Professor, Ph.D., Department of Psychology, Department of Neuroscience,

Department of Communication Sciences & Disorders

Marc Coutanch, Ph.D., Assistant Professor, Department of Psychology

Jessica Cantlon, Ph.D., Associate Professor, Department of Psychology, Carnegie Mellon

Univeristy

Dissertation Advisor: Melissa Libertus, Ph.D., Associate Professor, Department of Psychology,

University of Pittsburgh

THE NEURAL BASIS FOR SYMBOLIC NUMBERS: MULTI-CONSTITUENT NEURAL NETWORKS AND THE CONNECTIVITY

Ruizhe Liu, Ph.D.

University of Pittsburgh, 2020

We are able to understand numbers in various formats. For instance, we can read Arabic numerals (defined as the visual code in the current study) from a book and talk about these numbers (the verbal code). We can use our hands to express a number (the manual code). We can also compare the number of jellybeans in different jars without actually counting them (the semantics). How does the human brain represent these different number codes? Existing findings show that the number codes might be locally represented by unique brain regions. However, different number codes might be tightly connected to each other, e.g., one might be internally saying the number word when seeing an Arabic numeral and this potential integration between number codes has not been thoroughly explored in previous studies. Here, we used a number code localizer task to first examine the neural representation of the four number codes separately. Specifically, adults and third to fourth graders were asked to complete a number comparison task (the semantic task) and a phonological comparison (the verbal task) task in an MRI scanner. The stimuli were either Arabic numerals (the visual code) or hand images (the manual code) displaying different numbers. The contrast between different number codes yielded multiple unique brain regions supporting the neural representation of each number code. We then tested the context-dependent connectivity among all the brain regions yielded by the contrasting analyses and found that some brain regions were involved in representing more than one number code. The results stand against the localist view and support the notion that the neural representation of each number code is

distributed among a network consisting of brain regions unique to each number code as well as brain regions common to several number codes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 INTRODUCTION

Numbers in symbolic formats are unique human cultural inventions to describe the world and to communicate with each other. The underlying symbolic number system takes in various physical cues, such as the shape of a symbol or the sound of a number word, and generates a unified representation for one number. For example, across cultures symbolic numbers have different visual appearances (e.g., Arabic numerals 4, "四" in Chinese, and four fingers in sign language), verbal pronunciations (e.g., "/θri/" for 3 in English and "/sān/" in Chinese). Yet, the quantitative concept that each number symbol represents (i.e., the semantics) seems to be consistent across many cultures that have a number system. For example, "two" and "二"both represent a quantity that contains 1 more unit than "1". "Three" and "三" both represent a quantity that contains 2 more units than "1".

The semantic representation of symbolic numbers has long been argued to be governed by an analog number representation system which can also be accessed via numbers in non-symbolic formats across sensory domains (e.g., number of objects in a visual scene or number of sounds) and has been found in human infants (Coubart, Izard, Spelke, Marie, & Streri, 2014; Izard, Sann, Spelke, & Streri, 2009; Xu & Spelke, 2000), adults with and without precise number language (Dehaene, Izard, Spelke, & Pica, 2008; Pica, Lemer, Izard, & Dehaene, 2004), and non-human animals (Cantlon, Platt, & Brannon, 2009; Nieder, 2016). When asked to identify the larger of two symbolic numbers, humans' judgment is dependent on the numerical distance or ratio between the two numbers (Shepard, Kilpatric, & Cunningham, 1975). Similarly, when asked to identify the larger of two non-symbolic numbers, humans' judgment is dependent on the numerical distance or ratio between two non-symbolic numbers (Dehaene, Dupoux, & Mehler, 1990; Moyer & Bayer, 1976). As the analog number system is more fundamental and exists in human infants and young children, researchers argue that the symbolic number system may rest upon the analog representation system by integrating verbal and visual codes and their corresponding analog representations (Barth, Starr, & Sullivan, 2009; Fazio, Bailey, Thompson, & Siegler, 2014; Halberda, Mazzocco, & Feigenson, 2008; Mussolin, Nys, Leybaert, & Content, 2012; Starr, Libertus, & Brannon, 2013).

Similar to word recognition, the visual and verbal codes, and the semantics of symbolic numbers are integrated in skilled number readers. By looking at the written symbols “3” and “5”, one can activate the pronunciations (“/θri/” and “/faɪv/”) and the analog magnitudes (“5” is somewhat greater than “3” but not too different compared to other larger numbers such as “100”). By hearing the sounds “/θri/” and “/faɪv/”, one can understand the quantitative relation between the two numbers and can match them to written symbols. What neural mechanisms support this symbolic integration? Dehaene (Dehaene, 1992) first proposed the triple-code model for number representations in the human brain. This model postulates that there are three codes of symbolic numbers: a verbal code (i.e., verbal number words), a visual code (i.e., Arabic numerals), and a semantic representation that represents the quantitative meaning of number. The three codes interact with each other and such interactions are bidirectional (Dehaene, 1992; Dehaene & Cohen, 1995). Besides the three codes, some recent studies showed evidence for a potential fourth code, which is the manual number code (i.e., configurations of fingers to represent numbers) (Butterworth, 1999; Crollen & Noël, 2015; Penner-Wilger & Anderson, 2013).

The triple-code model is supported by human brain imaging studies as well as studies with brain lesion patients (Dehaene & Cohen, 1995; Dehaene, Piazza, Pinel, & Cohen, 2003; Shum et al., 2013; Zamarian, Ischebeck, & Delazer, 2009), which found distinct brain regions for each of the three codes. Specifically, findings suggest that the classic language regions such as the superior and middle temporal gyrus (STG, MTG) and angular gyrus (AG) are related to the verbal number code (Andin, Fransson, Rönnberg, & Rudner, 2015; Dehaene & Cohen, 1995); the inferior temporal cortex in the ventral visual pathway is related to the visual number code (Abboud, Maidenbaum, Dehaene, & Amedi, 2015; Shum et al., 2013); and the intraparietal sulcus (IPS) is related to the semantic representation (Hubbard, Piazza, Pinel, & Dehaene, 2005; Piazza, Pinel, Le Bihan, & Dehaene, 2007). Recent studies suggest that the precentral region is involved in representing the manual code (Andres, Seron, & Olivier, 2007; Kaufmann et al., 2008; Piazza, Mechelli, Price, & Butterworth, 2006).

While the functionality of these brain regions and their associated number codes have been fairly well described, the literature mainly examined each code separately or looked at only a subset of these codes. It also lacks a thorough examination of how potential brain regions that support different codes work together to generate mental representations of numbers. Is the activity and connectivity pattern among the regions of interest the same for each of the codes or are some activities or connections stronger than others? The first goal of the current work was to examine the activation in and the connectivity between different brain regions associated with each number code. Based on previous findings, which will be discussed in great detail below, it is predicted that each number code should be represented by unique brain regions. As for the connectivity among the brain regions that support the neural representation of the number codes, while it is expected all codes to be interconnected, the degree of this connectivity may vary.

Secondly, the learning of different number codes emerges at different ages. For example, children start learning verbal number words around the age of 2 years (Fuson, 2012; Wynn, 1990) and they use fingers extensively to facilitate counting and basic arithmetic throughout the early elementary school years. The learning of Arabic numerals starts around the age of 3 (Benoit, Lehalle, Molina, Tijus, & Jouen, 2013) and continues as children learn multi-digit numbers in early elementary school. While the use of number words and Arabic numerals extends into adulthood, the use of the manual code becomes less frequent. Therefore, the second goal was to compare the neural representation and the neural connectivity patterns of the different number codes in children, who are in the process of acquiring symbolic number knowledge, and adults, who have many years of experience with different number formats. As the manual code is more frequently used by children in elementary school (Geary, Hoard, Byrd-Craven, & DeSoto, 2004), we expected to see the manual code relevant regions to have stronger response and the functional connectivity between brain regions that support the manual code and other number codes to be stronger in children compared to adults.

1.1 THE SYMBOLIC NUMBER SYSTEM

1.1.1 The acquisition of the verbal, manual, and visual codes

1.1.1.1 Verbal code

The acquisition of symbolic numbers starts with learning to recite number words around 2 years of age, with gradually increasing understanding of their meaning (Fuson, 2012; Wynn, 1990). Researchers identified the cardinality principle as critical for children to understand the meaning of number words (R Gelman & Gallistel, 1978; Rochel Gelman & Meck, 1983; Rochel Gelman, Meck, & Merkin, 1986; Greeno, Riley, & Gelman, 1984). The cardinality principle states that the last element in the counting sequence represents the total number of elements in the set. It is commonly tested with a "Give-N" task (Condry & Spelke, 2008; Le Corre & Carey, 2007; Le Corre, Van de Walle, Brannon, & Carey, 2006), in which children are asked to generate a number of objects as requested by the experimenter. For example, when asked to give four cookies to a toy elephant, only children who understand the quantitative meaning of "four" can succeed and give the experimenter exactly four cookies. Using the "Give-N" task, it was found that children's understanding of number words develops slowly. First, they can give one but not two or more objects, followed by giving two objects but not three or more correctly, and then three objects. Children at this level are known as sub-set knowers (Le Corre & Carey, 2007; Le Corre et al., 2006; Wynn, 1990). Once children are able to understand numbers larger than 4 or 5, there seems to be a qualitative change in their understanding of numbers. They become cardinal principle knowers and are able to correctly produce higher numbers in their counting list (Le Corre et al., 2006; Wynn, 1990). Around 4 years of age children can typically count up to ten objects accurately, but they may still erroneously assume that one cannot count objects in a random order and may always have to go from left to right (Briars & Siegler, 1984), suggesting that it takes children years to truly understand all the principles of counting.

1.1.1.2 Manual code

As many cultures have a base-10 numerical system, the ten fingers seem to be an ideal tool to facilitate counting. In fact, across different cultures finger counting is an important and frequently used strategy for children, including typically developing children and children with visual disabilities (Crollen, Mahe, Collignon, & Seron, 2011) to learn counting (Butterworth, 1999; Fuson, 1982; Fuson & Willis, 1988; Shrager & Siegler, 1998) and simple arithmetic operations (Crollen & Noël, 2015). Previous studies suggest that finger counting in children is correlated with children's early numerical ability (Fayol, Barrouillet, & Marinthe, 1998; Gracia-Bafalluy & Noël, 2008; Lafay, Thevenot, Castel, & Fayol, 2013; Noël, 2005; Penner-Wilger & Anderson, 2013). For example, the frequency of spontaneous finger counting was positively correlated with 4- to 7-year-olds' performance in a "Give-N" task and this correlation remained significant after age was controlled (Lafay et al., 2013). Also, children's performance in a finger gnosia task (i.e., a task that asks children to sense an unseen touch on one finger and indicate the finger on a pair of cartoon hands) correlated with their number knowledge (Noël, 2005; Reeve, 2011). Training on the finger gnosia task also brought positive effects to early school-aged children's math skills, including using fingers to represent numbers and quantification (Gracia-Bafalluy & Noël, 2008).

Unlike number words and Arabic numerals, the manual code seems less used by adults. However, findings from a series of studies show that finger counting effects extend into adulthood. For instance, when asked to indicate symbolic numbers by pressing a key with one of their ten fingers, adults' performance was better when the number matched their counting habit (left starter or right starter)(Di Luca, Granà, Semenza, Seron, & Pesenti, 2006). If a person prefers to start from the thumb and count to five at the little finger on the right hand, his response to "4" with the ring finger on the right hand was faster than responding to "4" with the ring finger on the left hand. Such counting-habit advantage was also observed when adults were asked to name finger number configurations, e.g., different hand gestures for "three" (Di Luca & Pesenti, 2008, 2011). Moreover, using canonical (e.g., using 5+2 fingers to present 7) and non-canonical hand configurations (e.g., using 3+4 fingers to present 7) to prime the naming of Arabic numerals or verbal number words, canonical hand configurations successfully primed the symbolic numbers that were numerically close to them, suggesting a link between finger counting and other symbolic number formats in adults (Di Luca, Lefèvre, & Pesenti, 2010). Based on the findings, Di Luca and

Pesenti (Di Luca & Pesenti, 2011) argue that the manual number codes are an important type of numerical code that have symbolic features.

1.1.1.3 Visual code

The learning of Arabic numerals (the visual code) emerges around the age of 3 or 4 years, typically after children have started to learn the verbal code. One study examined 3-, 4-, and 5-year-old children's ability to map between verbal number words and dot arrays, Arabic numerals and dot arrays, and verbal number words and Arabic numerals (Benoit et al., 2013). They found that 3-year-olds were able to correctly map small verbal number words ("one", "two", and "three") to dot arrays above chance and *vice versa* but failed to do so in the other mapping tasks. Four-years-olds succeeded (performed above chance) in all mapping tasks, but their performance in the verbal number word-Arabic numeral mapping tasks were worse. At the age of 5, children were at ceiling in all the tasks. Another study looked at the same mapping between number words, Arabic numerals, and dot arrays and found that 3-years-olds passed the number word-dot array mapping and the Arabic numeral-number word mapping task but failed in the Arabic numeral-dot array mapping task (Hurst, Anderson, & Cordes, 2017). Four-year-olds in this study succeeded in all of mapping tasks, but their performance in the Arabic numeral-dot array tasks were worse compared to other tasks. The authors argued that the contradiction might have arisen from perceptual differences in the dot arrays as Benoit et al. (Benoit et al., 2013) used familiar dot arrays (such as dot arrays on a die) whereas Hurst et al. (Hurst et al., 2017)used dot arrays with varying dot sizes and spatial arrangements. Moreover, Hurst et al. performed mediation analyses which showed that the Arabic numeral-number word mapping mediated the path from word-dot mapping to Arabic numeral-dot mapping. These findings suggest that children are likely to associate Arabic numerals first with verbal number words. One study (Knudsen, Fischer, Henning, & Aschersleben, 2015) adds further evidence to this argument. In this study, 4-year-olds completed an Arabic numeral "Give-N" task (i.e., they saw an Arabic numeral and gave the corresponding number of objects) and an Arabic numeral naming task. Moreover, if children failed in the Arabic numeral "Give-N" task, experimenters changed it into a verbal "Give-N" task. Four-year-olds failed in the Arabic numeral "Give-N" task. They passed the other two tasks, but their performance in the Arabic numeral naming task was significantly lower than in the verbal "Give-N" task. As the "Give-N" task requires children to be able to produce a number, it requires the understanding of the cardinality of numbers. The result that 4-year-olds could map Arabic numerals with verbal number words but failed to reproduce Arabic numerals in terms of number of objects indicates that 4-year-olds map Arabic numerals and verbal number words before they really understand the meaning of Arabic numerals.

1.1.2 The semantic representation of symbolic numbers

One can use different ways to infer the semantics of symbolic numbers, e.g., using symbolic number comparison, calculation, or a number-space mapping task. One issue with these tasks is that they do not allow for a pure measurement of the precision of the semantic representations because they all tap into some degree of integration between symbolic number codes and their underlying meaning. It is assumed that the semantic code, or the meaning of symbolic numbers is rooted in the analog number system, which can be measured via non-symbolic number stimuli such as random dot arrays or sequences of rapidly presented tones. Thus, non-symbolic stimuli (also referred to as the "semantic code") provide a way to infer the semantic representation without the use of symbols and without confounding the measurement of the semantic representation with the measurement of integration between different codes.

The most common way to assess the analog number system is by using a non-symbolic number discrimination task, in which two non-symbolic numbers are presented too briefly to be counted and need to be compared based on their numerical quantity. In this task, the numerical ratio between the two non-symbolic numbers varies across trials while other perceptual dimensions of the stimuli, such as the total surface area and density, either co-vary with number or are counterbalanced across trials. Non-symbolic number discrimination is consistently found to be governed by Weber's law, i.e., the accuracy in determining the larger of the two numbers increases as the ratio but not the absolute quantitative difference between the numbers increases (Izard & Dehaene, 2008; Nieder & Miller, 2003; Shepard et al., 1975).

When investigating individual differences in the analog number system, research mainly focuses on the representation of numbers greater than 4 as smaller numbers seem to be represented by an exact system designed to track objects (Feigenson, Dehaene, & Spelke, 2004). It seems that the analog number system for numbers greater than 4 relies on noisy mental representations that are centered around the number to be represented (Dehaene & Changeux, 1993; Halberda & Feigenson, 2008; Verguts & Fias, 2004, 2005). The noise in each number representation is determined by the number multiplied by a person's specific Weber fraction as its standard deviation. Since the Weber fraction is assumed to be constant within any given individual, the variability in the representation increases with number. In other words, the overlap between neighboring numbers increases as numbers get larger. According to this theory, performance in non-symbolic number discrimination tasks is determined by the difference between the two number representations given their means and standard deviations. Following along this prediction, by measuring individuals' performance in non-symbolic number discrimination, one should be able to use accuracy to infer Weber fractions and these Weber fractions should follow a rule: people with higher accuracy in harder discrimination should have smaller Weber fractions. Indeed, this is what has been found in many studies. Weber fractions decrease monotonically with age while overall accuracy increases monotonically with age (Droit-Volet, Clément, & Fayol, 2003; Halberda & Feigenson, 2008; Huntley-Fenner & Cannon, 2000; Xu & Arriaga, 2007; Xu & Spelke, 2000).

1.2 SYMBOLIC NUMBERS IN THE HUMAN BRAIN

1.2.1 The verbal code

According to the triple-code model, the verbal code is a relatively complex representation consisting of multiple constituents, including the phonological, lexical, and syntactic aspects of number words. Hence, it is assumed that typical language regions in the left hemisphere (inferior frontal gyrus, IFG; superior temporal gyrus, STG; medial temporal gyrus, MTG) (Dehaene & Cohen, 1995) are involved in verbal number processing. Besides these language areas, it has been proposed that the left AG (see Figure 1) is a region of interest when considering the verbal code of symbolic numbers (Dehaene et al., 2003). The left AG has been consistently found to be activated in tasks related to symbolic arithmetic fact retrieval but not non-symbolic number processing tasks (Andin et al., 2015; Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999; Grabner et al., 2009; Zamarian et al., 2009), suggesting its role in processing the linguistic component but not the quantitative meaning of symbolic numbers. In one early work (Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002), adults performed six different tasks, including symbolic number subtraction, converting orthography to phonology (phoneme detection task), saccade, visual attention, finger pointing, and grasping. The left AG's activity was modulated by both number subtraction and phoneme tasks, suggesting its role in representing the verbal code. A recent meta-analysis of previous fMRI studies found the left AG to be involved in both arithmetic fact retrieval and phonological processing (Pollack & Ashby, 2017). However, in children they found bilateral superior frontal gyri, left precentral gyrus, left fusiform gyrus, and right insula involved in both arithmetic operations and phonological processing, suggesting the left AG activity might be associated with more skilled verbal processing of numbers.

1.2.2 The visual code

A sub-region in the left fusiform gyrus has been consistently found in relation to visual word recognition (Cohen et al., 2000; Cohen et al., 2002; Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002; McCandliss, Cohen, & Dehaene, 2003). The triple-code model suggests that processing of visual number codes relies on a similar region. While early fMRI studies provide mixed evidence for this assumption (Dehaene & Cohen, 1995; G. R. Price & Ansari, 2011), recent electrocorticography (ECoG) studies provide stronger support for this notion. In these ECoG studies (Shum et al., 2013), human adults were presented with Arabic numerals (0-9), letters, scrambled Arabic numerals, scrambled letter, and foreign numerals and were instructed to press a key if they thought they could pronounce the stimulus. In a second experiment they were visually presented with Arabic numerals, number words, and corresponding non-number words whose pronunciations were close to number words. The task was to read each stimulus aloud. Across participants, the electrodes mostly covered right ventral occipito-temporal regions (including the inferior temporal gyri, ITG, see Figure 1). The coverage in the left hemisphere was restricted. Differences in the local high gamma-band (65-150 Hz) power were found in the right posterior

ITG (pITG, MNI coordinates for the smoothed peak: 51, -54, and -24) differentiating Arabic numerals from morphologically similar, phonologically similar, and semantically similar stimuli. Surrounding regions showed preference to Arabic numerals and morphologically similar stimuli rather than phonologically or semantically similar stimuli. These findings support the existence of a visual number form area (NFA) in the pITG and were replicated by the same group in a different ECoG study (Daitch et al., 2016). Following these ECoG studies, several fMRI studies (Abboud et al., 2015; Grotheer, Herrmann, & Kovács, 2016) found the NFA in the ITG with highly similar coordinates as those given by Shum et al. (Shum et al., 2013).

1.2.3 A potential update to the triple-code model – the manual code

As mentioned earlier, the idea that manual number representation may be one component of symbolic numbers arises from the fact that the acquisition of symbolic numbers is based on counting and fingers are an important tool for learning how to count (Butterworth, 1999). Further evidence for the importance of the manual code comes from patients with Gerstmann syndrome, which is characterized by impaired representations of fingers, numerical abilities, and spatial attention, and commonly associated with posterior parietal brain damage (Gerstmann, 1940; Mayer et al., 1999). Finally, fMRI studies show similar brain activation pattern in number tasks and finger-related tasks. For example, in one fMRI study, adults were asked to perform a mental arithmetic task (subtraction and multiplication) and a visual finger discrimination task (judging which finger was pointing down in a picture). In both tasks, the horizontal IPS and posterior superior parietal lobule (SPL) were activated (Andres, Michaux, & Pesenti, 2012). This finding is in line with extensive findings in non-human primates and humans that the IPS is related to eye-, hand-, and arm-movement planning (Grefkes & Fink, 2005; Hubbard et al., 2005; Simon et al., 2002). In addition to the IPS, the pre- and post-central regions (motor and pre-motor regions, involved in grasping, see Figure 1) also seem to be involved in representing manual and numerical information (Kaufmann et al., 2008; Simon et al., 2002). One study asked 8-year-old children and adults to look at two palms with varied number of fingers raised, varied palm orientation, and varied colors on fingers across trials (Kaufmann et al., 2008). There were three tasks: number comparison ("which hand had more fingers raised?"), palm orientation identification, and color identification. Blood oxygenation level dependent (BOLD) signal changes indicating stronger activation in the number comparison task compared to the other tasks were observed in children's pre- and post- central regions, but stronger deactivation was observed in these regions in adults. The authors thus argued for a stronger finger-number association in children compared to adults.

1.2.4 The semantic code

Functional MRI studies revealed the importance of the parietal cortex, especially the IPS, for the analog number system in humans (Ansari, Dhital, & Siong, 2006; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Piazza et al., 2007; Sokolowski, Fias, Ononye, & Ansari, 2017) (see Figure 1). In an early study (Piazza et al., 2004), adults were adapted to one non-symbolic number that changed in other perceptual dimensions. Then a novel non-symbolic number was presented to probe the brain's response to numerical changes. Whole brain analyses revealed that the bilateral IPS was the only region tuned to the numerical change. The BOLD signal in the IPS decreased in the adaptation phase, recovered when the novel number was presented, and the strength of the recovery was proportional to the relative difference between the habituated and novel number. Importantly, these patterns of brain activation were not found when participants were adapted to shapes. These findings suggest that non-symbolic number is automatically represented in human IPS and that this brain activation is governed by Weber's law. Similar tuning to the semantic code in the IPS has been discovered in studies that used different experimental paradigms, e.g., non-symbolic number comparison (Ansari et al., 2006; Eger et al., 2009) or sequentially presented non-symbolic numbers (Dormal, Andres, Dormal, & Pesenti, 2010). Moreover, using a cross-format fMRI adaptation paradigm, Piazza and her colleagues (Piazza et al., 2007)extended the findings with non-symbolic numbers to both symbolic and non-symbolic numbers. Adults were adapted to non-symbolic numbers or symbolic numbers and then presented with novel numbers in either non-symbolic or symbolic format. Multiple brain regions, including the IPS, showed tuning to the cross-format numerical magnitude change. These findings provide strong evidence for the notion that IPS is involved in representing the semantic code of numbers across different formats. It is also widely proposed that the IPS is an important region for generating the semantic representations of symbolic numbers across sensory domains (Kadosh, Kadosh, Kaas, Henik, & Goebel, 2007; Klein, Moeller, Nuerk, & Willmes, 2010; Notebaert, Nelis, & Reynvoet, 2011; Piazza et al., 2004; Piazza et al., 2007; Pinel, Dehaene, Riviere, & LeBihan, 2001). For example, a recent study showed that the left IPS was the only brain region that was modulated by numerical ratios with both visual and auditory verbal numbers (S. E. Vogel et al., 2017).

