7-19-2012 12:00 AM

Symbolizing Number: fMRI investigations of the semantic, auditory, and visual correlates of Hindu-Arabic numerals

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

Recommended Citation

Holloway, Ian Douglas, "Symbolizing Number: fMRI investigations of the semantic, auditory, and visual correlates of Hindu-Arabic numerals" (2012). *Electronic Thesis and Dissertation Repository*. 711.
https://ir.lib.uwo.ca/etd/711

SYMBOLIZING NUMBER: FMRI INVESTIGATIONS OF THE SEMANTIC, AUDITORY, AND VISUAL CORRELATES OF HINDU-ARABIC NUMERALS

(Spine title: Neural correlates of Hindu-Arabic numerals)

(Thesis format: Integrated-Article)

by

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Graduate Program in Psychology

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

THE UNIVERSITY OF WESTERN ONTARIO
SCHOOL OF GRADUATE AND POSTDOCTORAL STUDIES

CERTIFICATE OF EXAMINATION

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The thesis by

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Doctor of Philosophy

Date__________________________ ________________________________
Chair of the Thesis Examination Board

Abstract

Humans are born with a sensitivity to numerical magnitude. In literate cultures, these numerical intuitions are associated with a symbolic notation (e.g..Hindu-Arabic numerals). While a growing body of neuroscientific research has been conducted to elucidate commonalities between symbolic (e.g. Hinud-Arabic numerals) and non-symbolic (e.g. arrays of objects) representations, relatively little is known about the neural correlates specific to the symbolic processing of numerical magnitude. To address this, I conducted the three fMRI experiments contained within this thesis to characterize the neuroanatomical correlates of the auditory, visual, audiovisual, and semantic processing of numerical symbols.

In Experiment 1, the neural correlates of symbolic and non-symbolic number were contrasted to reveal that the left angular and superior temporal gyri responded specifically to numerals, while the right posterior superior parietal lobe only responded to non-symbolic arrays. Moreover, the right intraparietal sulcus (IPS) was activated by both formats. The results reflect divergent encoding pathways that converge upon a common representation across formats.

In Experiment 2, the neural response to Hindu-Arabic numerals and Chinese numerical ideographs was recorded in individuals who could read both notations and a control group who could read only the numerals. A between-groups contrast revealed semantic processing of ideographs in the right IPS, while asemantic visual processing was found in the left fusiform gyrus. In contrast to the ideographs, the semantic processing of numerals was associated with left IPS activity. The role of these brain regions in the semantic and asemantic representation of numerals is discussed.

In Experiment 3, the neural response of the visual, auditory, and audiovisual processing of numerals and letters was measured. The regions associated with visual and auditory responses to letters and numerals were highly similar. In contrast, the audiovisual response to numerals recruited a region of the right supramarginal gyrus, while the audiovisual letters activated left visual regions. In addition, an effect of congruency in the audiovisual pairs was comparable across numeral-number name pairs and letter-letter name pairs, but absent in letter-speech sound pairs.

Taken together, these three experiments provide new insights into how the brain processes numerical symbols at different levels of description.

Keywords: Hindu-Arabic numerals, letters, symbols, ideographs, fMRI, numerical magnitude representation, audiovisual integration, intraparietal sulcus, fusiform gyrus, superior temporal gyrus

Statement of Co-Authorship

The research contained within this doctoral thesis was conducted in collaboration with my advisor Dr. Daniel Ansari. Dr. Ansari contributed to all aspects of the research contained within including, but not limited to experimental and analytical design, interpretation, and manuscript preparation. Dr. Gavin Price contributed to the analysis, interpretation, and write-up of the data contained in Chapter 2. Stephan Vogel provided valuable analysis ideas for Chapter 3. Christian Battista created the non-symbolic stimuli used in Chapter 3 and assisted in the creation of the audio files in Chapter 4. Nadia Nosworthy, the voice of numerical cognition, provided the voice for all of the auditory stimuli used in Chapter 4. The experimental design and analytical ideas in Chapter 4 were created in collaboration with Dr. Leo Blomert and Dr. Nienke van Atteveldt. At the time of examination, Chapter 2 is published, Chapter 3 is submitted in its 3rd incarnation, and Chapter 4 is in preparation. While all of the material contained in this document is my own work, it should be acknowledged that Dr. Ansari provided assistance editing and revising all of the written material.

Dedication

To my father, who taught me to take things one pitch at a time.

And to my mother, who taught me to value kindness over knowledge.

Acknowledgements

I would like to thank my examination committee, which consisted of Dr. Bruce Morton, Dr. Marc Joanisse, Dr. Chris Viger, and Dr. Jessica Cantlon. I would also like to acknowledge Dr. Debra Jared and Dr. Bruce Morton who served as my advisory committee.

A heartfelt thanks goes to the members, past and present, of the numerical cognition lab: Ian Lyons, Gavin Price, Stephan Vogel, Stephanie Bugden, Nadia Nosworthy, Christian Battista, Anna Matejko, and Bea Goffin. I'd also like to thank Bruce Morton who is a large part of the reason I am at the University of Western Ontario and who has been asking me hard questions since the first day I met him.