There seem to be differences between the left and right IPS. On the one hand, there is evidence suggesting that the left IPS specifically represents the meaning of symbolic numbers (Bugden, Price, McLean, & Ansari, 2012) (Cantlon & Li, 2013; Emerson & Cantlon, 2015; Holloway, Battista, Vogel, & Ansari, 2013; S. E. Vogel, Goffin, & Ansari, 2015). For example, one developmental study found that the left but not the right IPS activity during a symbolic comparison task increased with age (S. E. Vogel et al., 2015). In addition, the developmental change in the left IPS activity in a non-symbolic number – symbolic number matching task correlated with the developmental change in the performance in this task, emphasizing the role that the left IPS plays during the acquisition of symbolic number knowledge (Emerson & Cantlon, 2015).

The right IPS, on the other hand, seems to represent the meaning of symbolic and non-symbolic number stimuli. Its activation was widely observed in tasks that required both non-symbolic and symbolic number processing (Fias et al., 2003; Holloway & Ansari, 2010; Piazza et al., 2007; Venkatraman, Ansari, & Chee, 2005). For example, in the above-mentioned cross-format adaptation study (Piazza et al., 2007), it was found that in the right IPS, the BOLD signal recovery after the presentation of the novel numbers was dependent on numerical distance between the adapted number and the novel number but invariant to number formats, suggesting an abstract representation of the meaning of these numerical stimuli. However, the BOLD signal recovery in the left IPS was dependent on both numerical distance and number formats, suggesting format-specificity in this region.

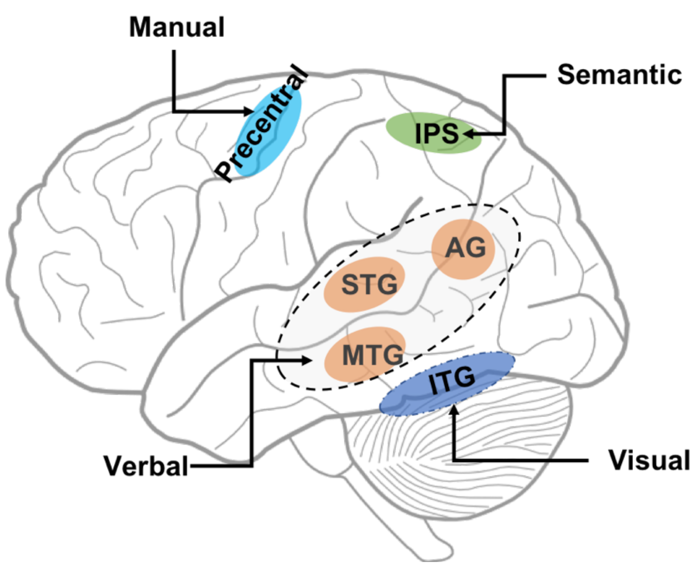


Figure 1. The brain regions for each of the four symbolic number codes.

IPS, intraparietal sulcus; AG, angular gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus.

1.2.5 The connectivity between the brain regions for the four number codes

Existing evidence suggests some of the key regions that support different number codes are functionally connected specifically under the context of numerical processing. For example, correlations between posterior ITG and anterior IPS activation during number recognition suggest a functional connectivity of the two brain regions that are assumed to be critical for the visual and semantic codes respectively. Daitch and colleagues (Daitch et al., 2016)showed participants Arabic numerals, letters, and foreign letters and asked participants to press a key if they thought they could read the symbol. In a second task, participants were asked to perform a symbolic arithmetic task and an autobiographical memory retrieval task. ECoG signals were recorded simultaneously from ITG and lateral parietal cortex. The authors found that neuronal activity in the ITG, specifically in the NFA was related to the processing of the visual code whereas the anterior IPS was related to arithmetic processing but not the visual code. Most interestingly, by taking off the mean stimulus-induced high-gamma response in the arithmetic task, the residuals in the posterior ITG and anterior IPS were correlated, suggesting functional connectivity. Also, similar analysis in different frequency bands revealed correlated activity in the two regions in the low frequency band (<1 Hz), suggesting intrinsic correlation between the ITG and IPS.

Another study examined the functional connectivity between the IPS and other regions in the brain (Park, Li, & Brannon, 2014). The authors asked children between 4.5-6.5 years old to perform a number comparison task with Arabic numerals, a non-symbolic number comparison task, and a line segment comparison task. They found right SPL activation in both numerical tasks.

However, symbolic number comparisons revealed greater activation of the pre- and post-central region compared to non-symbolic number comparisons. When using the right SPL region as a seed in a subsequent functional connectivity analysis, they found that the right precentral region and left SMG (an important area related to grapheme-phoneme mapping in language) (Booth et al., 2003) (Wilson, Tregellas, Slason, Pasko, & Rojas, 2011) were functionally connected to the right SPL. Given the fact that finger counting is extensively used by young children and the precentral regions have been found in children in number-related tasks (Kaufmann et al., 2008; Pollack & Ashby, 2017), the findings by Park and colleagues suggest that the communication between the IPS and precentral region is important for supporting the comparison of Arabic numerals, at least in childhood. The functional connectivity between the right IPS and the left precentral region was also found to support the neural representation of non-symbolic numbers in adults (Park, Park, & Polk, 2013). Across three non-symbolic number tasks (comparison, addition, and subtraction), the right IPS was functionally connected to the left precentral gyrus, and bilateral middle and inferior occipital cortex.

The functional connectivity between the key regions for different number codes has two possible implications. First, based on the assumption that each number code is locally represented by unique brain regions, the crosstalk between these regions indicates implicit integration between the corresponding number codes. For example, the functional connectivity between the ITG and the IPS might indicate the integration/coactivation of the visual code and the semantic code. The functional connectivity between the IPS and the precentral region might indicate the integration/coactivation of the semantic and the manual code. Alternatively, it might indicate that a number code is distributed in a network that consists of multiple brain regions and these brain regions might communicate with each other. However, the current literature lacks deeper understanding of the relation between the functional connectivity among brain regions and the neural representation of different number codes.

1.3 CHALLENGES TO THE EXISTING FINDINGS AND OUTLINE OF THE CURRENT WORK

Human brain imaging and physiological evidence suggest that several key regions across the brain are involved in supporting number representations. These regions mainly include the angular gyrus (AG), the superior temporal gyrus (STG), and the medial temporal gyrus (MTG) for the verbal code, the precentral region for the manual code, the inferior temporal gyrus (ITG) for the visual code, and the intraparietal sulcus (IPS) for the semantic code (see Figure 1). However, evidence for a localist neural representation of each number code is mixed. For example, Price and Ansari (G. R. Price & Ansari, 2011)had adults passively view Arabic numerals, scrambled Arabic numerals, and letters in an MRI scanner and predicted the contrast between Arabic numerals and other types of symbols would yield the NFA. Instead of finding the ITG, they found the left AG was the only region to show greater response to Arabic numerals compared to other symbols. This finding implies that either the AG was also involved in processing the visual form of Arabic numerals or viewing Arabic numerals automatically activated the verbal code.

A few other studies also showed that ITG was not merely processing the visual code of numbers but also possibly the semantics (Grotheer et al., 2016; Hermes et al., 2015). The most direct evidence came from Grotheer and her colleagues' work (Grotheer, Jeska, & Grill-Spector, 2018)in which they reported increased BOLD signals in pITG in response to tasks that required magnitude processing compared to tasks without such needs, importantly, regardless of the number format (i.e., Arabic numerals and non-symbolic dot arrays). Such findings again suggest two possibilities: the ITG is involved in representing numerical semantics and/or, as suggested by previous ECoG studies (Daitch et al., 2016), there is crosstalk between ITG and IPS.

Furthermore, some evidence suggested that if the cognitive/spatial attention load was minimized, the tuning between activity in the IPS and numerical semantics also decreased. Fornaciai and Park(Fornaciai & Park, 2018)parametrized numerosity (number of dots) and the confounding visual perceptual features (e.g., size and spacing) and constructed dot arrays from a parameter space that allowed for parametric manipulations of the visual perceptual features along with numerosity. They had adults passively view the dot arrays and found tuning to the ratios between the dot arrays in early visual cortex but did not find any tuning to the ratios in the IPS. Finally, regions in frontal cortex and motor cortex, for instance, the IFG, medial frontal gyrus (FG), and pre/post-central cortex, were widely found to be involved in representing numbers but less studied (Skagenholt, Träff, Västfjäll, & Skagerlund, 2018; Sokolowski et al., 2017).

Altogether, it is clear that the representation of numbers has different facets (e.g., the visual code and the verbal code) and hence is multi-constituent. Yet, whether the neural representations of different number codes are localized in unique brain regions or distributed across multiple brain regions seems to be less clear, which further limits our understanding of the functional connectivity between brain regions that support the four number codes. The current literature is restricted in two ways: the lack of isolating the number codes from each other in the same task and the lack of examination of the crosstalk among relevant regions. To study the underlying multi-constituent neural network outlined above, an ideal task should identify brain regions associated with the different number codes while minimizing the effects from other unnecessary number-related processing. Following this logic, the current work used a novel number code localizer task that tapped into brain regions associated with the visual, verbal, manual, and semantic codes respectively. The number code localizer task consisted of a semantic task (number comparison) and a verbal task (phoneme comparison) to isolate the verbal code from the semantic codes. Arabic numerals and hand images with various numbers of fingers raised were used for the visual code and manual codes respectively. Given the existing brain imaging and neurophysiological findings, it was predicted that the semantic task should elicit greater BOLD signal change in the IPS compared to the verbal task whereas the verbal task should evoke greater BOLD signal change in the language-related regions, especially in the left AG. The hand images should elicit greater BOLD signal change in the pre/post central cortex whereas the Arabic numerals should elicit greater BOLD signal change in the ITG.

Taken a step further towards isolating the number codes, the current work examined the four types of number codes in children and adults as previous studies suggest different developmental trajectories of different number codes. Moreover, existing fMRI findings imply developmental change in the left IPS for the semantic representation of numbers (Emerson & Cantlon, 2015; S. E. Vogel et al., 2015) and in precentral cortex for the manual representation of numbers (Kaufmann et al., 2008). These studies used developmental samples across a large age range (from 4.5-14 years old). An earlier study suggests children in elementary schools shift their strategy from finger counting to memory retrieval when solving addition problems. Hence, we focused on collecting data from children in third to fourth grade who had a few years of formal school learning but still used their fingers moderately (Geary et al., 2004). Therefore, it was expected that age difference in brain activity should be observed in the left IPS for the sematic code and in the precentral cortex for the manual code.

Finally, the current work aimed at examining the crosstalk among brain regions to support the neural representation of different number codes. Specifically, context-dependent connectivity among the brain regions that show involvement in processing number codes were tested with generalized psychophysiological interaction (gPPI) analyses. Another purpose of these analyses was to look at whether regions involved in representing a specific number code were also involved in representing other number codes and if so whether there was crosstalk among these regions. It was hypothesized that context-dependent connectivity should exist among multiple brain regions. However, the existing findings regarding crosstalk among regions that support different number codes are limited. Only the functional and structural connectivity between the ITG and IPS as well as the functional connectivity between the parietal cortex and precentral regions were strongly supported by previous studies (Daitch et al., 2016; Kay & Yeatman, 2017) (Park et al., 2014; Park et al., 2013). Therefore, it was predicted that among all regions that were tuned to any type of number codes in the current work, context-dependent connectivity between the IPS and ITG as well as between parietal cortex and precentral gyrus should be observed.

2.0 METHODS

2.1 PARTICIPANTS

Thirty-two adults (mean age = 23.2 ± 4.9 years, 14 female) and 36 third and fourth graders (mean age = 8.2 ± 0.6 years, 13 girls) participated in the study. The sample size for adults and children was about twice as the sample size adopted by previous studies that examined the neural development of numerical processing using task-based fMRI (Ansari & Dhital, 2006; Cantlon, Libertus, et al., 2009; Cantlon, Pinel, Dehaene, & Pelphrey, 2011). Written informed consent was obtained from all adult participants and all children's parents and written informed assent was obtained from all children before participating in accordance with a protocol approved by the Institutional Review Board at the University of Pittsburgh. All participants were monolingual native English speakers, right-handed, had normal or corrected-to-normal vision, and no history of learning disabilities, neurological disorders, or neurological surgeries. The participants were not diagnosed with any types of learning disabilities at the time of participation. Monetary compensation was provided to all participants. Among these participants, two adults and six children were excluded from the final data analysis due to excessive motion in the scanner (between-image displacement exceeded 0.5mm in more than 25% of the total number of images). This resulted in a final sample of thirty adults (mean age = 22.2 ± 4.4 years, 14 female) and thirty children (mean age = 8.6 ± 0.6 years, 11 girls).

2.2 STIMULI AND TASKS

2.2.1 Stimuli

The number code localizer task consisted of two types of stimuli: Arabic numerals and hand images. The Arabic numerals were single digits (range: 1-4 and 6-9), printed in white color on grey background at the center of the screen (*Figure 2*). The hand images contained two hand photographs on grey background. Across images, the number of fingers raised was varied to indicate the numbers 1 to 4 and 6 to 9. Only canonical representations were used (*Figure 2*). For numbers less than 5 (small number), the hand on the left side of the image was constantly closed to indicate 0. For numbers greater than 5 (large number), the hand on the right side of the image was constantly open to indicate 5.

Figure 2. Stimuli used in the number code localizer task.

Only single digit Arabic numerals were used. In the hand images, the counting started from the index finger on the hand on the right side of the stimuli. Only canonical representations were used in the hand images.

2.2.2 Task design

There were two types of tasks. In the semantic task, participants were asked to judge whether a stimulus represented a number greater or smaller than a target number (3, 4, 6, or 7; counterbalanced across blocks). In the verbal task, participants were asked to judge whether the first sound of the corresponding number word of a stimulus was the same as the first sound of the corresponding word of a target cartoon object, such as a "fan" (see *Figure 3* for an illustration of the experimental design). The example numbers and objects were imbedded in a prompt question in the beginning of each block (e.g., “Is the number greater than 6?” or “Same sound as [tape]?”; see *Figure 3*). For both of the semantic and the verbal tasks, participants were instructed to respond during the interval between the display of the stimulus and the termination of a subsequent fixation cross. They were instructed to press the index finger on their right hand to indicate YES and the middle finger on the right hand to indicate NO as quickly and accurately as possible. The number of YES versus NO responses were counterbalanced within each run.

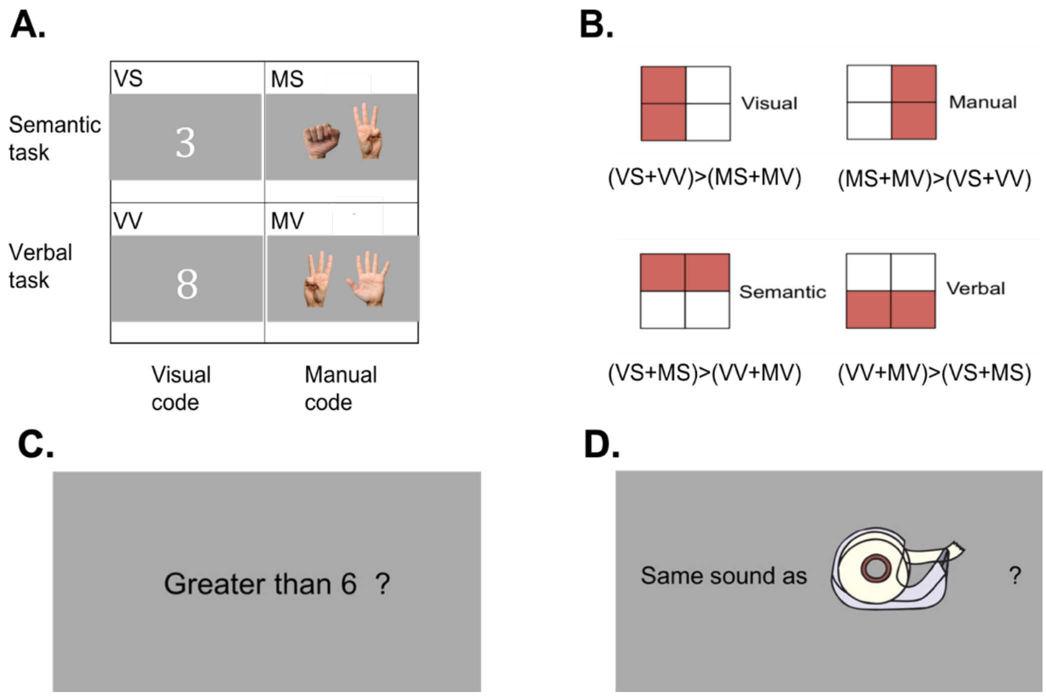


Figure 3. Illustration of the logic of the number code localizer task.

A. There were two types of stimuli (Visual (Arabic numerals) vs. Manual (hand images)) and two types of tasks (Semantic vs. Verbal task). This resulted in 4 conditions: VS, visual-semantic; MS, manual-semantic; VV, visual-verbal; MV, manual-verbal. B. The scheme shows the contrasts used in the general linear models. Contrasting different combinations of conditions enabled the examination of the brain activation for the visual, manual, semantic, and verbal codes. C. An example of the prompt questions for the sematic task. D. An example of the prompt questions for the verbal task.

A short block design was used in the number code localizer task. The experiment consisted of six runs in total, each consisting of 8 blocks (2 blocks for each of the 4 conditions; see *Figure 4*). Each block started with an 8-second-long prompt question screen, followed by 3 trials of the same condition (e.g., a semantic task with Arabic numerals). Each trial started with 2s of stimulus presentation, followed by 2s of a fixation screen (a black cross on gray background). The order of the 8 blocks was randomized within each run. Each block lasted 20 seconds. There was no break between blocks. After the last fixation, 4 dummy images were collected. Thus, each run consisted of 84 images and lasted 168 seconds (20 seconds × 8 blocks + 2 seconds × 4 dummy images). A short break was taken between runs for the experimenter to check in with participants. The entire task took about approximately 20 min to complete.

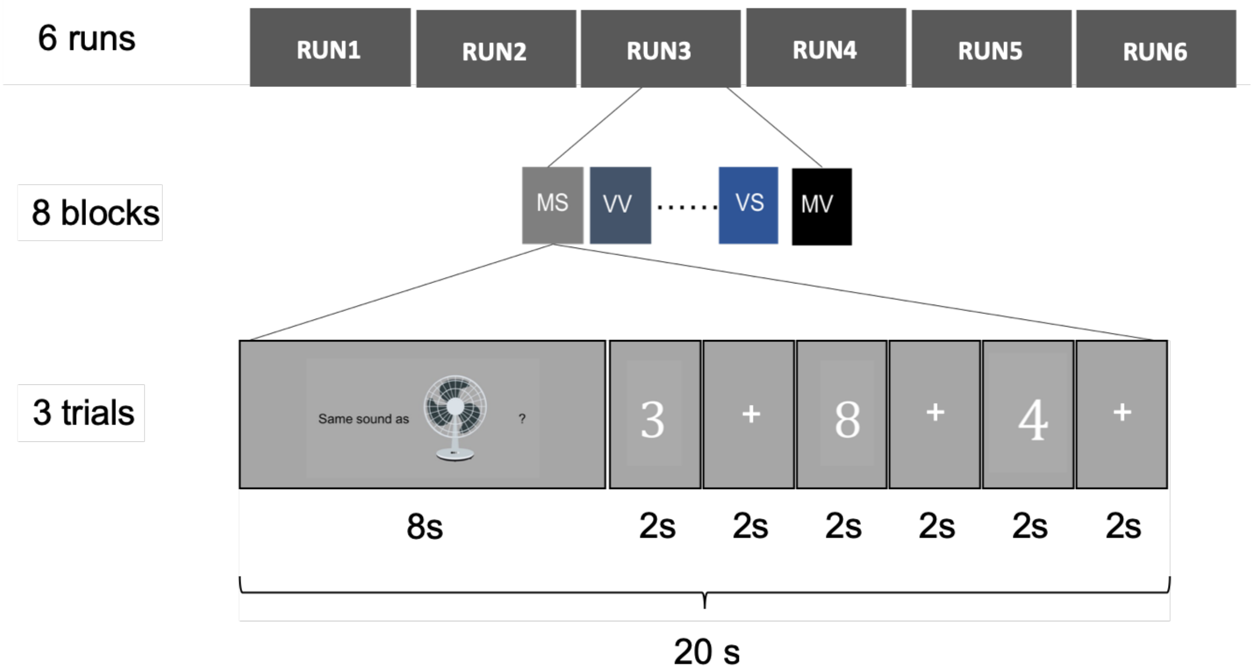


Figure 4. An illustration of the experimental design of the number code localizer task.

Each run consisted of 8 blocks, 2 blocks per condition. Each block started with a prompt question, followed by 3 trials of the same condition

2.3 PROCEDURE

2.3.1 Adult participants

Three runs of resting state data (5 minutes each) were first acquired, followed by an acquisition of structural images (approximately 10 minutes) and then six runs of the number code localizer task. Short breaks were provided between runs and different data acquisition phases. The resting state data are not reported since they are not relevant to the main interest of the current study. The entire experiment took one hour to complete. After the experiment, the participants were verbally debriefed.

2.3.2 Child participants

To familiarize child participants with an MRI scanner and the need to stay still as well as to practice the number code localizer task, children first completed a 1 h behavioral practice session. They practiced a shortened version of the localizer task, which consisted of 1 run of the original localizer task. They were required to repeat the practice task if they scored below 75% correct. After passing the localizer practice, children were brought to a mock scanner for practicing staying still with the head coil and the mirror projection system in an MRI scanner. A head tracking system was used to provide movement feedback to children while they were in the mock scanner. During the training in the mock scanner, children were also familiarized with the scanner noises of difference data acquisition sequences (e.g., MPRAGE and EPI, see below), what the stimuli would look like in the scanner, and a cartoon video clip for the structural image acquisition. The procedure of the actual MRI scan for children was the same as for the adults.

2.4 FMRI DATA ACQUISITION

MRI data were collected on a 3T Siemens Verio MR scanner using a 32-channel head coil at the Scientific Imaging and Brain Research Center at Carnegie Mellon University. Functional images were acquired using a T2* weighted echo-planar imaging (EPI) pulse sequence (TR=2000ms, TE=30 ms, voxel size = 2 × 2 × 2mm, flip angle = 79 degrees, matrix = 106 × 106, 69 axial slices). High-resolution anatomical images were acquired in the middle of the imaging acquisition using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 2,330 ms, TE = 1.97 ms, flip angle = 9 degrees, voxel size = 1 × 1× 1 mm, matrix = 256 × 256, 176 sagittal slices).

2.5 IMAGING DATA ANALYSIS

2.5.1 Preprocessing

Structural and functional imaging data from adults and children were analyzed in AFNI (Cox, 1996). Functional images went through slice timing correction, volume registration to the mean image, and low-frequency linear trend removal. In order to avoid removing task relevant frequencies, a low-pass filter at 0.01 Hz was used in the linear detrending, which yielded a cycle (100 seconds) much longer than the duration of each block (24 seconds). Functional images were co-registered to structural images, normalized to the Talairach space (Talairach & Tournoux, 1988), and then smoothed by using a Gaussian kernel of 6 mm full width at half maximum (FWHM). Motion was measured in 6 dimensions (rotation and shifts in x, y, z dimensions) and motion estimates were later entered into the general linear models as nuisance regressors.

2.5.2 General linear models (GLMs)

For each participant, two GLMs were used to examine the contrast between stimulus types (the visual code and the manual code) as well as the contrast between task types (the semantic code and the verbal code; *Figure 2b*). In each GLM, the stimulus onset times of each trial type were convolved with a box-car hemodynamic response function (HRF) while the response time of each trial was used to determine the duration of the HRF, using the "dmBLOCK" function in AFNI. The amplitude of the HRF was not specified in the GLM. Specifically, the 4 trial types were Arabic numeral stimuli across the sematic and the verbal task, hand stimuli across the semantic and the verbal task, the semantic task collapsing the Arabic numeral and hand stimuli, and the verbal task collapsing the Arabic numeral and hand stimuli. Motion estimates were entered as nuisance regressors. The results from individual level GLMs were submitted to group level analysis. Specifically, two mixed effects models were used to examine the main effects of stimulus type and task type as well as the age difference in the stimulus contrast and the task contrast. The estimated beta values from each condition > baseline contrast (e.g., manual code > baseline) from the first level GLM were submitted to a mixed effects model in which age and stimulus type/task type were entered as fixed effect factors and participants were entered as the random effect factor. Significant interactions should suggest age difference in a certain contrast. Moreover, the main effect of stimulus and task should yield the contrast between the visual code and the manual code as well as the contrast between the semantic code and the verbal code respectively. Both models were with a voxel-wise threshold set at $p < .0001$. In order to correct for multiple comparisons, random permutations were used to generate a large number of noise datasets and estimate the cluster size for *alpha* at .05. The clusters that survived the multiple comparison correction in the interactions and the main effects of stimulus type and task type were used as the regions of interest (ROIs) in subsequent context-dependent connectivity analyses. For large clusters that included more than one local minimum/maximum, we used a stringent threshold for voxel-wise *p*-values ($p = 0.5^{-10}$) and a less stringent *alpha* threshold (*alpha* = 0.5) to isolate the clusters around the local peaks (see Appendix A for the ROI peak coordinates).

2.5.3 Generalized psycho-physiological interaction (gPPI) analyses

Two separate gPPI models were used to investigate the context-dependent connectivity among brain regions involved in processing the visual code and the manual code (the stimulus contrast) as well as the semantic code and the verbal code (the task contrast). It is possible that some of the regions responded stronger to one number code compared to another but were also involved in representing other number codes. Therefore, each ROI yielded by a mixed effects model in the univariate contrast was used as the seed region once and the collection of all ROIs yielded by the same mixed effects model was used as the target regions in the corresponding gPPI model. For example, the PPI analysis for examining the connectivity between regions in the context of the Arabic numerals and the hand images were constrained within the ROIs yielded by the stimulus type contrast.

The gPPI model takes the following form (McLaren, Ries, Xu, & Johnson, 2012): $\boldsymbol{y}_i = \boldsymbol{H}(\boldsymbol{x}_a * \boldsymbol{G_p}) * \boldsymbol{\beta}_i + \left[\boldsymbol{y_k H}(\boldsymbol{G}_{p'})\boldsymbol{G}\right] * \boldsymbol{\beta}_G + \boldsymbol{e}_i$ where $\boldsymbol{y}_i$ is a vector representing the BOLD signals observed across time in the i^{th} voxel in the brain; $\boldsymbol{H}$ is the hemodynamic response function (HRF); $\boldsymbol{x}_a$ is a vector representing the neural activity from the selected seed region after deconvolving the observed BOLD signals from the seed region with the HRF; $\boldsymbol{G_p}$ is a binary matrix in which each column represents the at which TRs a stimulus in one experimental condition is on and each row represents a TR; $\boldsymbol{\beta}_i$ is a vector representing the estimated beta values for the interaction term; $\boldsymbol{y_k}$ is a vector representing the BOLD signals from the seed region; $\boldsymbol{G}_{p\prime}$ is a matrix that contains the onset time of each stimulus in each experimental condition; $\boldsymbol{G}$ is a matrix for the nuisance regressors, such as motion; $\boldsymbol{\beta}_G$ corresponds to the estimated beta values for each of the regressors; and finally $\boldsymbol{e}_i$ represents the residual.

The focus of the gPPI analyses is on how much variance in the observed BOLD signals in each voxel can be explained by the seed region's activity given the experimental context. Therefore, the estimated beta values of the interaction term ($\boldsymbol{\beta}_i$) were used in the group analysis to show regions that were affected by the seed region's activity in the selected experiment context. Given a certain experiment context (i.e., the stimulus contrast or the task contrast), the gPPI analyses started from selecting a seed region ROI, applying a mask of the seed region ROI to each participant, and reading out the peak voxel's coordinates within the seed region ROI. Then, a 6-mm radius spherical individual ROI around the individual peak was generated, which was used as the seed region in the first level gPPI model. The averaged BOLD signals from the individual seed region were deconvolved with a Gamma function whose peak was set at the end of a TR (2s). This gave the hypothetical neural responses from the BOLD signals. The deconvolved time series were then multiplied with the task regressors (i.e., $\boldsymbol{G_p}$) to represent the interaction between the psychological manipulation (i.e., the stimuli or the task) and the neural responses. Finally, the interaction time series were convolved with the Gamma function to generate the hemodynamic response time series for the psychophysiological interaction (i.e., the $\boldsymbol{H}(\boldsymbol{x}_a * \boldsymbol{G_p})$ term).

Positive/negative beta values in $\boldsymbol{\beta}_i$ indicate the seed region's activity in a particular task condition is positively/negatively related to the magnitude of the observed BOLD signals, which does not contain and information regarding the casual direction in the association between the seed region and the resulted region yielded by the gPPI models. At the group level, the estimated beta values in $\boldsymbol{\beta}_i$ for all participants were compared against each other to show the difference between such positive/negative relationship when contrasting different task conditions. For example, to look at whether the difference in the activity in the ITG ROI when processing the visual code versus the manual code was similar to the difference in other brain regions' activity or not, the time course of the BOLD signal was extracted from the individual ITG ROI, multiplied separately by the timing of the Arabic numeral stimuli and the timing of the hand stimuli, and entered in the gPPI model. In this case, the gPPI model was:

$$\boldsymbol{y}_i = \beta_{i1} * \boldsymbol{H}(\boldsymbol{g}_{timing\ of\ Arabic\ numerals} * \boldsymbol{x}_{ITG}) + \beta_{i2} * \boldsymbol{H}(\boldsymbol{g}_{timing\ of\ hands} * \boldsymbol{x}_{ITG}) + \left[\boldsymbol{y}_{ITG}\boldsymbol{H}(\boldsymbol{G}_{p\prime})\boldsymbol{G}\right] * \boldsymbol{\beta}_G + \boldsymbol{e}_i$$

where $\boldsymbol{G}_{p\prime}$ had 2 columns: one column contained the onset time for the Arabic numerals and the other column contained the onset time of the hand images. The two estimated beta values β_{i1} and β_{i2} were then compared. Stronger difference between the two beta values should indicate that the

ITG ROI's activity was related to greater magnitude of the contrast between the visual code condition and the manual code condition.

The first level gPPI GLM included four interaction terms for all four possible conditions (verbal task with Arabic numerals, verbal task with hand images, semantic task with Arabic numerals, and semantic task with hand images). The estimated beta coefficients entered a group-level mixed effects model to examine the difference between stimulus/task types in terms of the context-dependent connectivity to the seed region. In the mixed effects model, if the seed regions were yielded by the task contrast, then the PPI beta values from the semantic task and the verbal task were compared to ensure the context was consistent between the seed regions and the target regions. Similarly, if the seed regions were yielded by the stimulus contrast, then the PPI beta values from the hand images and the Arabic numerals were compared. The group level analyses were run separately for adults and children. The voxel-wise threshold was set at $p < .005$. All statistical maps in the group analyses were corrected for multiple comparisons with random permutations and clusters were thresholded at *alpha* =.05.

3.0 RESULTS

3.1 BEHAVIORAL RESULTS

Repeated measures ANOVAs were used to examine the effect of age, stimulus type, and task type on participants' accuracies and response times (RTs) in the number code localizer task. There was no main effect of age in accuracy ($F(1,231) = 2.62$, $p > .10$) or RT ($F(1,231) = 2.30$, $p > .10$). There was also no main effect of stimulus type in accuracy ($F(1,231) = 1.29$, $p > .20$). In contrast, there was a main effect of stimulus type in RT ($F(1,231) = 50.81$, $p < .0001$) with adults and children providing faster responses in the Arabic numerals condition compared to the hand image condition. In addition, there was a significant main effect of task type on accuracy ($F(1,231) = 11.53$, $p < .001$) and RT ($F(1,231) = 16.71$, $p < .0001$). Adults and children responded faster and more accurately in the semantic task than the verball task (see Figure 5). No interactions among age, stimulus type, and task type were found (all ps $> .10$).

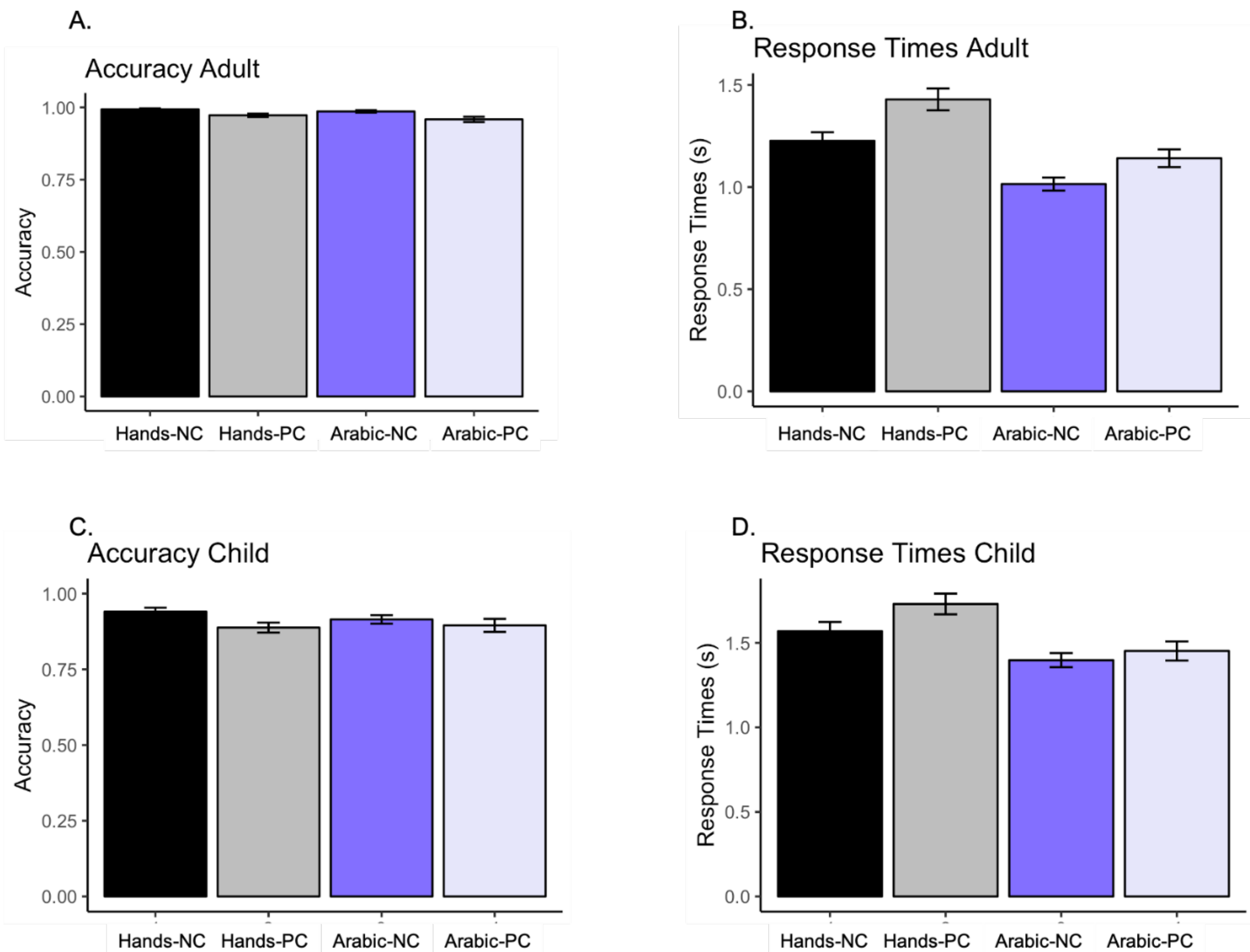


Figure 5. Accuracy and response time results in the four task conditions in the number code localizer task for the adult (A & B) and child participants (C & D).

Error bars represent the standard error of the mean. Color scheme: Black – semantic task with hand images; gray – verbal task with hand images; blue – semantic task with Arabic numerals; and light blue – verbal task with Arabic numerals.

3.2 UNIVARIATE FMRI ANALYSES

In the first mixed effects model, we examined the main contrast between the semantic task and the verbal task as well as an interaction between task and age. The main effect of age was not examined because it was not of interest for the purposes of this study. For the main effect of task, the semantic task > verbal task contrast yielded clusters located in the right inferior parietal lobule extending into right precentral cortex, the left postcentral gyrus, bilateral fusiform gyrus/lingual gyrus (LG), and bilateral middle occipital gyrus (MOG). The verbal task > semantic task contrast yielded clusters in left frontal cortex, medial frontal cortex, left IPS, left ITG, posterior cingulate cortex, bilateral insula, and regions in the cerebellum (see Table 1 and Figure 6). Significant interactions between age and task were found in clusters located in the left IPS and IFG. This interaction was mainly driven by a stronger task effect in the adults. As shown in Figure 7 and Table 2, these two regions showed larger BOLD signal changes relative to baseline in the verbal task compared to the semantic task in adults but not in children.

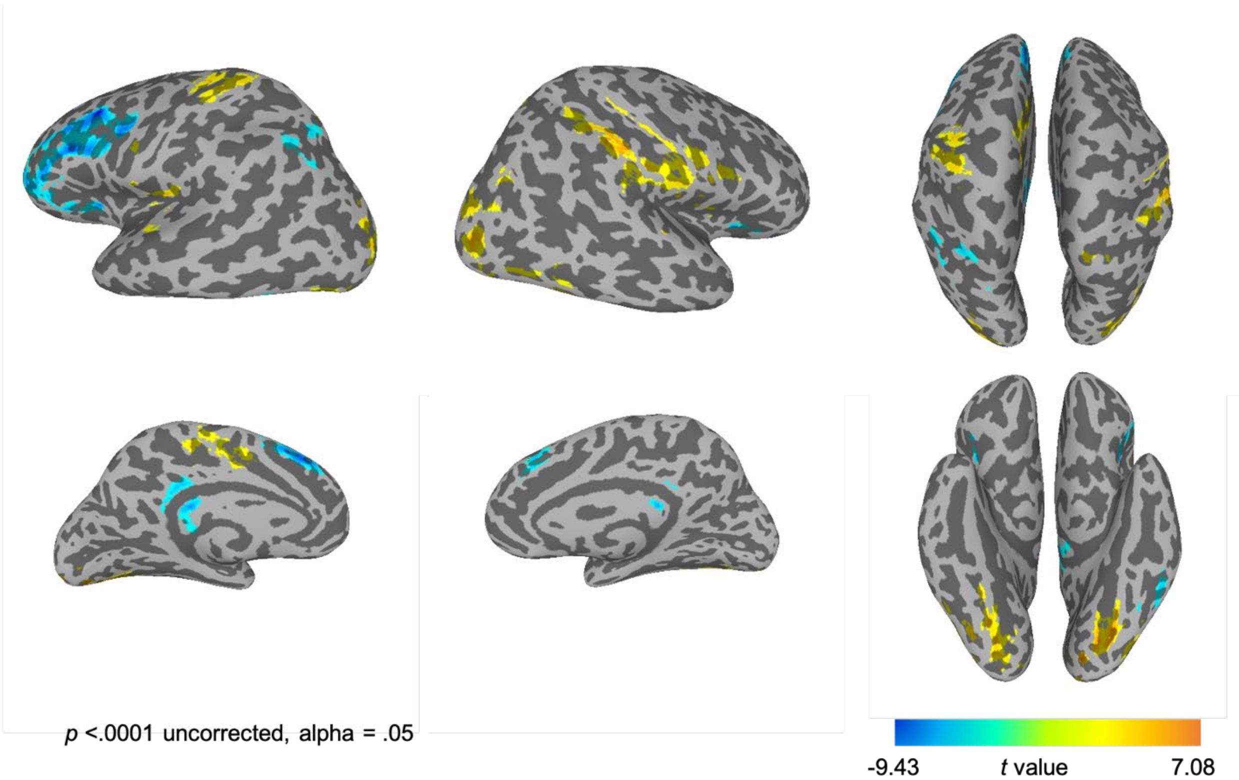


Figure 6. Main effects of task type, collapsing across the two age groups.

Color scheme: warm colors – semantic task > verbal task; cool colors – verbal task > semantic task.

Table 1. Main effect of task type in the univariate analyses

Region	Hemisphere	*t* value	# of voxels	x	y	z
Number >phonological						
Supramarginal gyrus/Inferior parietal lobule	R	7.06	1175	49	-35	46
Lingual gyrus/fusiform gyrus	R	6.98	777	29	-71	-12
	L	7.08	489	-9	-85	-8
Pre/postcentral gyrus	L	5.50	399	-35	-31	58
Somatosensory association area	L	5.43	209	-9	-29	46
Middle occipital cortex	L	5.60	149	-21	-87	10
Superior occipital gyrus	R	5.00	86	33	-77	30
Precuneus	R	5.38	43	11	-63	48
Precentral gyrus	L	4.67	34	-55	-9	8
Phonological > number						
Inferior frontal junction	L	-9.43	2013	-49	9	36
Medial frontal gyrus	--	-8.06	651	-1	29	42
Posterior cingulate gyrus	L	-7.2	211	-1	-35	24
Intraparietal sulcus	L	-5.46	211	-31	-61	40
Inferior temporal gyrus	L	-5.63	152	-45	-53	-16
Cerebellum	R	-5.52	116	33	-61	-38
	L	-7.56	114	9	-67	-24
Insula	R	-6.05	67	33	19	0

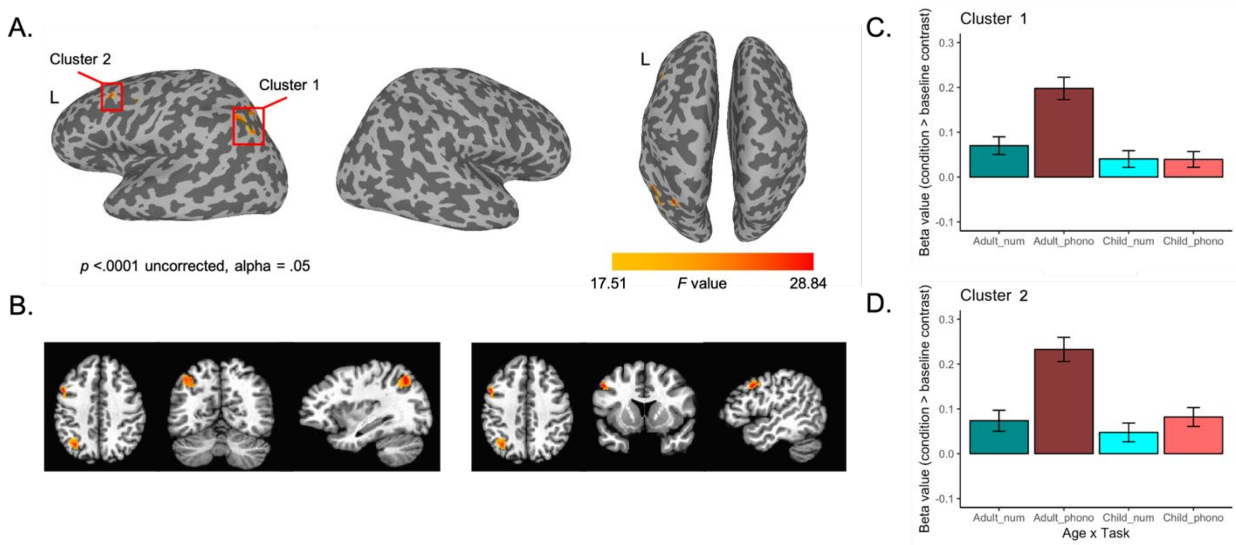


Figure 7. Interactions between age and task type.

A. Two clusters located in the left IPS (Cluster 1) and the left IFG (Cluster 2) showed a significant interaction between age and task type. B. Right panel: Cluster 1 in axial, coronal, and sagittal view. Left panel, Cluster 2 in axial, coronal, and sagittal view. C. The estimated beta value for each task type > baseline contrast in each age group for the left IPS cluster. D. The estimated beta value for each task type > baseline contrast in each age group for the left IFG cluster. Error bars represents the standard error of the mean. Color scheme: dark cyan – semantic task in adults; dark red – verbal task in adults; light cyan – semantic task in children; and coral – verbal task in children.

Table 2. Age x Task type interaction in the univariate analyses

Region	Hemisphere	*F* value	# of voxels	x	y	z
Intraparietal sulcus	L	29.57	183	-33	-61	44
Inferior frontal gyrus	L	32.74	62	-47	9	38

In the second mixed effects model, we examined the main contrast between the manual code and visual code as well as the interaction between stimulus type and age. As for the main effect of stimulus type, the manual code > visual code contrast revealed large regions in the bilateral visual pathways, covering the primary visual cortex, the ventral pathway, and the dorsal pathway. In addition, it also yielded clusters in bilateral thalamus, the right IFG, the right medial FG, right posterior cingulate cortex, bilateral cuneus, and regions in cerebellum. The visual code > manual code contrast revealed activation in the left pre/post-central gyrus, bilateral AG, right cuneus, and regions in the cerebellum (see Table 3 and Figure 8). Significant interactions between age and stimulus type were found in 8 clusters primarily located in primary visual cortex and the ventral visual pathway, including bilateral cuneus, right MOG, bilateral fusiform gyrus, and bilateral LG. The interaction found in 7 out of these 8 clusters was driven by greater BOLD signal change relative to baseline in the hand image condition relative to the Arabic numeral condition in adults. However, one cluster located in the right cuneus showed greater BOLD signal change in the Arabic numeral condition compared to the hand image condition in children and the opposite pattern in adults (see Table 4 and Figure 9).