Leo Blomert, Bert de Smedt, Nienke van Atteveldt, Roland Grabner, and Minna Hannula have all, in one way or another, contributed to my thinking. Leo and Nienke in particular should be thanked for helping me think about and study audiovisual processing.

Dr. Ladi Malhotra helped me get through a lot of the emotional turmoil of completing a PhD. In the same vein, the folks at Moksha Yoga London have provided me, in addition to years of stress relief, a second family and a home away from home.

I thank Jil Shimer, Stephen Szucs, Annamarie Burgess, and Vanessa Eyre for the emotional and tactical support during the write-up of this document. Of course, appropriate thanks should also be given to Kit Kat who never shied away from reminding me that life continues outside of the world of research.

Most importantly, I thank Daniel Ansari for his tireless efforts to nurture me as a scientific scholar. His even-handed guidance and marked generosity have been greatly appreciated. He has taught me how to think more clearly, write more clearly, and quite a bit about soccer as well. From our first serendipitous meeting through the final struggles of writing this thesis, he has been a rock of encouragement and enthusiasm. Most importantly, he never gave up on me, not matter how much doubt I felt in my own abilities. Without him, I would have never come so far.

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1.1 Introduction to numerical symbols

> "This profoundly human invention [number systems] is also the most universal of inventions. In more than one sense, it binds humanity together. There is no Tower of Babel for numbers: once grasped, they are everywhere understood in the same way. There are more than four thousand languages, of which several hundred are widespread; there are several dozen alphabets and writing systems to represent them; today, however, there is but one single system for writing numbers. The symbols of this system are a kind of visual Esperanto: Europeans, Asiatics, Africans, Americans or Oceanics, incapable of communicating by the spoken word, understand each other perfectly when they write numbers using the figures 0, 1, 2, 3, 4… and this is one of the most notable features of our present number-system. In short, numbers are today the one true universal language. Anyone who thinks that number is inhuman would do well to reflect on this fact" (Ifrah, 1981, p 594).

Numerical symbols, and the Hindu-Arabic numerals in particular, are perhaps the most ubiquitous type of symbolic representation in the world today. In the industrialized West, our lives are inundated with numerals across almost every aspect of our lives: sports scores, grocery bills, ISBN numbers, medication doses, and calendar dates, to name a few examples. The ability to effectively use these types of symbols is crucial to navigating our environment.

Numerical symbols provide a unique opportunity to learn how the human brain learns, decodes, and represents symbols. How is it, for example, that numerical symbols become connected with their referents, such as their semantic meaning or their verbal name? How does the brain accomplish this task? Does the manner in which a numeral is used change its relationship to its meaning? Are different levels of representation, such as nominal, ordinal, or ratio, processed in parallel? Yet despite the ubiquity of numeral use and the diversity of rich questions that can be asked about it, little is known about the neural processing of numerical symbols.

In the following body of work, three empirical studies are presented that begin to fill in this gap in our knowledge. After a brief historical introduction to numerical symbols, the two most principal referents of numerals (semantic and auditory) will be discussed. The discussion then turns to what is currently known about the neuroanatomical correlates underlying the semantic and asemantic processing of numerals. The first chapter concludes with an overview of the three unanswered questions that guide each of the empirical studies that were conducted and the methodologies used to address them. Following the conclusion of Chapter 1, each of the studies and their results will then be described in detail within their own chapters. Between each of these empirical chapters, an interim summary will be provided to transition from one study to the next. The thesis will conclude with a fifth chapter discussing what can be learned from these studies and future directions that research into the neurobiology of numerical symbol processing can take.

1.1.1 A brief history of numerals

Although the first formal writing system can be dated to 3,000 B.C.E. in ancient Sumer, systems for expressing numerical information developed somewhat later than writing systems. All numerical notation systems found their origins in language, as every culture first expressed their numbers as words (Menninger, 1992). Eventually, some cultures developed special symbols for representing numerical values, a process which occurred independently in several cultures. These symbols slowly replaced numerical icons such as tally sticks, knotted ropes, as well as idiosyncratic (personal or community-based) number writing systems.

In the western world, the first numeral systems were created by using alphabetic characters as numerals. In one archaic practise, the number words were abbreviated such that the first letter of the number word was used to represent that number (Ifrah, 1981, p. 220). This would be equivalent to English speakers representing the numbers seven, eight, and nine with S, E, and N, respectively. The Babylonians developed a more advanced numeral system in which two Cuneiform symbols (a symbol similar to Y was used for single units and one similar to < was used for ten units) and a primitive place-value system was used to represent numbers 1-59. Thus the number 32 would be represented as <<<YY (Ifrah, 1981, p. 88). This notation system is, like the Greek and Roman numeral systems were pseudosymbolic as the numerical referent is not independent from the sign that represents it (Peirce, 1976). Later, sometime after the 11th Century B.C.E., the ancient Greeks began using the sequence of their alphabetic

characters to build a numerical notation (Menninger, 1992). Here the first letter in the alphabet corresponded to the first symbol in the numeral sequence and the 10th letter in the alphabet corresponded to the tenth numeral, etc. This type of system spread into the Semitic languages of the Middle East and later into the Roman Empire, whose numerals we still use in limited contexts in the present day.