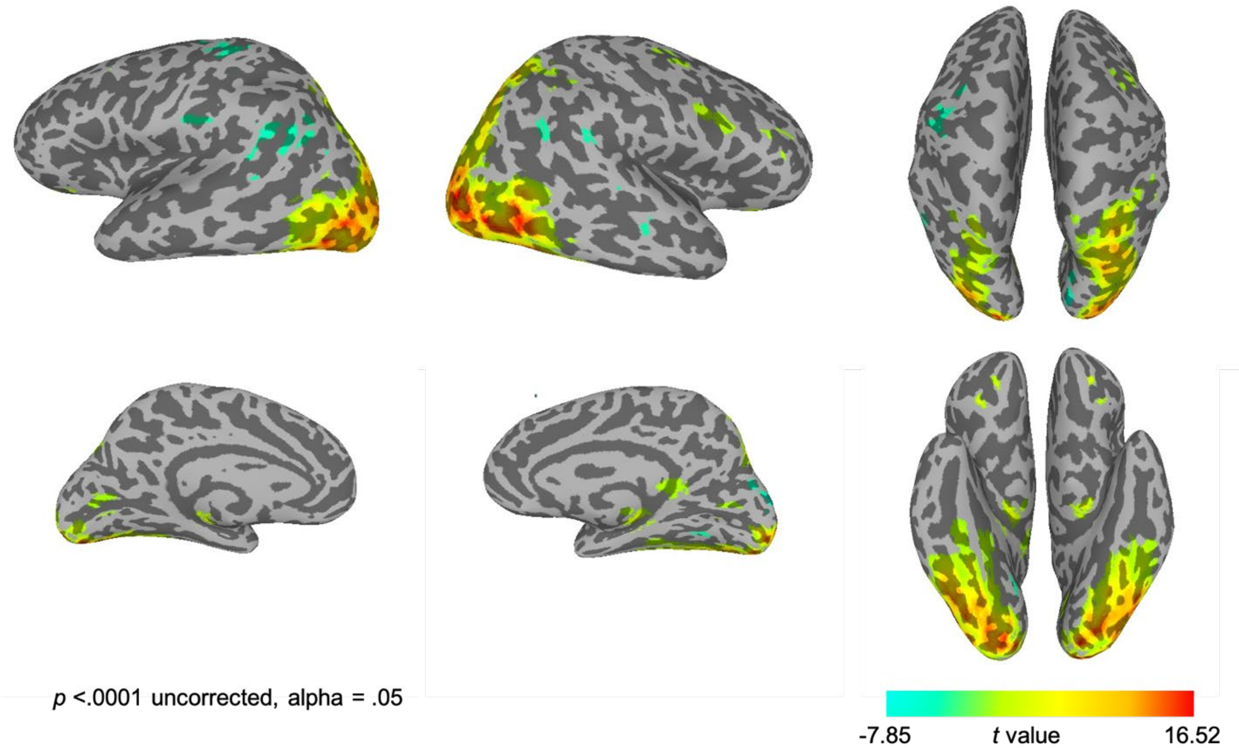


Figure 8. Main effects of the stimulus type, collapsing across the two age groups.

Color scheme: warm colors – manual code > visual code; and cool colors – visual code > manual code.

Table 3. Main effect of stimulus type in the univariate analyses

Region	Hemisphere	*t* value	# of voxels	x	y	z
Hands > Arabic numerals						
Visual cortex	R	16.34	8633	31	-81	6
	L	16.52	7100	-19	-93	10
Thalamus	R	10.08	313	19	-27	0
	L	11.55	257	-21	-25	0
Inferior frontal gyrus	R	6.08	238	45	1	28
Middle frontal gyrus	R	5.76	125	31	-5	54
	R	5.49	105	49	37	20
Cuneus	L	5.03	86	-9	-75	8
	R	5.33	50	7	-39	14
	R	4.81	37	17	-65	8
Cerebellum	L	7.30	85	-19	-29	-38
	L	5.70	108	-9	-63	-34
Arabic numerals > hands						
Pre/post central gyrus	L	-5.95	239	-35	-27	52
Angular gyrus	L	-5.78	237	-49	-51	24
	R	-5.13	99	57	-49	26
Cuneus	R	-7.85	107	11	-83	18
Precentral gyrus	L	-4.78	55	-55	-19	18
Middle temporal gyrus	R	-5.09	30	59	-29	0
Cerebellum	R	-4.84	43	13	-53	-8

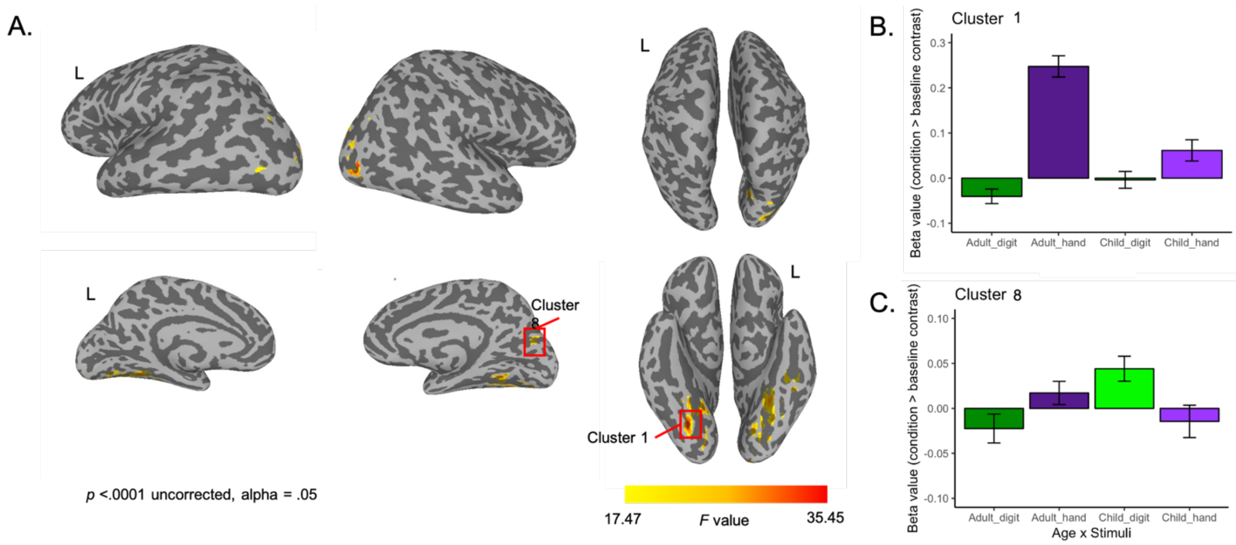


Figure 9. Interactions between age and stimulus type.

A. Multiple clusters mainly located in the primary visual cortex and the ventral visual pathway showed a significant age X stimulus type interaction. B. The estimated beta value for each stimulus type > baseline contrast in each age group for Cluster 1. Clusters 2 – 7 showed similar patters as seen in Cluster 1 (see Appendix B for the bar graphs for Clusters 2 – 7). C. The estimated beta value for each stimulus type > baseline contrast in each age group for Cluster 8. Error bars represents the standard error of the mean. Color scheme: dark green – Arabic numerals in adults; dark purple – hand images in adults; green – Arabic numerals in children; and violet hand images in children.

Table 4. Age x Stimulus type interaction in the univariate analyses

Region	Hemisphere	*F* value	# of voxels	x	y	z
Lingual gyrus	L	29.57	348	-15	-69	-6
	R	32.74	287	25	-65	-14
			137	27	-85	20
Middle occipital gyrus	R	27.55	71	37	-81	4
	L	35.45	64	-37	-37	-16
Fusiform	L	28.04	64	-7	-95	-6
Lingual gyrus	L	31.85	59	15	-71	20
Cuneus	R	24.40	25	-19	-91	10

3.3 ADULT GENERALIZED PSYCHOPHYSIOLOGICAL INTERACTION (GPPI) ANALYSES

The gPPI analyses revealed context-dependent connectivity between multiple brain regions in the adult participants. In the semantic task versus verbal task contrast, context-dependent connectivity in the positive direction was found between the right LG and the left IPS, the left ITG and the left IPS, the left somatosensory association cortex and the right SPL, the right ITG and the left IFG as well as the medial FG (see Figure 10). In the same contrast, context-dependent connectivity in the negative direction was found between the left IFG and the right MOG as well as between the right insula and the left LG (see Figure 11).

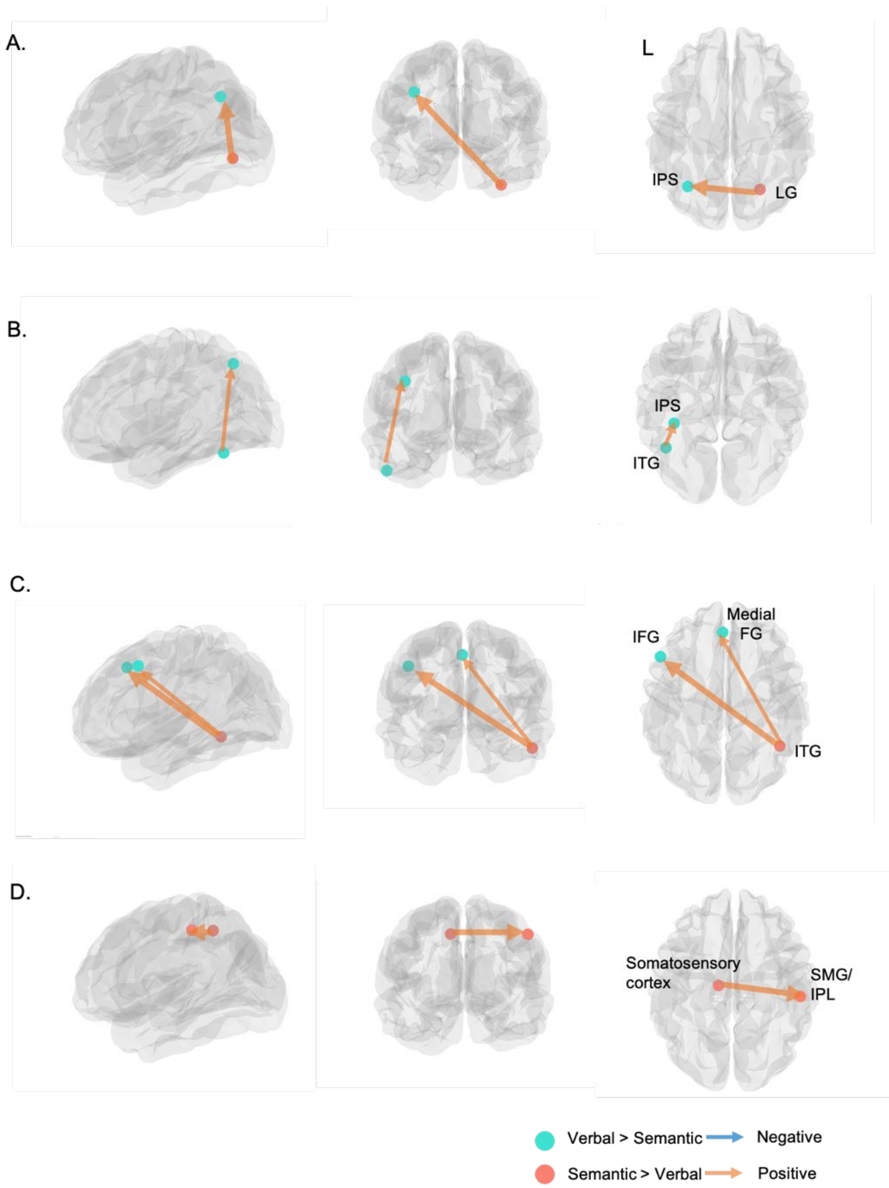


Figure 10. gPPI results for the semantic task > verbal task PPI contrast in the adult participants.

A. The positive PPI between the right LG and left IPS. B. The positive PPI between the left ITG and left IPS. C. The positive PPI between the right ITG and left IFG as well as left medial FG. D. The positive PPI between the left somatosensory association cortex and right IPL. Left column: sagittal view (left-right). Middle column: coronal view (back – front). Right column: axial view (top – down). The arrows start from the seed regions and point at the target regions. The arrows do not represent any direction of causal relation between the seed region and target region.

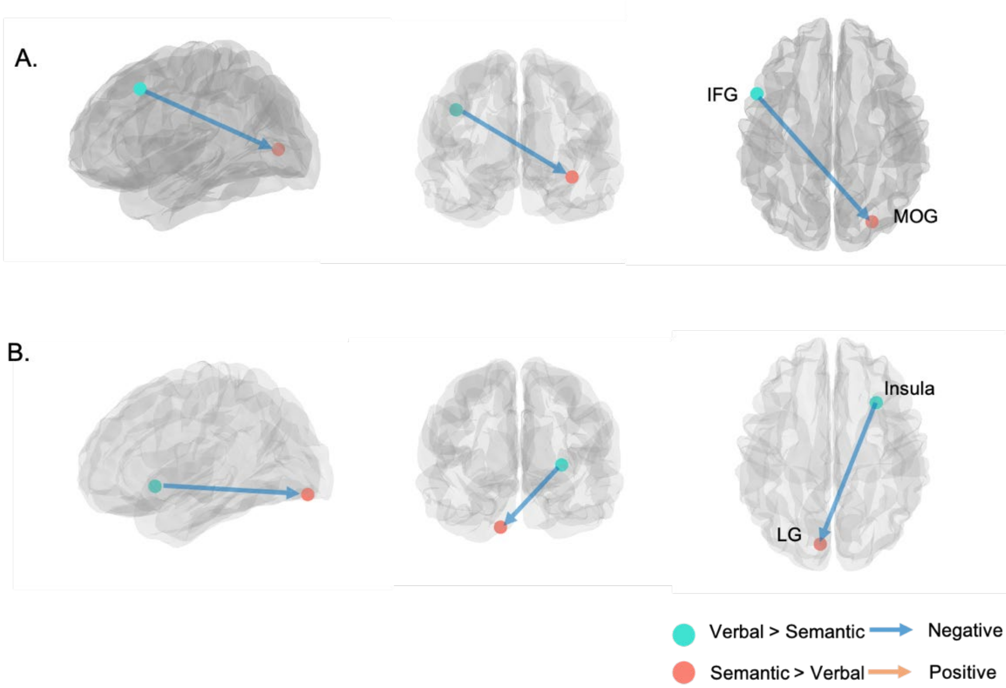


Figure 11. gPPI results the verbal task > semantic task PPI contrast in the adult participants.

A. The negative PPI between the left IFG and right MOG. B. The positive PPI between the left LG and right insula. Left column: sagittal view (left-right). Middle column: coronal view (back – front). Right column: axial view (top – down). The arrows start from the seed regions and point at the target regions. The arrows do not represent any direction of causal relation between the seed region and target region.

In the visual code versus manual code contrast, context-dependent connectivity in the positive direction was found between the right IFG and the left pre/post-central gyrus (see Figure 12). In the same contrast, connectivity in the negative direction was found between the right MOG and the left occipital pole as well as between the right cuneus and the right AG (see Figure 13).

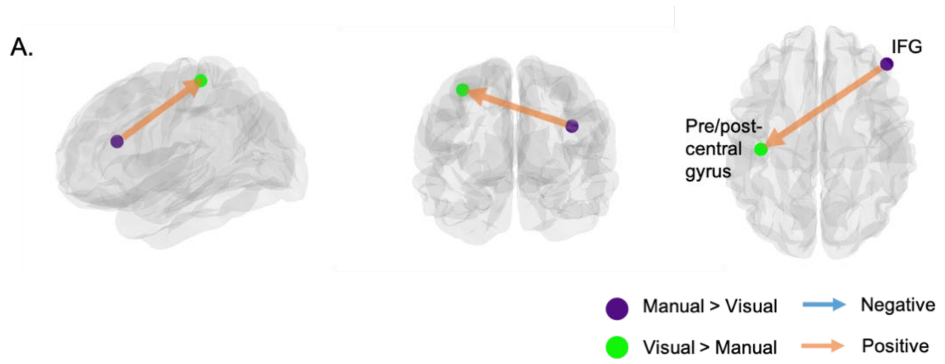


Figure 12. gPPI results for the manual code > visual code PPI contrast in the adult participants.

Left column: sagittal view (left-right). Middle column: coronal view (back – front). Right column: axial view (top – down). The arrows start from the seed regions and point at the target regions. The arrows do not represent any direction of causal relation between the seed region and target region.

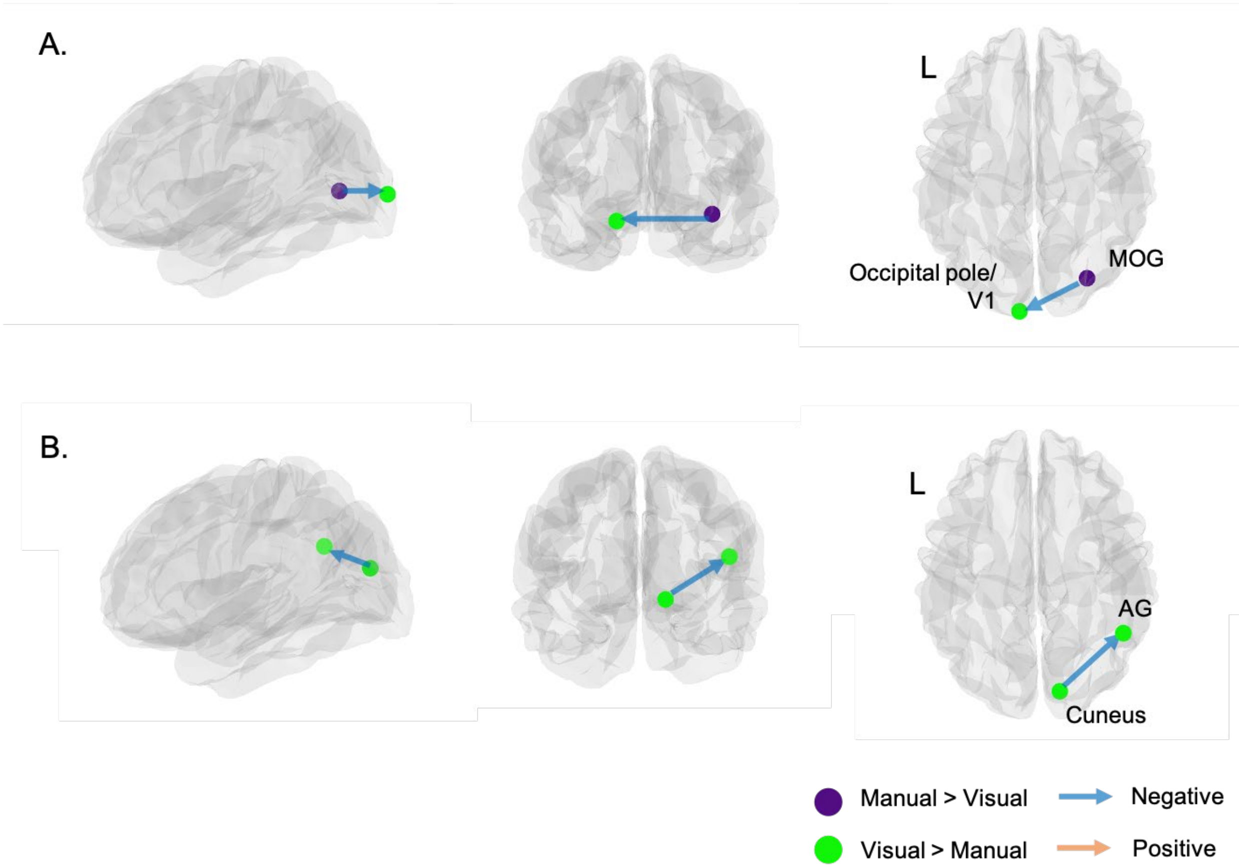


Figure 13. gPPI results for the visual code > manual code PPI contrast in the adult participants.

A. The negative PPI between the right MOG and left visual cortex B. The negative PPI between the right cuneus and right AG. Left: sagittal view (left-right). Middle: coronal view (back – front). Right: axial view (top – down). The arrows start from the seed regions and point at the target regions. The arrows do not represent any direction of causal relation between the seed region and target region.

3.4 CHILD GPPI ANALYSES

In children, only one context-dependent connectivity was found. When contrasting the semantic task and the verbal task, connectivity in the negative direction between the right SPL and the left pre/post-central gyrus (see Figure 14).

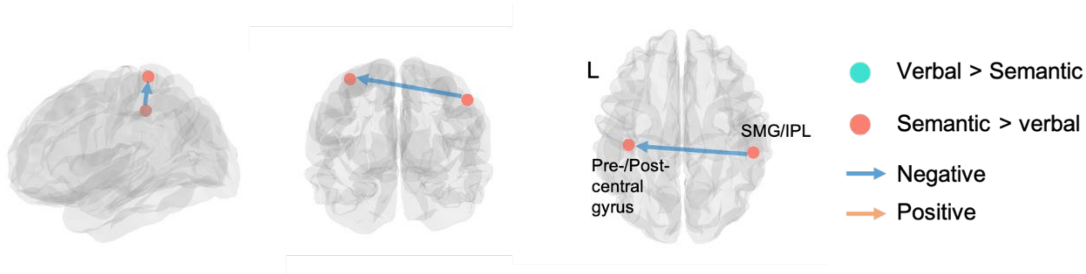


Figure 14. gPPI results for the seed region yielded by the semantic task > verbal task contrast in the child participants.

Left: sagittal view (left-right). Middle: coronal view (back – front). Right: axial view (top – down). The arrows start from the seed regions and point at the target regions. The arrows do not represent any direction of causal relation between the seed region and target region.

4.0 DISCUSSION

The focus of the current work is to gain a better understanding of the representation of symbolic numbers in the brain. We defined four types of codes associated with symbolic numbers based on previous findings: the semantic code, the verbal code, the visual code, and the manual code. Using a novel number code localizer task, we tested whether each number code was represented by unique brain regions or groups of brain regions. Specifically, we predicted that the semantic code should be supported by the intraparietal sulcus (IPS), the verbal code should be supported by the left angular gyrus (AG), the visual code should be supported by the inferior temporal gyrus (ITG), and the manual code should be supported by the pre-/post-central gyrus. Adults and third to fourth graders were asked to complete a semantic task and a verbal task while we recorded their brain activation using functional magnetic resonance imaging. The stimuli were either Arabic numerals (the visual code) or hand images (the manual code) displaying different numbers.

At the behavioral level, both adults and children performed faster and more accurately in the semantic task compared to the verbal task. They performed equally well in the visual code condition and the manual code condition but were both faster at responding to the visual code compared to the manual code. Importantly, no significant age differences were found in any of the tasks or stimulus conditions, suggesting the number code localizer task was equally difficult for adults and children.

We contrasted the semantic task with the verbal task to locate unique brain regions corresponding to the semantic code and the verbal code. We also contrasted the visual code and the manual code to reveal unique brain regions for each of them. We found multiple brain regions in each contrast condition, suggesting distributed instead of local neural representations for each number code. Specifically, the semantic code network primarily consisted of the right inferior parietal lobule (IPL), bilateral lingual gyri (LG)/fusiform gyri, and the pre-/post-central gyrus. Clusters in the medial frontal gyrus (FG), a large area that peaked in the left inferior frontal gyrus (IFG) and extended into the inferior frontal junction (IFJ) and left insula, the left IPS, and the left ITG mainly formed the network for the verbal code. The visual code activated a network that mainly consisted of the bilateral AG and the pre-/post-central gyrus. Finally, the manual code majorly employed bilateral visual areas including the primary visual cortex, the dorsal and the ventral visual pathways, as well as the right IFG. Thus, these findings did not support our hypothesis. In fact, some regions that were predicted to support one number code turned out to be involved in representing another number code. For instance, the left AG was predicted to support the verbal code but was found to support the visual code. The ITG was predicted to represent the visual code but was found to support the semantic code. We will discuss the implications of these finding in more detail below.

To explore the connectivity among the above-mention regions and test the possibility that some of the regions involved in representing multiple number codes, we examined the context-dependent connectivity between the major clusters within each contrast. As predicted, we found functional connectivity between the ITG and IPS as well as between parietal cortex and precentral gyrus. However, the overall connectivity covered more brain regions, which will be discussed in greater detail below. These results suggested that many regions indeed participated in the neural representation of multiple number codes, indicating functional shifts in these regions in different task conditions.

4.1 BEHAVIORAL RESULTS

We found that adults and children performed better and faster when they were comparing numbers than when they were comparing phonemes, which is likely because participants had more experience with comparing numbers than comparing phonemes. They also responded faster to the visual code compared to manual code. This is likely related to the more frequent usage of Arabic numerals in everyday life in both adults and children. The fact that we did not find any age differences at the behavioral level in any of the tasks implies that the number code localizer did not induce significant differences in the cognitive processes required by adults and children to solve the tasks. Since we found significant response time differences between the two task conditions and the two stimulus conditions, we controlled for response times at the trial level in all fMRI data analyses to reduce the impact of these differences on the fMRI results.

4.2 UNIVARIATE CONTRASTS

4.2.1 The semantic code

The IPS has been widely found to support the semantics of symbolic numbers (Piazza et al., 2007; S. E. Vogel et al., 2017). Surprisingly, we did not find strong neural representation of the semantic code in the IPS. Instead, a region in the right IPL centered on the supramarginal gyrus (SMG) in both adults and children was found to have stronger BOLD signal change in the semantic task > verbal task contrast, replicating the previous finding that the right parietal cortex supports the semantic representation of symbolic numbers. Besides the right parietal cortex, several other regions were also found to support the semantic code in both adults and children, including the bilateral lingual gyri extending into the fusiform gyri, the right post-central gyrus, the left pre-/post-central gyrus, somatosensory cortex, and bilateral middle occipital gyrus (MOG).

4.2.1.1 The hypothesized involvement of the IPS

It is possible that the IPS was activated but responded weaker in the semantic task relative to the verbal task in our study. Indeed, the left IPS appeared in the semantic task > baseline contrast (see Appendix C, Figure 7) but showed greater response to the verbal task than the semantic task when contrasting the two tasks. In contrast, the right IPS was not reported in either contrast. When using a lower threshold, the right IPS appeared in the semantic task > verbal task contrast but its activation was weaker compared to other regions, such as the right SMG and bilateral LG (see Appendix C, Figure 8). Thus, it is possible that the right IPS was activated for the semantics of numbers in both the semantic task and the verbal task and the contrast between the two tasks removed some of the activations in IPS. It turned out that the verbal task > baseline contrast revealed activation in the right IPS (see Appendix C, Figure 9). In summary, it seems that bilateral IPS were involved in representing the semantic code (as yielded by the semantic > baseline contrast and the semantic > verbal task contrast) but only to a limited extent that did not surpass the level of involvement in the verbal task used in the current study.

It should be noted that in the current study, both the semantic task and the verbal task involved not only a type of mental representation of symbolic numbers but also the corresponding manipulations. In the semantic task, the participants had to remember the quantitative meanings of the initial standard and the subsequent number stimuli and compare them. In the verbal task, the participants had to remember the beginning sound of the standard word and the beginning sounds of the number stimuli and compare them. The contrast should take away the general comparison manipulation. However, it is unclear whether comparing quantitative meanings is the same as comparing phonemes. If each type of comparison has its specificity, the observed difference in the task type contrast results could be a result of the mental representational difference, a result of the difference between comparing magnitudes and comparing phonemes, or both.

It seems likely that the neural substrates reflecting the semantic code depend on how the semantic code is measured. For instance, Piazza and colleagues (Piazza et al., 2007)used an cross-format adaptation paradigm to examine the mental representation underlying the symbolic numbers and non-symbolic numbers. Participants were adapted to either Arabic numerals or dot arrays within a certain numerical range and then shown a deviant number either close to or far from the adapted numerical range. It was found that the brain response in multiple regions, including bilateral IPS, IFG, and occipital cortex was modulated by the numerical distance between the deviant numbers and the adapted numbers. This finding implicates that these brain regions were able to represent the quantitative meaning of numbers when using Arabic numerals and dot arrays without explicit top-down control. In another same-format adaptation study, Vogel and colleagues (S. E. Vogel et al., 2017)used Arabic numerals and auditory stimuli for number words to study the brain responses to deviant numbers. They found the responses in the left IPS and fusiform gyrus were tuned to the numerical distance in the Arabic numeral condition. In contrast, in the auditory number word condition, regions in the left parietal cortex, bilateral auditory cortex, and frontal cortex were modulated by the numerical distance. Comparing these two adaptation studies and our current study, it seems clear that the bottom-up processing of the semantics of symbolic number is context-dependent and employs different neural substrates in different contexts. Therefore, contextual information needs to be taken into account when concluding the underlying the neural substrates of the semantics of symbolic numbers.

4.2.1.2 Post-hoc interpretations of activations in SMG/IPL, NFA, pre-/post-central gyrus and somatosensory area, and MOG

The IPL, including the SMG, in the right but not left hemisphere showed greater responses in the semantic task compared to the verbal task. While unexpected, this finding is in line with existing findings suggesting that the right parietal cortex may provide support of the analog representation of numbers whereas the processing of numbers in the left parietal cortex may be more language related. For example, the cross-format adaptation fMRI study described above showed that the activity in the right parietal cortex was tuned to the numerical distances between the adapted and deviant numbers but was invariant to number formats whereas the tuning to numerical ratios in left parietal cortex was modulated by the number format of the adapted and the deviant numbers (Piazza et al., 2007). In the current work, as the stimuli were the same in the number comparison task and the verbal task, the number versus phonological contrast should remove the common neural activities associated with the visual processing of the stimuli and any possible automatic verbal or semantic representation of the visual code and manual code. The main residual in the number representation in the semantic task > verbal task contrast is the semantic representation related to the specific task demand – the numerical magnitude comparison, which is close to the analog numerical representation. It is interesting that the right IPL and SMG but not the right IPS showed the strongest response to the semantic task. The right IPL/SMG is known for the phonological processing of visual words (Booth et al., 2003; Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012; Stoeckel, Gough, Watkins, & Devlin, 2009; Wilson et al., 2011). Thus, it seems that after taking out the phonological processing of numbers in the verbal task, the semantic processing still required phonological processing of numbers.

Another surprising finding in the semantic task > verbal task contrast was in the bilateral LG and partially in the bilateral fusiform gyri. The lingual and fusiform gyri are known for processing the global shape and local visual features of words respectively (Mechelli, Humphreys, Mayall, Olson, & Price, 2000). Importantly, a small but noteworthy area in the right ITG was found to be more active for the semantic task compared to the verbal task. Its peak coordinates (x=49, y=-55, z=-6) are close to the coordinates of the number form area (NFA) reported by previous studies, such as the cluster in the right ITG reported in a recent fMRI meta-analysis (cluster peak coordinates: x=50, y=-48, z=-10) (Yeo, Wilkey, & Price, 2017) and the cluster (peak coordinates: x=55, y=-52, z=-9) reported in the ECoG study by Hermes and colleagues (Hermes et al., 2015). However, it is interesting that these regions were only seen in the semantic task > verbal task contrast as this contrast should take away any shared visual processing of the visual code and manual code in both task conditions. Thus, these results imply that an extra-level of visual processing was needed for generating the semantic representation of numbers across formats. The finding that these visual processing-related regions showed specific strong response to number comparison is in accordance with a previous study that found clusters in the ventral visual pathway to be more responsive to tasks requiring access to the semantic representations of numbers (e.g., addition) compared to tasks that do not require access to semantic representations (e.g., naming), regardless of the number formats (e.g., Arabic numerals, cartoonish hands, and dice)(Grotheer et al., 2018).

Unexpected results in motor-related regions reported in the semantic task > verbal task contrast, including the left pre-/post-central gyrus and left somatosensory cortex, were also seen in other studies (Dehaene et al., 1996; Hongchuan, Qi, & Xinlin, 2007; Skagenholt et al., 2018; Sokolowski et al., 2017). Yet the mechanism for the relation between motor cortex and number representations is not well-understood. A few studies suggest counting might be a key factor in this relation because of its important role during the acquisition of the semantics of symbolic numbers. For instance, using hand images as the stimuli, Kaufmann and colleagues (2008) found a stronger response in a number comparison task compared with color and orientation judgment tasks in the pre-/post-central gyrus in children relative to adults, suggesting a stronger finger-number association in children. This result supports our finding that the pre-/post-central regions were associated with the semantic representation of numbers collapsing across the visual code and manual code. However, no task type by age interaction was found in these regions in the current study. This suggests no developmental difference between the adults and children with respect to the involvement of pre-/post-central regions in representing the semantics of symbolic numbers when hand images and Arabic numerals were both used. Together, our findings in the pre-/post-central regions seem to support the notion of embodied and abstract-symbolic semantics, which argues that the semantics for symbols are grounded in "perception and action systems of the mind and brain" (*p*. 458) (Pulvermüller, 2013). It also argues that different sensory and motor systems support different categories or symbols, such that the left inferior frontal cortex is more associated with verbs whereas the left inferior parietal cortex is more associated with spatial words. Since counting plays an important role in the early acquisition of the semantics of symbolic numbers, it is possible that motor-related regions become involved in representing the semantics of symbolic numbers.

Finally, bilateral middle occipital gyri were also more responsive in the semantic task relative to the verbal task. While unexpected, a recent study (Merkley, Conrad, Price, & Ansari, 2019) that aimed at locating the NFA by using stringent contrasts between Arabic numerals and scrambled numerals, letters, as well as scrambled letters also found that the bilateral MOG instead of the NFA had stronger response to Arabic numerals than other types of symbols. These results in conjunction with our own indicate the possible engagement of the MOG in the visual processing of Arabic numerals that may warrant future exploration.

Together, the regions yielded by the semantic task > verbal task contrast in the current study seem to form a network consisting of regions related to visual processing, phonological processing, and movement processing to yield the semantic representation of symbolic numbers. More importantly, the processing of Arabic numerals and hand images in the context of a number comparison seems to be functionally different from the phonological processing of the same symbolic numbers as required by our phonological comparison task.

4.2.2 The verbal code

The verbal task yielded significantly greater activation than the semantic task in the left IPS, the medial FG, the left IFG extending into the left inferior frontal junction, a cluster in the left ITG that is known as the visual word form area (VWFA), posterior cingulate cortex, and regions in right cerebellum. The left AG, which was predicted to be yielded by this contrast, was not found in the results.

4.2.2.1 The hypothesized involvement of the left AG

Unexpectedly, we did not find a significant difference in brain activation in the left AG in the verbal task > semantic task contrast. Similar to the argument for the IPS, it could be the case that the left AG was equally involved in both the semantic and the verbal task so that the contrast removed the left AG. However, when we examined the verbal task > baseline and the semantic task > baseline contrasts, the left AG was missing in both baseline contrasts. In fact, the left AG appeared in the baseline > phonological contrast and the baseline > semantic task contrast (see Appendix C, Figure 7 and 9). Since the baseline includes the targets and the fixations between stimuli, it is possible that the participants were rehearsing the target numbers/phonemes and the phonological working memory was activated during the baseline phase. Therefore, it is possible that the lack of left AG activation is an artifact of our particular experimental paradigm.

4.2.2.2 Post-hoc interpretations of activations in left IPS, medial FG, left IFG, and VWFA

The majority of the reported regions, including the left IPS, IFG, medial FG, and VWFA, are part of a network that supports phonological working memory (Bitan et al., 2005; Cao, Bitan, & Booth, 2008). While unexpected given the vast literature on verbal number processing, these regions were also reported in a recent meta-analysis that examined the overlap between the network for arithmetic and phonological processing in adults and children (Pollack & Ashby, 2017). Specifically, left IPL and left IFG were reported to be involved in both arithmetic and phonological processing in adults and left superior frontal gyrus, right superior frontal gyrus, left precentral gyrus, right insula, and left fusiform gyrus were reported as the overlapping regions in children. The peak of the clusters in the left IPS, left IFG, left ITG, and the right insula found in the current work are close to the corresponding clusters found by Pollack and Ashby (Pollack & Ashby, 2017). Given that the verbal task required phonological working memory (i.e., participants had to keep the target phonemes in their mind to compare), it is not surprising that regions involved in the phonological processing of symbolic numbers were found. However, such phonological processing was not associated with the semantic representation of symbolic numbers.

The semantic and the verbal task are different in two aspects that might induce the observed differences in brain activity. One is that the semantic task required access to the semantics of the target numbers and the stimuli whereas the verbal task did not require semantic representations of the targets and the stimuli. Another is that the targets the participants needed to keep in their working memory while doing the comparisons were also different between tasks. In the semantic task, participants needed to keep a target number in their mind, either phonologically or visually, and compare it to three different numbers. In the verbal task, participants needed to keep the first phoneme from a non-number word in their mind and compare it to the first phoneme of a number word. However, the baseline in the GLMs includes the targets and the fixations between stimuli when participants still needed to remember the same information related to the target. Task-specific working memory components should thus be partially, if not completely, removed by the subtraction of the baseline in the GLMs. Therefore, we conclude that the main driving force of the differences in the results is the variation in semantic or phonological processing.

4.2.3 The interaction between age and task type

Adult participants showed larger responses to the verbal task relative to the semantic task in the left IPS and left IFG while child participants did not show such differences between the comparison tasks. We did not have any a priori hypotheses in this regard; however, these results are consistent with previous findings that the left IPS showed developmental changes related to the development of symbolic number knowledge (Ansari & Dhital, 2006; Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon & Li, 2013; Emerson & Cantlon, 2015; S. E. Vogel et al., 2015). The developmental changes in the left hemisphere might be related to the change in mapping between the semantics and the verbal code as children are at the stage of learning the association between the verbal codes and their semantics (Emerson & Cantlon, 2015; Kadosh et al., 2007). In the current work, the interaction between age and task was mostly driven by the fact that the response to the verbal task was much stronger relative to the response in the semantic task in adults but not in children. If the mapping between the semantics and the verbal code of numbers was indeed stronger in adults than in children as previously suggested, adults would require less phonological processing in the semantic task compared to the phonological task. In contrast, both tasks would require similar amounts of phonological processing and hence yield similar levels of activation in the left IPS and IFG in children.

Interestingly, no interactions between age and task types were found at the behavioral level. Both adults and children were less accurate and slower in the verbal task. As the RTs were modeled in the analysis of the fMRI data, it suggested that the difference between the neural response in the semantic and the verbal task in adults cannot be explained by variations in task difficulty.

4.2.4 The visual code

Even though the hand images (manual code) in the current study carried more visual information, the Arabic numerals (visual code) elicited greater BOLD signal changes in bilateral AG, the left pre-/post-central gyrus, and right cuneus. Unexpectedly, we did not find any significant effects in the ITG. We will discuss each of these findings in more detail below.

4.2.4.1 The hypothesized involvement of the ITG

We did not find the ITG to support the neural representation of the visual code. There are two main foci in the ITG, the VWFA and the NFA, which are both shown to process the visual information of symbols (Yeo et al., 2017). The VWFA is known for processing visual words (Cohen et al., 2002; McCandliss et al., 2003; C. J. Price & Devlin, 2003), while the NFA has previously been shown to be involved in processing the visual code (Abboud et al., 2015; Grotheer et al., 2016; Shum et al., 2013; Yeo et al., 2017). However, more recent findings suggest the function of the VWFA and NFA might be driven by task demand. For example, the VWFA has been shown to provide visual information of objects, including words and non-words stimuli, required by reading tasks(McCandliss et al., 2003; Reich, Szwed, Cohen, & Amedi, 2011; A. C. Vogel, Petersen, & Schlaggar, 2014). For the NFA, the evidence for its specificity in tuning to the visual code is mixed (Grotheer et al., 2016; Merkley et al., 2019; G. R. Price & Ansari, 2011). Rather, one study suggests the NFA holds a similar function as the VWFA in number comparison tasks (Grotheer et al., 2018), i.e., it may be responding to number comparison tasks regardless of the visual format of numbers.

Our results are consistent with the notion that the response in the VWFA and the NFA is task-relevant instead of stimulus-relevant. Here, the VWFA was found to support the verbal representations of symbolic numbers whereas the NFA was found to support the semantic representation of symbolic numbers. Most importantly, our stimuli included both Arabic numerals and hand images, which were the same across the semantic and the verbal task. To eliminate the possibility that the response observed in the VWFA and the NFA was mainly driven by the Arabic numerals, we examined whether the contrasts between the semantic and verbal tasks with only hand images as stimuli would yield similar results or not. We found similar patterns – the VWFA showed stronger activation in the verbal task while the NFA showed stronger activation in the semantic task (see Appendix C, Figure 10), suggesting that the VWFA and NFA were not specifically tuned to Arabic numerals. In summary, our results support the notion that the VWFA and the NFA are not solely tuned to words or Arabic numerals but provide visual information required by ongoing tasks. More importantly, the VWFA seems to be employed by tasks that require phonological processing whereas the NFA seems to be employed by tasks that require semantic processing of numbers.

4.2.4.2 Post-hoc interpretations of activations in the AG, left pre-/post-central gyrus, and right cuneus

First, even though the greater activation in bilateral AG for the visual code compared to the manual code in the current study was surprising, it is in line with previous work by Price and Ansari (G. R. Price & Ansari, 2011). In their study, the authors attempted to locate the NFA by contrasting Arabic numerals versus scrambled Arabic numerals and letters. Instead of finding activation in the NFA in the ITG, the contrast revealed a cluster in the left AG (peak coordinates: x=-45, y=-61, z=29), which is close to the cluster in the left AG (peak coordinates: x=-49, y=-51, z=24) found in the current work. Price and Ansari proposed two possible interpretations for the role that the AG might play in processing Arabic numerals. One is that the presentation of Arabic numerals elicits phonological processing as the AG has been shown to support the phonological processing of symbolic numbers. The other is related to the hypothesis that the AG is involved in detecting whether a visual symbol has semantic meanings and/or mapping the visual symbol and the semantic meanings if it exists (Seghier, Fagan, & Price, 2010). Given that the bilateral AG did not appear to be involved in the semantic representation of symbolic numbers or in the phonological processing of symbolic numbers in the current study, it is also plausible that the AG was involved in identifying the meaning of a visual number symbol. In other words, the AG differentiated the visual code and the manual code because the visual code consisted of more formally learned symbols compared to the manual code.

Second, we predicted that the pre-/post-central gyrus would be more active for the manual code compared to the visual code, but we found the opposite effect. It was discussed earlier that the pre-/post-central gyrus might support the embodiment of the semantic representation of symbolic numbers. If the AG was involved in differentiating the visual code from the manual code based on which one is "more symbolic", it is possible that semantic representations were more strongly associated with the visual code compared to the manual code, including in the pre-/post-central regions.

Finally, a cluster in the right cuneus was unexpectedly found to have stronger tuning to the visual code than manual code. Even though we did not hypothesize this finding, a similar cluster has been previously reported as having greater response to Arabic numerals compared to non-symbolic numbers (peak coordinates: x=9, y=-89, z-20) (Holloway, Price, & Ansari, 2010). The cuneus is generally known for its role in basic visual processing. Given that the Arabic numerals carried less visual information than the hand images in the current study, the right cuneus might be a candidate region that is specifically responsible for early visual processing of the visual code.

4.2.5 The manual code

We did not find the pre-/post-central gyrus to support the manual code. Instead, the bilateral visual pathways, including the primary visual cortex, ventral temporal/occipital cortex, and the parietal cortex, as well as bilateral thalamus, cuneus, and right IFG, showed stronger responses to the manual code over the visual code.

4.2.5.1 The hypothesized involvement of the pre-/post-central gyrus

We expected the pre-/post-central gyrus to show greater activation to hand images compared to Arabic numerals. Our prediction was based on a previous study that found stronger responses in the pre-/post-central gyrus in a number comparison task with hand images as stimuli compared with color and orientation judgments on the same stimuli (Kaufmann et al., 2008). However, the pre-/post-central gyrus also seems to be a region consistently found in number comparison tasks with other number stimuli (Park et al., 2013; Piazza et al., 2007; Skagenholt et al., 2018). For example, in a recent study Skagenholt and colleagues (Skagenholt et al., 2018)examined the brain responses in an Arabic numeral comparison task, a number comparison task using number words, and a non-symbolic number comparison task. The response in the left pre-central gyrus was found to be modulated by the numerical distance across the three tasks, suggesting its role in representing the semantics of numbers.

Moreover, in Kaufmann and colleagues' study (Kaufmann et al., 2008), the authors did not compare hand images to Arabic numerals in the same number comparison context. When we compared the two type of stimuli in the same task context, the results suggested that the pre-/post-central gyrus was more involved in processing Arabic numerals than hand images. As discussed earlier, it might indicate the embodiment of the semantics of symbolic numbers. Together, our findings suggest the pre-/post-central gyrus might play a more important role in representing the semantic code instead of the manual code.

4.2.5.2 Post-hoc interpretation of the activation in bilateral visual pathways and the right IFG

The unexpected involvement of bilateral visual pathways was most likely due to the fact that the hand images contained a larger amount of visual information compared to the Arabic numerals, such as the number of pixels, color, and luminance. However, another cluster in the right IFG also showed stronger responses to the manual code. This region has been previously defined as a candidate region in the mirror neuron system that is sensitive to hand gestures or movements (Macuga & Frey, 2011; Rocca, Falini, Comi, Scotti, & Filippi, 2008) and is shown to be involved in mapping sounds to hand movements (Lahav, Saltzman, & Schlaug, 2007). It is possible that the IFG observed in the manual code > visual code contrast reflects the activation of the mirror neuron system. However, whether this region was also involved in mapping the phonological code to the hand images remains unknown.

4.2.6 The interaction between age and stimulus type

Significant interactions between age and stimulus type were found in clusters primarily located in regions associated with visual processing, including the bilateral lingual gyri/fusiform gyri, bilateral cuneus, and the right MOG. The interaction in most of these clusters was driven by larger difference between the manual code and the visual code in adults compared to children. This could be driven by the functional specialization in these regions in adults. For instance, it may be easier for adults to differentiate the visual code from the manual code compared to children. However, one cluster located in the right cuneus showed stronger response to the visual code compared to the manual code in children and the opposite pattern in adults. This region is close to the right cuneus cluster reported by Holloway and colleagues (Holloway et al., 2010) that showed a stronger response to Arabic numerals than dot arrays. The interaction found in the right cuneus region indicates the tuning to the visual code seems to be stronger in children.

4.3 CONTEXT-DEPENDENT CONNECTIVITY

We found that different number codes were supported by a large network of regions across the brain. As the contrasts between task types and stimulus types were intended to isolate the network for each number code, we cannot rule out the possibility that some of the regions yielded by a particular contrast still participated in the opposite contrast. As discussed earlier, it is indeed the case that some regions like the IPS appeared in two opposite contrasts. Therefore, we used generalized psychophysiological interaction (gPPI) analyses to understand the connectivity between the regions within the number network under different experimental conditions.

In general, gPPI models examine to what degree the BOLD signal observed in a certain voxel can be explained by the interaction between the neural activity in a seed region and a task or stimulus condition. Importantly, because the task or stimulus contrast and the seed region's neural activity are also modeled, the variance explained by the PPIs is above and beyond these factors. At the group level, the estimated beta weights for the PPIs in a gPPI model are compared against each other to show the difference of connectivity under different contexts. For instance, in the gPPI models for the task type contrast in the current study, the estimated PPI beta weights were compared as the semantic task minus the verbal task. Here, positive differences between the PPI beta weights suggest stronger connectivity between the seed region and the target region during the semantic task relative to the verbal task. Negative differences between the PPI beta weights suggest stronger connectivity between the seed region and the target region during the verbal task relative to the sematic task. The same explanation of the positive and negative difference applies to the stimulus contrast. As predicted, we found context-dependent connectivity between the IPS and ITG as well as parietal cortex and pre-/post-central gyrus. We also found more complicated connectivity patterns. Possible interpretations for these patterns will be discussed in this section.

4.3.1 The hypothesized connectivity between IPS, ITG, and LG in adults

Stronger connectivity between the IPS and VWFA in the left ITG as well as between the IPS and the right LG was found in the semantic task in adults. The IPS has been shown to have structural connectivity (Kay & Yeatman, 2017), intrinsic connectivity during resting state (Chen et al., 2019), and functional connectivity in number-related tasks (Daitch et al., 2016; Liu et al., 2019; Park et al., 2013) to regions in the ventral temporal/occipital regions, especially the ITG. For example, a recent ECoG study (Baek, Daitch, Pinheiro-Chagas, & Parvizi, 2018)showed functional connectivity between the IPS and ITG during an arithmetic task but not in a memory task. Using fMRI, Park and colleagues (Park et al., 2013)used dot arrays in a number matching task and a shape matching task and investigated the PPI between the right IPS and other brain regions in different task conditions. Stronger PPI was found between the right IPS and bilateral inferior occipital cortex, including the LG when participants were asked to compare the number of dots relative to comparing the shape of the dots. They focused on the right IPS as the seed region as previous findings suggested that the right IPS is less number format-selective whereas the left IPS seems to be more specialized for representing symbolic numbers.

In the current work, connectivity between the left IPS and the VWFA as well as the right LG was found to be stronger when access to the semantics of numerical stimuli was needed to complete the task. The left IPS and the VWFA showed greater modulation by the phonological task but still yielded greater connectivity in the semantic task. This finding suggests that the two regions were employed by the semantic task, but the response was weaker relative to the phonological task.

It is important to note that we cannot draw conclusions about the directionality of the connectivity between the IPS and ventral temporal/occipital observed here. However, recent modeling work by Kay and Yeatman (Kay & Yeatman, 2017)provides some insights into the relation between the two regions. In their study, adults passively viewed face images and words to localize two object recognition regions in the left ventral temporal cortex: the fusiform face area (FFA) and the VWFA. Face/word categorization tasks were then used to measure the activity in the two areas during a cognitive task. It was found that the activity in the FFA and VWFA was modulated by the bottom-up visual information and task demands. Functional connectivity analysis showed that the left IPS had the strongest connectivity to the FFA and VWFA. The authors then used computational models to show that the activity observed in the FFA/VWFA could be explained by the visual information carried by the stimuli and the IPS activity. They concluded that IPS down-regulated the object recognition regions by scaling up the visual processing in these regions. They also suggested that top-down control from the IPS might be driven by the task demands as the IPS is well known for its role in perceptual decision making (Heekeren, Marrett, Bandettini, & Ungerleider, 2004). Following this logic, the IPS should show stronger connectivity to the ITG in the verbal task because it was harder than the semantic task. But we found stronger connectivity in the semantic task. If indeed the IPS was down-regulating the ITG, our finding then suggests that the top-down control IPS might also be driven by the level of spatial processing requested by the cognitive task. Number comparison has long been argued to have close connections to spatial processing (Walsh, 2003) and the role of the IPS in spatial attention has been well established (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Szczepanski, Konen, & Kastner, 2010). Thus, it is possible that the sematic representation of symbolic numbers involves more spatial processing compared to the verbal representation and thus results in stronger connectivity between the IPS and brain regions associated with object recognition (e.g., ITG) and visual processing (e.g., LG). However, the current work cannot fully address this question and further examinations are needed.

4.3.2 The hypothesized connectivity between the pre-/post-central gyrus and right SMG in children

We found the expected connectivity between the left pre-/post-central gyrus and the SMG in the right parietal cortex in favor of the verbal task in children, but not in adults. The two regions appeared to have greater response to the semantic task than the verbal task. This finding is partially consistent with our prediction that connectivity between parietal cortex and pre-/post-central regions should be observed. It is also partially in line with findings by Park and colleagues (Park et al., 2014)who asked 5-year-old children to complete a number comparison task with Arabic numerals and found connectivity between the right superior parietal lobule and the left SMG as well as the right precentral gyrus. It seems the SMG and precentral gyrus are also likely to be connected. The SMG has been shown to be an important region in Arabic number reading (Roux, Lubrano, Lauwers-Cances, Giussani, & Démonet, 2008). In this study, the authors applied electrostimulation to various brain regions while patients were reading either alphabetic scripts or Arabic numerals. Patients' reading of Arabic numerals was disrupted when stimulations were applied to electrodes in the left IFG, left ITG, and primarily in the left SMG. Moreover, only lesions to the left SMG were associated with phonological paraphasias. Phonological paraphasias generally refer to a type of language production error of replacing smaller components (e.g., a syllable) of a word with incorrect ones, such as saying " gingerjed" instead of "gingerbread". This finding suggests that the left SMG may serve as an important region to support the phonological processing of symbolic numbers. As discussed earlier, the right SMG found in our study is likely to play a similar role in the phonological processing of symbolic numbers as the left SMG. The left precentral gyrus is also a region widely found in number comparison tasks across number formats and was suggested to reflect the embodiment of the semantics of symbolic numbers as discussed previously (Kaufmann et al., 2008; Skagenholt et al., 2018). The current study is the first to report stronger connectivity between the SMG and pre-central gyrus – two regions associated with the semantic code – to be related to the phonological processing of numbers.

Importantly, the connectivity between the SMG and pre-central gyrus was only seen in children. One possible explanation is that the integration between the semantic code and the verbal code is stronger in children than adults because children learned the meaning of numbers by verbally counting numbers with their hands more recently and may still be using their hands to show numerical information more regularly. Another explanation is that the function of the two regions was shifted in the verbal task. Anecdotally, we observed that child participants tended to say the target word and the target sound aloud when practicing the verbal task. Therefore, the precentral gyrus might not be reflecting numerical-related processing but actually movement-related processing as the children verbalized the sounds.

4.3.3 Post-hoc interpretations of the connectivity observed in the semantic task in adults

4.3.3.1 The connectivity between ITG, IFG, and medial FG

Unexpectedly, the PPI between the right ITG and left IFG as well as the medial FG was stronger in the semantic task than the verbal task. As discussed earlier, the right ITG cluster seems to be the previously defined NFA (Abboud et al., 2015; Grotheer et al., 2016; Shum et al., 2013; Yeo et al., 2017). One study by Nemmi and colleagues (Nemmi, Schel, & Klingberg, 2018) examined the resting state connectivity between the NFA and other brain regions and found the NFA to be connected to regions in bilateral ITG, IPS, and frontal cortex, including the IFG and medial FG. The authors also reported that the connectivity between the NFA and bilateral IFG increased with age (from 4 – 20 years old). It is important to note that the left IFG cluster found in the current work (peak coordinates: x=-49, y=9, z=36) is close to the left IFG cluster (peak coordinates: x=-48, y=18, z=30) found by Nemmi and colleagues. Thus, our finding confirms the importance of the connectivity between the right ITG, or the NFA, and the left IFG as well as the medial FG in representing the semantics of symbolic numbers. Importantly, this connectivity between the right ITG and left IFG was found in adults but not children in the current study, supporting the possibility that this connectivity increases with age.

4.3.3.2 The connectivity between the right SMG and left somatosensory association area

The functional connectivity between the right SMG and the anterior portion of the left somatosensory association area is less understood in the literature. Among all clusters appearing in the semantic task > verbal task contrast, these are the only two clusters that showed stronger connectivity in the same contrast of the PPI. The somatosensory association area sits between the post-central gyrus and the posterior parietal cortex. It is described to integrate somatosensory information for guiding movement (Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975; Pandya & Seltzer, 1982). Some evidence shows this region is structurally connected to the SMG (Catani et al., 2017). One possible explanation of the connectivity found between the right SMG and the left somatosensory association area is related to the embodiment of the semantic representation of numbers discussed earlier. When learning symbolic numbers by counting on fingers, it is possible that not only the movements of fingers and hands but also the sensory information associated with these movements is integrated with the semantic representation of numbers. The integrated sensory information might be stronger than the integrated movement information when the semantic representation is needed compared to when the phonological representation is needed.

4.3.4 Post-hoc interpretation of the connectivity observed in the verbal task in adults

We observed unanticipated greater connectivity between the left IFG and the right MOG as well as between the right insula and the left LG in the verbal task compared to the semantic task. Notably, the right MOG and the left LG responded more strongly to the semantic task than to the verbal task. This means that the two regions participated in representing the verbal code of symbolic numbers even though their overall response was stronger in the semantic task compared to the phonological task. These connectivity patterns were not previously seen in the number processing literature. Nevertheless, evidence from studies that investigated phonological processing and visual word reading can provide some insights. In a study by McNamara and colleagues (McNamara et al., 2008), adults were asked to learn the association between novel sounds and meaningless gestures. Increased PPI between a left IFG cluster and the right MOG was observed along with improvement in learning. In another study, adults were asked to perform a one-back match task with words, pseudowords, letter strings, and false fonts (Bokde, Tagamets, Friedman, & Horwitz, 2001). It was found that the left IFG activity was correlated with the activity in multiple brain regions, including two clusters in the MOG in the words, pseudowords, and letter strings condition but not in the false fonts condition. The authors hence argued that the connectivity between the IFG and other regions support the phonological processing of symbols. The right insula and the left LG are also involved in the phonological processing of visual words (Borowsky et al., 2006; Mechelli et al., 2000; C. Price, Moore, & Frackowiak, 1996), but the connectivity between the two regions is still unclear.

4.3.5 Post-hoc interpretation of the connectivity observed in the visual code condition in adults

Unexpectedly, we found stronger connectivity between the right cuneus and AG as well as between the right MOG and left occipital pole in the visual code condition than in the manual code condition. For the connectivity between the right cuneus and AG, both regions appeared to have stronger response to the visual code than the manual code, which replicated previous findings (G. R. Price & Ansari, 2011). As discussed earlier, the AG could be either representing the verbal code associated with a visual number symbol or detecting the semantics of a visual symbol and/or mapping the symbol to its meaning. Our finding suggests that compared to the hand images, the visual input of an Arabic numeral is either more likely to be associated with a verbal code or is more likely to be associated with a semantic representation. More importantly, here we are showing that the cuneus is a candidate region to provide the visual information specific to the visual code to the AG and this connectivity seems to be restricted to the right hemisphere.

In addition to the connectivity between the right cuneus and the AG, it is also interesting to see that the left occipital pole showed stronger connectivity to the right MOG. The right MOG was more responsive to the manual code than the visual code in the univariate contrast but also appeared to be a region that responded stronger to the semantic task relative to the verbal task. As mentioned earlier, the bilateral MOG was found to have stronger response to Arabic numerals relative to other types of symbols (Merkley et al., 2019). It might be the case that the right MOG and the left occipital pole work together to provide low-level visual information of Arabic numerals needed by other processes, such as the above-mentioned process of associating a verbal code or semantic code with Arabic numerals. Yet, the upstream of the processing is unclear as we did not find connectivity to other regions, such as the AGs from the right MOG and the left occipital pole.

4.3.6 Post-hoc interpretation of the connectivity observed in the hand image condition in adults

Greater connectivity between the right IFG and the left pre-/post-central region was found in the manual code condition compared to the visual code condition. While both regions are reported to encode hand gestures (Mizuguchi, Nakata, & Kanosue, 2014; Shibata, Inui, & Ogawa, 2011) (Yang, Andric, & Mathew, 2015), much attention has been paid to the right IFG as a hub in the mirror neuron system (Kilner, Neal, Weiskopf, Friston, & Frith, 2009). One study by Macuga and Frey (Macuga & Frey, 2011)showed that activity in the right IFG was modulated by whether the observed hand movements were from the perspective of oneself or the perspective from another person (mirroring). In the current work, the hands were not mirroring one's own hands during counting as the right and left hand were flipped in our stimuli. It is possible that the right IFG and the precentral cortex were communicating with each other to process this mismatching information. Another possibility for observing the connectivity between the right IFG and the left pre-/post-central regions is related to the mapping between hand movements and sound in the bilateral IFG as well as motor cortex (Lahav et al., 2007). A meta-analysis of neuroimaging findings of language areas in the left hemisphere suggested that the pre-central gyrus was involved in silent rehearsal and mouth and tongue movement (C. J. Price, 2012). The connectivity between the right IFG and the left pre-/post-central region could also be involved in representing verbal codes for hands. Moreover, despite the fact that the manual code activated massive visual regions, the lack of connectivity to other regions suggests that the processing of the manual code was predominately restricted to visual areas and that the amount of crosstalk between regions was less compared to the processing of the visual code.

4.3.7 General discussion for the context-dependent connectivity findings

In general, we found greater levels of connectivity in adults compared to children. On the one hand, this finding suggests domain-specific developmental changes in the neural networks for different number codes as the experience with using symbolic numbers increases with age. On the other hand, this finding might reflect a domain-general change related to the notion of the functions in the brain shifting from "distributed" to "local" with increasing age (Fair et al., 2009). In the study by Fair and colleagues (Fair et al., 2009), the authors modeled the resting-state functional connectivity of young children and young adults. They found that functional connectivity was more likely to be organized by anatomical proximity in children and more likely to be organized by domain-general and domain-specific functionality in adults. In the context of the current study, on the one hand children were still at the age of learning more fundamental symbolic number knowledge compared to adults, which may constantly alter the child brain. On the other hand, adults have learned more symbolic number knowledge and become highly efficient at using the knowledge. Following Fair and colleagues' theory, the connectivity in the adult brain becomes more distributed. Therefore, more connectivity was observed within separated networks that hold different functions for each number code in adults.

We also observed regions that showed stronger response in one experimental condition connected to regions that showed stronger response in the opposite experimental condition. It suggests that the same region can participate in representing more than one type of number code. Therefore, unlike univariate contrasts that isolate brain regions specific to a particular number code, connectivity analyses provide partial depictions of neural networks for different number codes and their overlap. The actual neural networks underlying each number code seem to consist of more regions than the regions found in the univariate contrast analyses and might be more similar to each other. Taken a step further, our finding suggests that the same brain region, or even a network at a small scale, might shift its function when the task demands change.

4.4 EXPERIMENTAL DESIGN-RELATED LIMITATIONS

In this study, we used a novel experimental design that provided a number of advantages to identify the neural networks associated with each number code. However, there are also a number of limitations that need to be considered. As discussed earlier, the neural substrates underlying the semantic code are likely to depend on the measurement of the semantic code. In the context of our study, the semantic code was measured via a number comparison task as compared to a phonological comparison task on the same stimuli, while the verbal code was measured via the phonological comparison task in comparison to the number comparison task. Importantly, unlike the visual and the manual code, the verbal code was measured via a task type contrast instead of a stimulus type contrast. The neural substrates of the verbal code consisted of regions for representing the verbal information and/or the manipulation of the mental representation. In contrast, most previous studies measured the verbal code via a stimulus type contrast. For example, Eger and colleagues (Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003) used a passive viewing task to study the neural substrates for the visual code and the verbal code. Participants passively viewed Arabic numerals and listened to number words in the MRI scanner. It was shown that bilateral auditory cortex responded stronger to the number words relative to the

Arabic numerals. Compared to the number words, the Arabic numerals elicited stronger responses in the bilateral fusiform gyri and inferior occipital gyri. While Eger and colleagues induced passive phonological processing of number symbols using auditory stimuli, the verbal task in the current work required phoneme production and comparison. Thus, it is possible that different neural networks for verbal codes were found in our study compared to theirs because the tasks involved different types of phonological processing under different contexts. Moreover, Eger and colleagues also found that the Arabic numerals > auditory number words contrast yielded different regions from the result for the visual code in the current study. This further suggests that the findings from fMRI studies are limited by experimental designs and contrasts and always need to be interpreted with these limitations in mind.

Our findings in the connectivity analyses are also highly constrained by our experimental design. Our connectivity patterns need to be interpreted as the relative strength in one condition compared to another condition in the same contrast and should not be over-generalized to the other contrast. For example, the PPI between the left ITG and the left IPS implies the two regions might have more cross talk when comparing numbers relative to comparing phonemes. Here, the implication is twofold: first the left ITG and the left IPS might also talk to each other when comparing phonemes and second it does not imply the relative connectivity between the two regions for processing the visual code or the manual code. Moreover, because the task type contrast induced manipulation of the verbal code and the semantic code whereas the stimulus type contrast did not, the connectivity yielded by the two contrasts should also be interpreted differently. The connectivity found in the task type contrast might be supporting the mental representation of the semantic and verbal code and/or the manipulation of the mental representation. The connectivity yielded by the stimulus type contrast might be only supporting the mental representation of the visual code and manual code.

4.5 CLOSING REMARKS

The current work aimed at locating the semantic, verbal, visual, and manual code of symbolic numbers in the brain. It was hypothesized that if each of the number codes were represented locally by a specific region in the brain, the intraparietal sulcus, the inferior temporal gyrus, the left angular gyrus, and the pre-/post-central gyrus would be the foci for the four number codes respectively. The results stand against this hypothesis and support the notion that the neural representation for each number code measured by our number code localizer task is distributed among a network consisting of brain regions unique to each code (as yielded by the contrasts between number codes) and brain regions common to several number codes (as yielded by the examination of the context-dependent connectivity). Our findings highlight the importance of the right parietal cortex, the left pre-/post-central gyrus, and bilateral ventral temporal cortex for the processing of the semantic code, the visual word form area, the left intraparietal sulcus, the left inferior frontal gyrus, and right insular for the processing of the verbal code, the bilateral angular gyrus and the right cuneus for the visual code, and the right inferior frontal gyrus for the manual code. The generalized psychophysiological interaction analyses suggest some brain regions support more than one type of number code and are functionally connected with other brain regions. In the adult participants, we observed connectivity primarily between inferior temporal cortex and intraparietal sulcus as well as frontal cortex to support the semantic code. The connectivity between frontal cortex and visual cortex seems to support the verbal code. Stronger connectivity between regions in the inferior parietal lobule and visual cortex was seen to support the visual code, while the connectivity between regions in inferior frontal cortex and motor cortex was found to support the manual code. There was much less crosstalk between regions in children compared to adults. Only the connectivity between the right inferior parietal cortex and the pre-/post-central gyrus was found to support the semantic code in children. We conclude that the failure to isolate each number code in the predicted brain region urges future studies to further investigate the function of these regions under different numerical processing contexts. Moreover, the finding that different patterns of connectivity between brain regions support the neural representation of different number codes calls for new approaches to examine the dynamics in these neural networks at a large scale.

APPENDIX A THE REGIONS OF INTEREST

We selected regions of interest (ROIs) from the univariate analyses and used these regions in the generalized psychophysiological interaction (gPPI) analyses. Specifically, among each collection of ROIs yielded by a univariate contrast (e.g., the semantic task versus verbal task contrast), each ROI was used as a seed region once. The collection of all regions was used as the target regions. The table shows the peak of each ROI in each collection.

Appendix Table 1. Peak coordinates of the ROIs used in the gPPI analyses for the semantic code and verbal code

Region	Hemisphere	x	y	z
Supramarginal gyrus/Inferior parietal lobule	R	49	-35	46
Lingual gyrus/fusiform gyrus	R	29	-71	-12
	L	-9	-85	-8
Pre/postcentral gyrus	L	-35	-31	58
Somatosensory association area	L	-9	-29	46
Middle occipital cortex	L	-21	-87	10
Superior occipital gyrus	R	33	-77	30
Precuneus	R	11	-63	48
Precentral gyrus	L	-55	-9	8
Inferior frontal junction	L	-49	9	36
Medial frontal gyrus	--	-1	29	42
Posterior cingulate gyrus	L	-1	-35	24
Intraparietal sulcus	L	-31	-61	40
Inferior temporal gyrus	L	-45	-53	-16
Cerebellum	R	33	-61	-38
	L	9	-67	-24
Insula	R	33	19	0

Appendix Table 2. Peak coordinates of the ROIs used in the gPPI analyses for the visual code and manual code

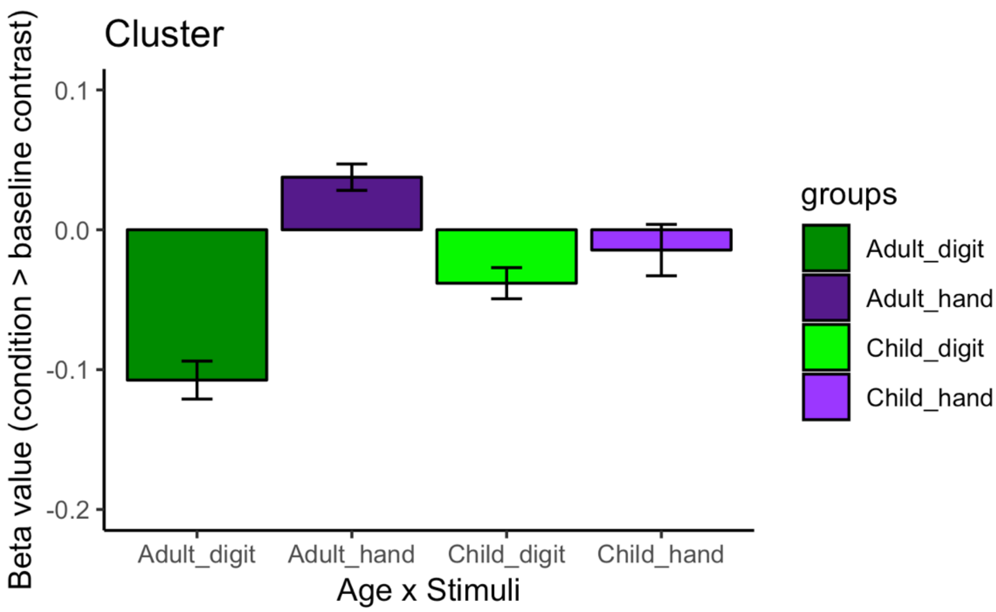
Region	Hemisphere	x	y	z
Visual cortex	R	31	-81	6
	R	19	-81	10
	L	-19	-93	10
	L	-9	097	6
Inferior temporal gyrus	L	-41	-73	6
Thalamus	R	19	-27	0
	L	-21	-25	0
Inferior frontal gyrus	R	45	1	28
Middle frontal gyrus	R	31	-5	54
	R	49	37	20
Intraparietal sulcus	R	27	-69	42
Cuneus	L	-9	-75	8
	R	7	-39	14
	R	17	-65	8
	R	11	-83	18
Cerebellum	L	-19	-29	-38
	L	-9	-63	-34
	R	13	-53	-8
Pre/post central gyrus	L	-35	-27	52
Angular gyrus	L	-49	-51	24

Appendix Table 2. Continued

Angular gyrus	R	57	-49	26
Precentral gyrus	L	-55	-19	18
Middle temporal gyrus	R	59	-29	0
Lingual gyrus	L	-15	-69	-6
	R	25	-65	-14
		27	-85	20
Middle occipital gyrus	R	37	-81	4
	L	-37	-37	-16
Fusiform	L	-7	-95	-6
Lingual gyrus	L	15	-71	20
Cuneus	R	-19	-91	10

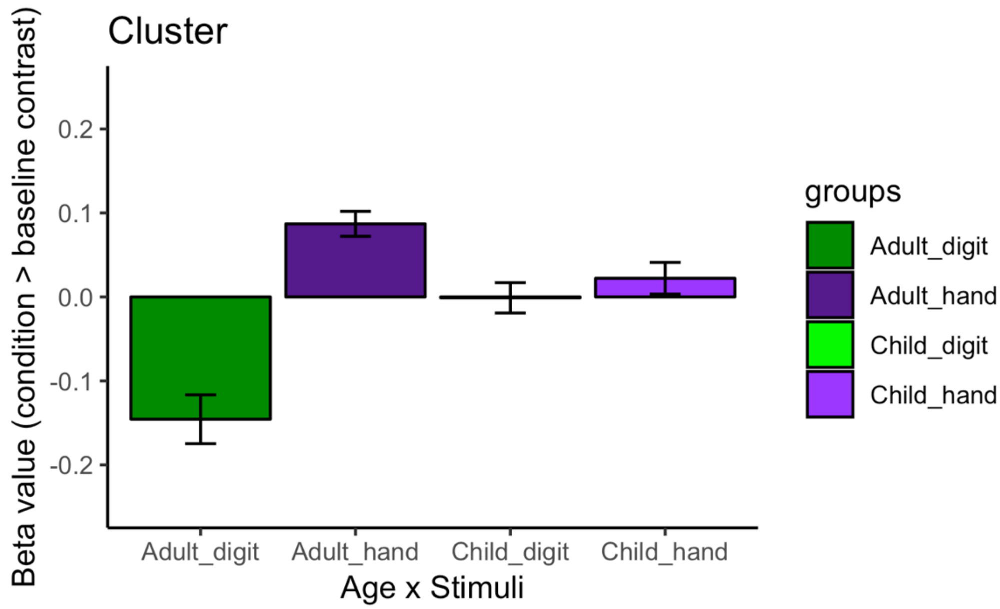
APPENDIX B THE STIMULUS TYPE BY AGE INTERACTION

Significant interactions between stimulus type and age were found in 8 clusters primarily located in primary visual cortex and the ventral visual pathway, including bilateral cuneus, right MOG, bilateral fusiform gyrus, and bilateral LG. The averaged estimated beta values for each stimulus type > baseline contrast in each age group for Clusters 2 – 7 are shown in Figure 1 – Figure 6.

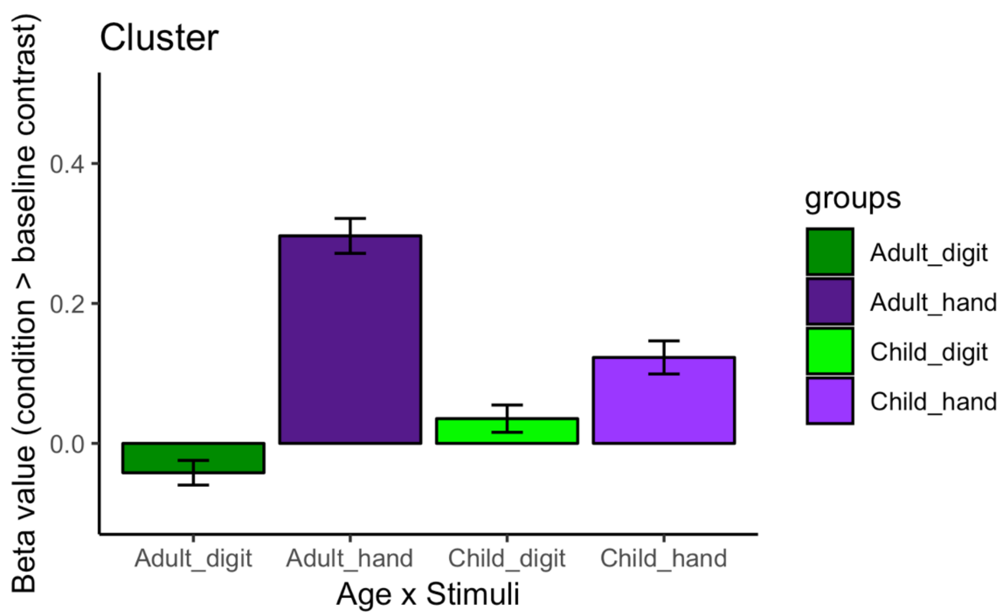


Appendix Figure 1. Average estimated beta values for each stimulus type > baseline contrast in each age group for Cluster 2.

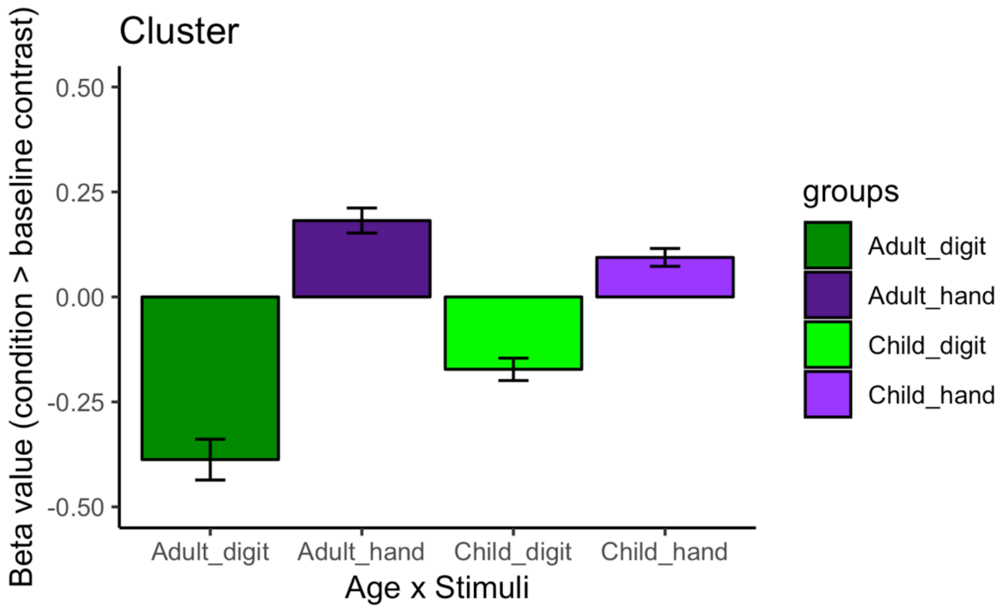
Error bars represent the standard error of the mean. Color scheme: dark green – Arabic numerals in adults; dark purple – hand images in adults; green – Arabic numerals in children; and violet - hand images in children (same for Figure 2 – 6 below).



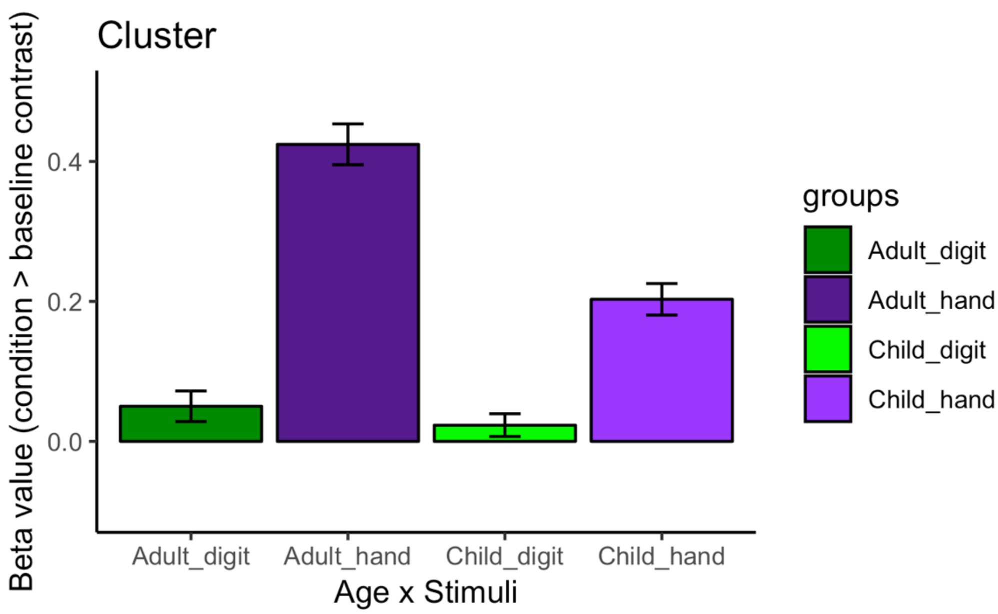
Appendix Figure 2. Averaged estimated beta values for each stimulus type > baseline contrast in each age group for Cluster 3.



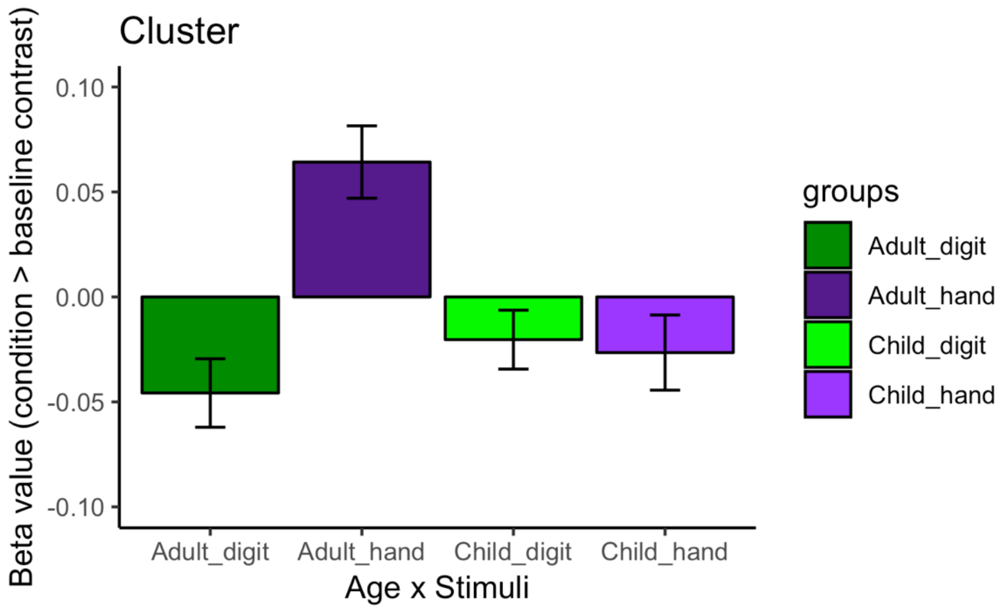
Appendix Figure 3. Averaged estimated beta values for each stimulus type > baseline contrast in each age group for Cluster 4.



Appendix Figure 4. Averaged estimated beta values for each stimulus type > baseline contrast in each age group for Cluster 5.



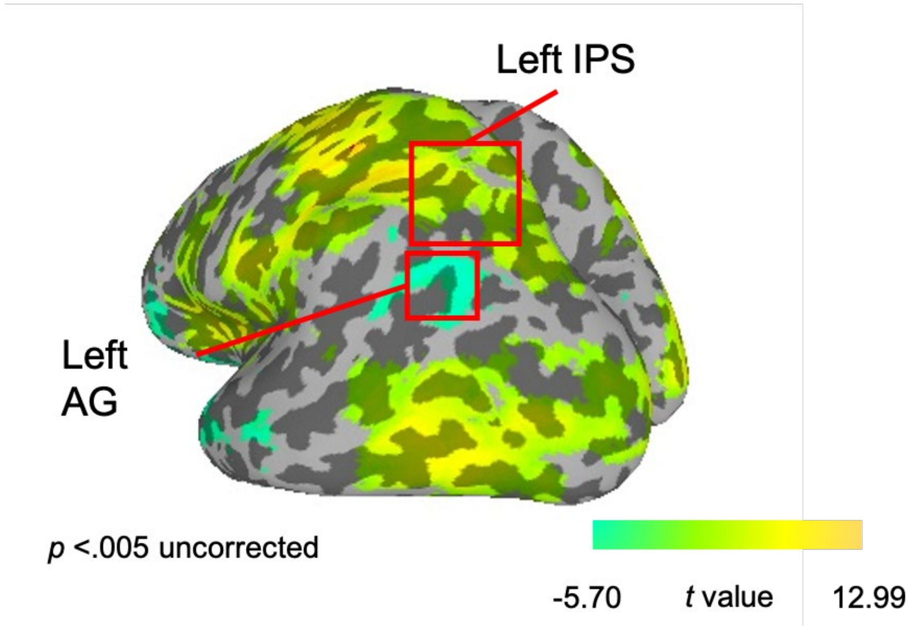
Appendix Figure 5. Averaged estimated beta values for each stimulus type > baseline contrast in each age group for Cluster 6.



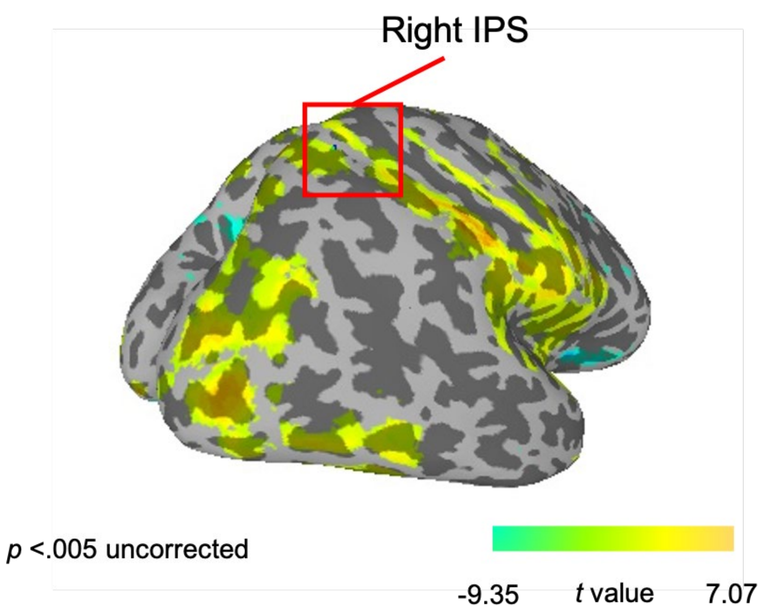
Appendix Figure 6. Averaged estimated beta values for each stimulus type > baseline contrast in each age group for Cluster 7.

APPENDIX C SUPPORTIVE RESULTS FOR BASELINE CONTRASTS

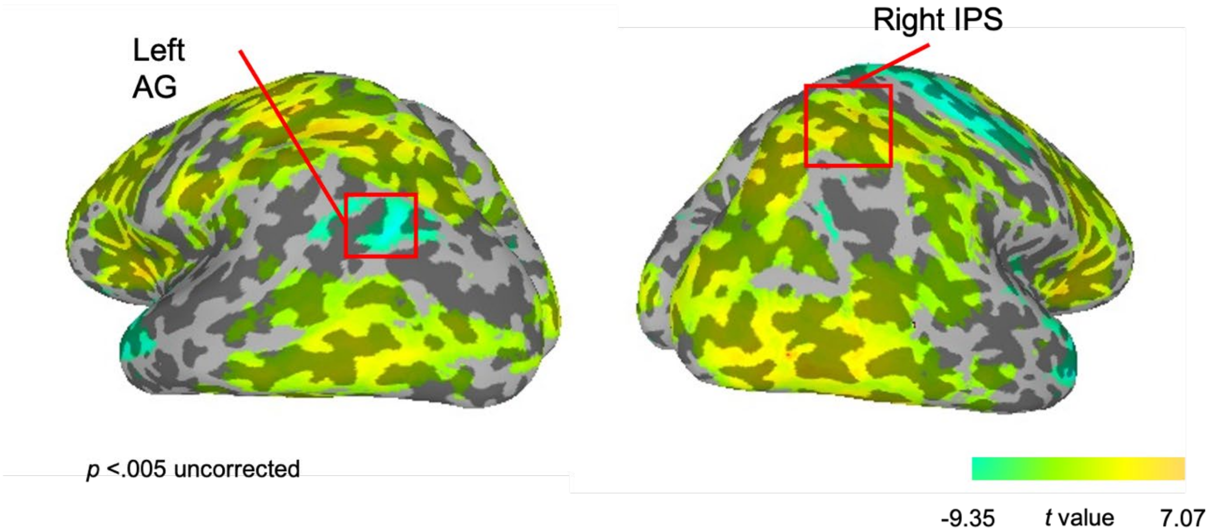
In this section, two baseline contrasts (semantic task versus baseline and verbal task versus baseline) were shown to illustrate the involvement of the bilateral intraparietal sulcus (IPS) and the left angular gyrus (AG) (Figures 7 and 9). Moreover, the semantic task > verbal task contrast with a lowered *p*-threshold ($p<.001$) was used to show the involvement of the right IPS (Figure 8). Finally, Figure 10 shows the visual word form area (VWFA) and the number form area (NFA) were involved in the semantic task versus verbal task contrast with hand images only.



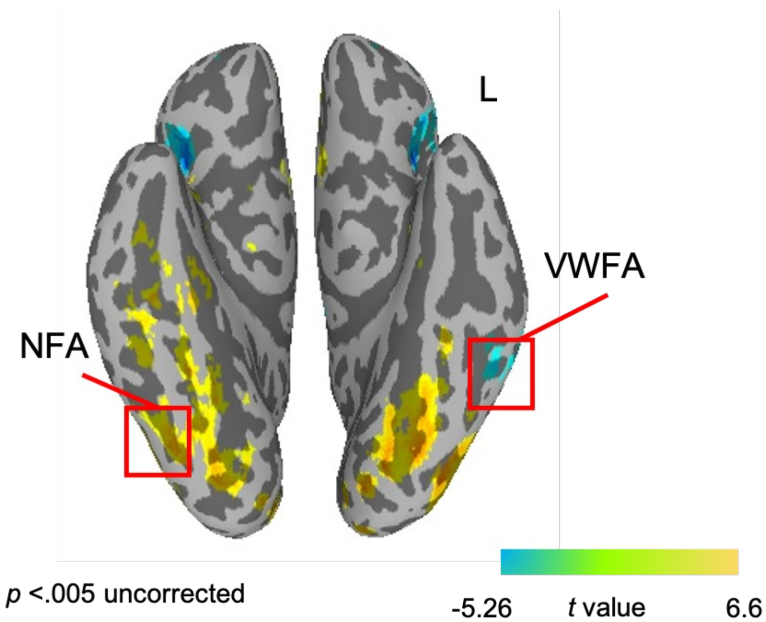
Appendix Figure 7. The left IPS was shown in the semantic task > baseline contrast whereas the left AG was shown in the baseline > semantic task contrast.



Appendix Figure 8. The right IPS was shown in the semantic task > verbal code contrast when a less stringent threshold was used (p<.005).



Appendix Figure 9. Left panel: The left AG was shown in the baseline verbal task contrast. Right panel: The right IPS was shown in the verbal task > baseline contrast.



Appendix Figure 10. When examining the semantic and verbal task contrast only for hand images, the NFA was shown in the semantic task > verbal task contrast while the VWFA was shown in the opposite contrast.

BIBLIOGRAPHY

Abboud, S., Maidenbaum, S., Dehaene, S., & Amedi, A. (2015). A number-form area in the blind. *Nature communications, 6*, 6026.

Andin, J., Fransson, P., Rönnberg, J., & Rudner, M. (2015). Phonology and arithmetic in the language–calculation network. *Brain and language, 143*, 97-105.

Andres, M., Michaux, N., & Pesenti, M. (2012). Common substrate for mental arithmetic and finger representation in the parietal cortex. *Neuroimage, 62*(3), 1520-1528.

Andres, M., Seron, X., & Olivier, E. (2007). Contribution of hand motor circuits to counting. *Journal of cognitive neuroscience, 19*(4), 563-576.

Ansari, D., & Dhital, B. (2006). Age-related changes in the activation of the intraparietal sulcus during nonsymbolic magnitude processing: an event-related functional magnetic resonance imaging study. *Journal of cognitive neuroscience, 18*(11), 1820-1828.

Ansari, D., Dhital, B., & Siong, S. C. (2006). Parametric effects of numerical distance on the intraparietal sulcus during passive viewing of rapid numerosity changes. *Brain research, 1067*(1), 181-188.

Ansari, D., Garcia, N., Lucas, E., Hamon, K., & Dhital, B. (2005). Neural correlates of symbolic number processing in children and adults. *Neuroreport, 16*(16), 1769-1773.

Baek, S., Daitch, A. L., Pinheiro-Chagas, P., & Parvizi, J. (2018). Neuronal Population Responses in the Human Ventral Temporal and Lateral Parietal Cortex during Arithmetic Processing with Digits and Number Words. *Journal of cognitive neuroscience*, 1-8.

Barth, H., Starr, A., & Sullivan, J. (2009). Children's mappings of large number words to numerosities. *Cognitive Development, 24*(3), 248-264.

Benoit, L., Lehalle, H., Molina, M., Tijus, C., & Jouen, F. (2013). Young children's mapping between arrays, number words, and digits. *Cognition, 129*(1), 95-101.

Bitan, T., Booth, J. R., Choy, J., Burman, D. D., Gitelman, D. R., & Mesulam, M.-M. (2005). Shifts of effective connectivity within a language network during rhyming and spelling. *Journal of Neuroscience, 25*(22), 5397-5403.

Bokde, A. L., Tagamets, M.-A., Friedman, R. B., & Horwitz, B. (2001). Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli. *Neuron, 30*(2), 609-617.

Booth, J. R., Burman, D. D., Meyer, J. R., Gitelman, D. R., Parrish, T. B., & Mesulam, M. (2003). Relation between brain activation and lexical performance. *Human brain mapping, 19*(3), 155-169.

Borowsky, R., Cummine, J., Owen, W. J., Friesen, C. K., Shih, F., & Sarty, G. E. (2006). FMRI of ventral and dorsal processing streams in basic reading processes: insular sensitivity to phonology. *Brain topography, 18*(4), 233-239.

Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *Journal of Neuroscience, 28*(40), 10056-10061.

Bugden, S., Price, G. R., McLean, D. A., & Ansari, D. (2012). The role of the left intraparietal sulcus in the relationship between symbolic number processing and children's arithmetic competence. *Developmental cognitive neuroscience, 2*(4), 448-457.

Butterworth, B. (1999). *What counts: How every brain is hardwired for math*: The Free Press.

Cantlon, J. F., & Li, R. (2013). Neural activity during natural viewing of Sesame Street statistically predicts test scores in early childhood. *PLoS biology, 11*(1), e1001462.

Cantlon, J. F., Libertus, M. E., Pinel, P., Dehaene, S., Brannon, E. M., & Pelphrey, K. A. (2009). The neural development of an abstract concept of number. *Journal of cognitive neuroscience, 21*(11), 2217-2229.

Cantlon, J. F., Pinel, P., Dehaene, S., & Pelphrey, K. A. (2011). Cortical representations of symbols, objects, and faces are pruned back during early childhood. *Cerebral cortex, 21*(1), 191-199.

Cantlon, J. F., Platt, M. L., & Brannon, E. M. (2009). Beyond the number domain. *Trends in cognitive sciences, 13*(2), 83-91.

Cao, F., Bitan, T., & Booth, J. R. (2008). Effective brain connectivity in children with reading difficulties during phonological processing. *Brain and language, 107*(2), 91-101.

Catani, M., Robertsson, N., Beyh, A., Huynh, V., de Santiago Requejo, F., Howells, H., . . . Dyrby, T. B. (2017). Short parietal lobe connections of the human and monkey brain. *cortex, 97*, 339-357.

Chen, L., Wassermann, D., Abrams, D. A., Kochalka, J., Gallardo-Diez, G., & Menon, V. (2019). The visual word form area (VWFA) is part of both language and attention circuitry. *Nature communications, 10*(1), 1-12.

Cohen, L., Dehaene, S., Naccache, L., Lehéricy, S., Dehaene-Lambertz, G., Hénaff, M.-A., & Michel, F. (2000). The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain, 123*(2), 291-307.

Cohen, L., Lehéricy, S., Chochon, F., Lemer, C., Rivaud, S., & Dehaene, S. (2002). Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. *Brain, 125*(5), 1054-1069.

Condry, K. F., & Spelke, E. S. (2008). The development of language and abstract concepts: The case of natural number. *Journal of Experimental Psychology: General, 137*(1), 22.

Coubart, A., Izard, V., Spelke, E. S., Marie, J., & Streri, A. (2014). Dissociation between small and large numerosities in newborn infants. *Developmental Science, 17*(1), 11-22.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research, 29*(3), 162-173.

Crollen, V., Mahe, R., Collignon, O., & Seron, X. (2011). The role of vision in the development of finger–number interactions: Finger-counting and finger-montring in blind children. *Journal of experimental child psychology, 109*(4), 525-539.

Crollen, V., & Noël, M.-P. (2015). The role of fingers in the development of counting and arithmetic skills. *Acta psychologica, 156*, 37-44.

Daitch, A. L., Foster, B. L., Schrouff, J., Rangarajan, V., Kaşikçi, I., Gattas, S., & Parvizi, J. (2016). Mapping human temporal and parietal neuronal population activity and functional coupling during mathematical cognition. *Proceedings of the National Academy of Sciences, 113*(46), E7277-E7286.

Dehaene, S. (1992). Varieties of numerical abilities. *Cognition, 44*(1-2), 1-42.

Dehaene, S., & Changeux, J.-P. (1993). Development of elementary numerical abilities: A neuronal model. *Journal of cognitive neuroscience, 5*(4), 390-407.

Dehaene, S., & Cohen, L. (1995). Towards an anatomical and functional model of number processing. *Mathematical cognition, 1*(1), 83-120.

Dehaene, S., Dupoux, E., & Mehler, J. (1990). Is numerical comparison digital? Analogical and symbolic effects in two-digit number comparison. *Journal of Experimental Psychology: Human Perception and Performance, 16*(3), 626.

Dehaene, S., Izard, V., Spelke, E., & Pica, P. (2008). Log or linear? Distinct intuitions of the number scale in Western and Amazonian indigene cultures. *Science, 320*(5880), 1217-1220.

Dehaene, S., Le Clec'H, G., Poline, J.-B., Le Bihan, D., & Cohen, L. (2002). The visual word form area: a prelexical representation of visual words in the fusiform gyrus. *Neuroreport, 13*(3), 321-325.

Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cognitive neuropsychology, 20*(3-6), 487-506.

Dehaene, S., Spelke, E., Pinel, P., Stanescu, R., & Tsivkin, S. (1999). Sources of mathematical thinking: Behavioral and brain-imaging evidence. *Science, 284*(5416), 970-974.

Dehaene, S., Tzourio, N., Frak, V., Raynaud, L., Cohen, L., Mehler, J., & Mazoyer, B. (1996). Cerebral activations during number multiplication and comparison: a PET study. *Neuropsychologia, 34*(11), 1097-1106.

Di Luca, S., Granà, A., Semenza, C., Seron, X., & Pesenti, M. (2006). Finger–digit compatibility in Arabic numeral processing. *Quarterly Journal of Experimental Psychology, 59*(9), 1648-1663.

Di Luca, S., Lefèvre, N., & Pesenti, M. (2010). Place and summation coding for canonical and non-canonical finger numeral representations. *Cognition, 117*(1), 95-100.

Di Luca, S., & Pesenti, M. (2008). Masked priming effect with canonical finger numeral configurations. *Experimental Brain Research, 185*(1), 27-39.

Di Luca, S., & Pesenti, M. (2011). Finger numeral representations: more than just another symbolic code. *Frontiers in Psychology, 2*, 272.

Dormal, V., Andres, M., Dormal, G., & Pesenti, M. (2010). Mode-dependent and mode-independent representations of numerosity in the right intraparietal sulcus. *Neuroimage, 52*(4), 1677-1686.

Droit-Volet, S., Clément, A., & Fayol, M. (2003). Time and number discrimination in a bisection task with a sequence of stimuli: A developmental approach. *Journal of experimental child psychology, 84*(1), 63-76.

Eger, E., Michel, V., Thirion, B., Amadon, A., Dehaene, S., & Kleinschmidt, A. (2009). Deciphering cortical number coding from human brain activity patterns. *Current Biology, 19*(19), 1608-1615.

Eger, E., Sterzer, P., Russ, M. O., Giraud, A.-L., & Kleinschmidt, A. (2003). A supramodal number representation in human intraparietal cortex. *Neuron, 37*(4), 719-726.

Emerson, R. W., & Cantlon, J. F. (2015). Continuity and change in children's longitudinal neural responses to numbers. *Developmental Science, 18*(2), 314-326.

Fair, D. A., Cohen, A. L., Power, J. D., Dosenbach, N. U., Church, J. A., Miezin, F. M., . . . Petersen, S. E. (2009). Functional brain networks develop from a “local to distributed” organization. *PLoS computational biology, 5*(5).

Fayol, M., Barrouillet, P., & Marinthe, C. (1998). Predicting arithmetical achievement from neuro-psychological performance: A longitudinal study. *Cognition, 68*(2), B63-B70.

Fazio, L. K., Bailey, D. H., Thompson, C. A., & Siegler, R. S. (2014). Relations of different types of numerical magnitude representations to each other and to mathematics achievement. *Journal of experimental child psychology, 123*, 53-72.

Feigenson, L., Dehaene, S., & Spelke, E. (2004). Core systems of number. *Trends in cognitive sciences, 8*(7), 307-314.

Fias, W., Lammertyn, J., Reynvoet, B., Dupont, P., & Orban, G. A. (2003). Parietal representation of symbolic and nonsymbolic magnitude. *Journal of cognitive neuroscience, 15*(1), 47-56.

Fornaciai, M., & Park, J. (2018). Early numerosity encoding in visual cortex is not sufficient for the representation of numerical magnitude. *Journal of cognitive neuroscience, 30*(12), 1788-1802.

Fuson, K. C. (1982). An analysis of the counting-on solution procedure in addition. *Addition and subtraction: A cognitive perspective*, 67-81.

Fuson, K. C. (2012). *Children's counting and concepts of number*: Springer Science & Business Media.

Fuson, K. C., & Willis, G. B. (1988). Subtracting by counting up: More evidence. *Journal for Research in Mathematics Education*, 402-420.

Geary, D. C., Hoard, M. K., Byrd-Craven, J., & DeSoto, M. C. (2004). Strategy choices in simple and complex addition: Contributions of working memory and counting knowledge for children with mathematical disability. *Journal of experimental child psychology, 88*(2), 121-151.

Gelman, R., & Gallistel, C. (1978). Young children's understanding of numbers. *Cambridge, MA*.

Gelman, R., & Meck, E. (1983). Preschoolers' counting: Principles before skill. *Cognition, 13*(3), 343-359.

Gelman, R., Meck, E., & Merkin, S. (1986). Young children's numerical competence. *Cognitive Development, 1*(1), 1-29.

Gerstmann, J. (1940). Syndrome of finger agnosia, disorientation for right and left, agraphia and acalculia: local diagnostic value. *Archives of Neurology & Psychiatry, 44*(2), 398-408.

Grabner, R. H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., & Neuper, C. (2009). To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. *Neuropsychologia, 47*(2), 604-608.

Gracia-Bafalluy, M., & Noël, M.-P. (2008). Does finger training increase young children's numerical performance? *cortex, 44*(4), 368-375.

Greeno, J. G., Riley, M. S., & Gelman, R. (1984). Conceptual competence and children's counting. *Cognitive psychology, 16*(1), 94-143.

Grefkes, C., & Fink, G. R. (2005). The functional organization of the intraparietal sulcus in humans and monkeys. *Journal of anatomy, 207*(1), 3-17.

Grotheer, M., Herrmann, K.-H., & Kovács, G. (2016). Neuroimaging evidence of a bilateral representation for visually presented numbers. *Journal of Neuroscience, 36*(1), 88-97.

Grotheer, M., Jeska, B., & Grill-Spector, K. (2018). A preference for mathematical processing outweighs the selectivity for Arabic numbers in the inferior temporal gyrus. *Neuroimage, 175*, 188-200.

Halberda, J., & Feigenson, L. (2008). Developmental change in the acuity of the" Number Sense": The Approximate Number System in 3-, 4-, 5-, and 6-year-olds and adults. *Developmental Psychology, 44*(5), 1457.

Halberda, J., Mazzocco, M. M., & Feigenson, L. (2008). Individual differences in non-verbal number acuity correlate with maths achievement. *Nature, 455*(7213), 665.

Heekeren, H. R., Marrett, S., Bandettini, P. A., & Ungerleider, L. G. (2004). A general mechanism for perceptual decision-making in the human brain. *Nature, 431*(7010), 859-862.

Hermes, D., Rangarajan, V., Foster, B. L., King, J.-R., Kasikci, I., Miller, K. J., & Parvizi, J. (2015). Electrophysiological responses in the ventral temporal cortex during reading of numerals and calculation. *Cerebral cortex, 27*(1), 567-575.

Holloway, I. D., & Ansari, D. (2010). Developmental specialization in the right intraparietal sulcus for the abstract representation of numerical magnitude. *Journal of cognitive neuroscience, 22*(11), 2627-2637.

Holloway, I. D., Battista, C., Vogel, S. E., & Ansari, D. (2013). Semantic and perceptual processing of number symbols: evidence from a cross-linguistic fMRI adaptation study. *Journal of cognitive neuroscience, 25*(3), 388-400.

Holloway, I. D., Price, G. R., & Ansari, D. (2010). Common and segregated neural pathways for the processing of symbolic and nonsymbolic numerical magnitude: An fMRI study. *Neuroimage, 49*(1), 1006-1017.

Hongchuan, Z., Qi, D., & Xinlin, Z. (2007). Premotor Cortex and Numerical Processing: A Meta-analysis of Functional Neuroimaging Studies [J]. *Psychological Science, 1*.

Hubbard, E. M., Piazza, M., Pinel, P., & Dehaene, S. (2005). Interactions between number and space in parietal cortex. *Nature Reviews Neuroscience, 6*(6), 435.

Huntley-Fenner, G., & Cannon, E. (2000). Preschoolers' magnitude comparisons are mediated by a preverbal analog mechanism. *Psychological Science, 11*(2), 147-152.

Hurst, M., Anderson, U., & Cordes, S. (2017). Mapping among number words, numerals, and nonsymbolic quantities in preschoolers. *Journal of Cognition and Development, 18*(1), 41-62.

Izard, V., & Dehaene, S. (2008). Calibrating the mental number line. *Cognition, 106*(3), 1221-1247.

Izard, V., Sann, C., Spelke, E. S., & Streri, A. (2009). Newborn infants perceive abstract numbers. *Proceedings of the National Academy of Sciences, 106*(25), 10382-10385.

Kadosh, R. C., Kadosh, K. C., Kaas, A., Henik, A., & Goebel, R. (2007). Notation-dependent and-independent representations of numbers in the parietal lobes. *Neuron, 53*(2), 307-314.

Kaufmann, L., Vogel, S. E., Wood, G., Kremser, C., Schocke, M., Zimmerhackl, L.-B., & Koten, J. W. (2008). A developmental fMRI study of nonsymbolic numerical and spatial processing. *cortex, 44*(4), 376-385.

Kay, K. N., & Yeatman, J. D. (2017). Bottom-up and top-down computations in word-and face-selective cortex. *Elife, 6*, e22341.

Kilner, J. M., Neal, A., Weiskopf, N., Friston, K. J., & Frith, C. D. (2009). Evidence of mirror neurons in human inferior frontal gyrus. *Journal of Neuroscience, 29*(32), 10153-10159.

Klein, E., Moeller, K., Nuerk, H.-C., & Willmes, K. (2010). On the neuro-cognitive foundations of basic auditory number processing: an fMRI study. *Behavioral and Brain Functions, 6*(1), 42.

Knudsen, B., Fischer, M. H., Henning, A., & Aschersleben, G. (2015). The development of Arabic digit knowledge in 4-to 7-year-old children. *Journal of Numerical Cognition, 1*(1), 21-37.

Lafay, A., Thevenot, C., Castel, C., & Fayol, M. (2013). The role of fingers in number processing in young children. *Frontiers in Psychology, 4*, 488.

Lahav, A., Saltzman, E., & Schlaug, G. (2007). Action representation of sound: audiomotor recognition network while listening to newly acquired actions. *Journal of Neuroscience, 27*(2), 308-314.

Le Corre, M., & Carey, S. (2007). One, two, three, four, nothing more: An investigation of the conceptual sources of the verbal counting principles. *Cognition, 105*(2), 395-438.

Le Corre, M., Van de Walle, G., Brannon, E. M., & Carey, S. (2006). Re-visiting the competence/performance debate in the acquisition of the counting principles. *Cognitive psychology, 52*(2), 130-169.

Liu, J., Yuan, L., Chen, C., Cui, J., Zhang, H., & Zhou, X. (2019). The Semantic System Supports the Processing of Mathematical Principles. *Neuroscience, 404*, 102-118.

Macuga, K. L., & Frey, S. H. (2011). Selective responses in right inferior frontal and supramarginal gyri differentiate between observed movements of oneself vs. another. *Neuropsychologia, 49*(5), 1202-1207.

Mayer, E., Martory, M.-D., Pegna, A. J., Landis, T., Delavelle, J., & Annoni, J.-M. (1999). A pure case of Gerstmann syndrome with a subangular lesion. *Brain, 122*(6), 1107-1120.

McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: expertise for reading in the fusiform gyrus. *Trends in cognitive sciences, 7*(7), 293-299.

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage, 61*(4), 1277-1286.

McNamara, A., Buccino, G., Menz, M. M., Gläscher, J., Wolbers, T., Baumgärtner, A., & Binkofski, F. (2008). Neural dynamics of learning sound—action associations. *PloS one, 3*(12).

Mechelli, A., Humphreys, G. W., Mayall, K., Olson, A., & Price, C. J. (2000). Differential effects of word length and visual contrast in the fusiform and lingual gyri during. *Proceedings of the Royal Society of London. Series B: Biological Sciences, 267*(1455), 1909-1913.

Merkley, R., Conrad, B., Price, G., & Ansari, D. (2019). Investigating the visual number form area: a replication study. *Royal Society Open Science, 6*(10), 182067.

Mizuguchi, N., Nakata, H., & Kanosue, K. (2014). Effector-independent brain activity during motor imagery of the upper and lower limbs: an fMRI study. *Neuroscience letters, 581*, 69-74.

Mountcastle, V. B., Lynch, J., Georgopoulos, A., Sakata, H., & Acuna, C. (1975). Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *Journal of neurophysiology, 38*(4), 871-908.

Moyer, R. S., & Bayer, R. H. (1976). Mental comparison and the symbolic distance effect. *Cognitive psychology, 8*(2), 228-246.

Mussolin, C., Nys, J., Leybaert, J., & Content, A. (2012). Relationships between approximate number system acuity and early symbolic number abilities. *Trends in Neuroscience and Education, 1*(1), 21-31.

Nemmi, F., Schel, M. A., & Klingberg, T. (2018). Connectivity of the human number form area reveals development of a cortical network for mathematics. *Frontiers in human neuroscience, 12*, 465.

Nieder, A. (2016). The neuronal code for number. *Nature Reviews Neuroscience, 17*(6), 366.

Nieder, A., & Miller, E. K. (2003). Coding of cognitive magnitude: Compressed scaling of numerical information in the primate prefrontal cortex. *Neuron, 37*(1), 149-157.

Noël, M.-P. (2005). Finger gnosia: a predictor of numerical abilities in children? *Child Neuropsychology, 11*(5), 413-430.

Notebaert, K., Nelis, S., & Reynvoet, B. (2011). The magnitude representation of small and large symbolic numbers in the left and right hemisphere: an event-related fMRI study. *Journal of cognitive neuroscience, 23*(3), 622-630.

Pandya, D. N., & Seltzer, B. (1982). Association areas of the cerebral cortex. *Trends in Neurosciences, 5*, 386-390.

Park, J., Li, R., & Brannon, E. M. (2014). Neural connectivity patterns underlying symbolic number processing indicate mathematical achievement in children. *Developmental Science, 17*(2), 187-202.

Park, J., Park, D. C., & Polk, T. A. (2013). Parietal functional connectivity in numerical cognition. *Cerebral cortex, 23*(9), 2127-2135.

Penner-Wilger, M., & Anderson, M. L. (2013). The relation between finger gnosis and mathematical ability: Why redeployment of neural circuits best explains the finding. *Frontiers in Psychology, 4*, 877.

Piazza, M., Izard, V., Pinel, P., Le Bihan, D., & Dehaene, S. (2004). Tuning curves for approximate numerosity in the human intraparietal sulcus. *Neuron, 44*(3), 547-555.

Piazza, M., Mechelli, A., Price, C. J., & Butterworth, B. (2006). Exact and approximate judgements of visual and auditory numerosity: An fMRI study. *Brain research, 1106*(1), 177-188.

Piazza, M., Pinel, P., Le Bihan, D., & Dehaene, S. (2007). A magnitude code common to numerosities and number symbols in human intraparietal cortex. *Neuron, 53*(2), 293-305.

Pica, P., Lemer, C., Izard, V., & Dehaene, S. (2004). Exact and approximate arithmetic in an Amazonian indigene group. *Science, 306*(5695), 499-503.

Pinel, P., Dehaene, S., Riviere, D., & LeBihan, D. (2001). Modulation of parietal activation by semantic distance in a number comparison task. *Neuroimage, 14*(5), 1013-1026.

Pollack, C., & Ashby, N. C. (2017). Where arithmetic and phonology meet: The meta-analytic convergence of arithmetic and phonological processing in the brain. *Developmental cognitive neuroscience*.

Price, C., Moore, C., & Frackowiak, R. (1996). The effect of varying stimulus rate and duration on brain activity during reading. *Neuroimage, 3*(1), 40-52.

Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage, 62*(2), 816-847.

Price, C. J., & Devlin, J. T. (2003). The myth of the visual word form area. *Neuroimage, 19*(3), 473-481.

Price, G. R., & Ansari, D. (2011). Symbol processing in the left angular gyrus: evidence from passive perception of digits. *Neuroimage, 57*(3), 1205-1211.

Pulvermüller, F. (2013). How neurons make meaning: brain mechanisms for embodied and abstract-symbolic semantics. *Trends in cognitive sciences, 17*(9), 458-470.

Reeve, R. (2011). Five-to 7-year-olds' finger gnosia and calculation abilities. *Frontiers in Psychology, 2*, 359.

Reich, L., Szwed, M., Cohen, L., & Amedi, A. (2011). A ventral visual stream reading center independent of visual experience. *Current Biology, 21*(5), 363-368.

Rocca, M. A., Falini, A., Comi, G., Scotti, G., & Filippi, M. (2008). The mirror-neuron system and handedness: A "right" world? *Human brain mapping, 29*(11), 1243-1254.

Roux, F.-E., Lubrano, V., Lauwers-Cances, V., Giussani, C., & Démonet, J.-F. (2008). Cortical areas involved in Arabic number reading. *Neurology, 70*(3), 210-217.

Seghier, M. L., Fagan, E., & Price, C. J. (2010). Functional subdivisions in the left angular gyrus where the semantic system meets and diverges from the default network. *Journal of Neuroscience, 30*(50), 16809-16817.

Shepard, R. N., Kilpatric, D. W., & Cunningham, J. P. (1975). The internal representation of numbers. *Cognitive psychology, 7*(1), 82-138.

Shibata, H., Inui, T., & Ogawa, K. (2011). Understanding interpersonal action coordination: an fMRI study. *Experimental Brain Research, 211*(3-4), 569-579.

Shrager, J., & Siegler, R. S. (1998). SCADS: A model of children's strategy choices and strategy discoveries. *Psychological Science, 9*(5), 405-410.

Shum, J., Hermes, D., Foster, B. L., Dastjerdi, M., Rangarajan, V., Winawer, J., . . . Parvizi, J. (2013). A brain area for visual numerals. *Journal of Neuroscience, 33*(16), 6709-6715.

Simon, O., Mangin, J.-F., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron, 33*(3), 475-487.

Skagenholt, M., Träff, U., Västfjäll, D., & Skagerlund, K. (2018). Examining the Triple Code Model in numerical cognition: An fMRI study. *PloS one*.

Sliwinska, M. W. W., Khadilkar, M., Campbell-Ratcliffe, J., Quevenco, F., & Devlin, J. T. (2012). Early and sustained supramarginal gyrus contributions to phonological processing. *Frontiers in Psychology, 3*, 161.

Sokolowski, H. M., Fias, W., Ononye, C. B., & Ansari, D. (2017). Are numbers grounded in a general magnitude processing system? A functional neuroimaging meta-analysis. *Neuropsychologia, 105*, 50-69.

Starr, A., Libertus, M. E., & Brannon, E. M. (2013). Number sense in infancy predicts mathematical abilities in childhood. *Proceedings of the National Academy of Sciences, 110*(45), 18116-18120.

Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *cortex, 45*(9), 1091-1096.

Szczepanski, S. M., Konen, C. S., & Kastner, S. (2010). Mechanisms of spatial attention control in frontal and parietal cortex. *Journal of Neuroscience, 30*(1), 148-160.

Talairach, J., & Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. 1988. *Theime, Stuttgart, Ger, 270*(132), 90128-90125.

Venkatraman, V., Ansari, D., & Chee, M. W. (2005). Neural correlates of symbolic and non-symbolic arithmetic. *Neuropsychologia, 43*(5), 744-753.

Verguts, T., & Fias, W. (2004). Representation of number in animals and humans: A neural model. *Journal of cognitive neuroscience, 16*(9), 1493-1504.

Verguts, T., & Fias, W. (2005). Neighbourhood effects in mental arithmetic. *Psychology Science, 47*(1), 132.

Vogel, A. C., Petersen, S. E., & Schlaggar, B. L. (2014). The VWFA: it's not just for words anymore. *Frontiers in human neuroscience, 8*, 88.

Vogel, S. E., Goffin, C., & Ansari, D. (2015). Developmental specialization of the left parietal cortex for the semantic representation of Arabic numerals: an fMR-adaptation study. *Developmental cognitive neuroscience, 12*, 61-73.

Vogel, S. E., Goffin, C., Bohnenberger, J., Koschutnig, K., Reishofer, G., Grabner, R. H., & Ansari, D. (2017). The left intraparietal sulcus adapts to symbolic number in both the visual and auditory modalities: Evidence from fMRI. *Neuroimage, 153*, 16-27.

Walsh, V. (2003). A theory of magnitude: common cortical metrics of time, space and quantity. *Trends in cognitive sciences, 7*(11), 483-488.

Wilson, L. B., Tregellas, J. R., Slason, E., Pasko, B. E., & Rojas, D. C. (2011). Implicit phonological priming during visual word recognition. *Neuroimage, 55*(2), 724-731.

Wynn, K. (1990). Children's understanding of counting. *Cognition, 36*(2), 155-193.

Xu, F., & Arriaga, R. I. (2007). Number discrimination in 10-month-old infants. *British Journal of developmental psychology, 25*(1), 103-108.

Xu, F., & Spelke, E. S. (2000). Large number discrimination in 6-month-old infants. *Cognition, 74*(1), B1-B11.

Yang, J., Andric, M., & Mathew, M. M. (2015). The neural basis of hand gesture comprehension: a meta-analysis of functional magnetic resonance imaging studies. *Neuroscience & Biobehavioral Reviews, 57*, 88-104.

Yeo, D. J., Wilkey, E. D., & Price, G. R. (2017). The search for the number form area: A functional neuroimaging meta-analysis. *Neuroscience & Biobehavioral Reviews, 78*, 145-160.

Zamarian, L., Ischebeck, A., & Delazer, M. (2009). Neuroscience of learning arithmetic—Evidence from brain imaging studies. *Neuroscience & Biobehavioral Reviews, 33*(6), 909-925.