Eventually, the Greek system was replaced by the Hindu-Arabic numerals first developed in ancient India and brought to Europe by the Arabic people of ancient Persia. This numeral system expressed quantities using a place value system and included a way of expressing zero. The Hindu-Arabic numerals were fully developed by around 500 C.E., having grown out of the earlier Brahmi numeric script (Ifrah, 1985). This numeral system was popularized in Europe by Fibonacci in 1202 and also spread eastward into China. Before this, Chinese represented numbers using number words rather than a separate notational system. Because of the widespread use of the Hindu-Arabic numerals, numerical notation systems have a much greater degree of cultural homogeneity than writing systems as expressed in the quote inscribing the beginning of this discussion.

1.1.2 Numerals and their referents

In Figure 1.1, nine symbols are presented. To anyone unfamiliar with these symbols, it is impossible to know much about them. One could perhaps guess that they come from an East Asian script. However, to anyone who reads the script of the Thai language, several things would be clear. Each symbol has a name, an auditory referent that is associated with the visual form. In addition, these symbols are numerical in nature and therefore are associated with a semantic referent. The symbols also relate to each other in an ordinal system that implies that each subsequent numeral is 1 greater than the numeral before it.

๑ ๒ ๓ ๔ ๕ ๖ ๗ ๘ ๙

Figure 1.1 Numerals 1-9 in the Thai script.

Like all true symbols, numerals refer to their referents in a purely arbitrary way (Peirce, 1976). That is, there is no features of the Numeral 7, which give any information regarding either the auditory number word "seven" or the cardinal value "*******". The arbitrary nature of the numeral-referent connection implies that numerals are culturally transmitted representations that must be formally learned. In this way, a symbolic representation of number can be differentiated from an acultural non-symbolic representation described in the next section.

1.1.2.1 Semantic referents of numerals

While the association between a numeral and its semantic referent requires some type of formal or informal training, the understanding of the semantic referent (referred to as numerical magnitude) has its roots in a phylogenetically continuous capacity for perceiving numerical information. Sensitivity to numerical magnitude can be seen in the wide varieties of animal species that have demonstrated the ability to make behavioral decisions based on numerical information (Brannon, 2006; Nieder & Dehaene, 2009). Across the phyla, mammals (Cantlon & Brannon, 2006; Meck & Church, 1983; Roitman, Brannon, & Platt, 2007), birds (Roberts & Mitchell, 1994), and even amphibians (Krusche, Uller, & Dicke, 2010) and fish (Agrillo, Dadda, Serena, & Bisazza, 2009), are able to perceive numerical magnitudes. Such perceptions provide adaptive information about their natural environments, such as the number of predators, amount of food items, or the number of calls of a particular kind.

In humans, this basic perception of numerical magnitude can be seen in infants, (Antell & Keating, 1983; Feigenson, Carey, & Spelke, 2002; Libertus & Brannon, 2009; Lipton & Spelke, 2004; Wynn, 1992; F Xu & Spelke, 2000a, 2000b; Fei Xu, Spelke, & Goddard, 2005), as well as in human cultures who use extremely few or no number words (Butterworth, Reeve, Reynolds, & Lloyd, 2008; Gordon, 2004; Pica, Lemer, Izard, & Dehaene, 2004). Taken together, studies of non-human animals, human infants, and individuals without number words provides strong evidence that the capacity to perceive numerical magnitude is a predisposition of the human mind adapted for by evolution rather than something that needs to be instructed. These pre-verbal representations of numerical magnitude are the essence of the semantic representation that becomes associated with numerical symbols. As such, it is important to understand the nature of the representation of numerical magnitude in order to study how numerical symbols are semantically processed.

The pre-verbal representation of number described above is approximate and non-symbolic. The perception of numerical magnitude is bound by Weber's Law and becomes less precise as the size of the to-be-represented number increases. Psychophysically, the imprecision of numerical magnitude representations result in two related effects called the distance effect and the size effect. These effects are important for understanding the semantic processing of numerical symbols. The size effect states that larger numerical values are characterized by greater representational imprecision. This fact is utilized by the classic raffle game in which one must guess how many objects (for example jellybeans) are in a container. As everyone who has ever played this or similar games is familiar with, large collections of jellybeans are notoriously difficult to precisely enumerate. The distance effect refers to the influence numerical magnitude has on quantitative decisions. Numerical magnitudes that are numerically more similar (smaller numerical distance) are more difficult to distinguish than quantities that are numerically more dissimilar (larger numerical distance). For example, if one were asked to distinguish 31 from 37 jellybeans, one would have a much more difficult time (i.e., higher error rate and longer reaction times) than if one were asked to distinguish 42 from 91 jellybeans. More contemporary research has combined these two effects into the numerical ratio effect, which states that discrimination performance decreases as the numerical ratio between two numbers increases. Thus, 31 vs. 62 (ratio of 0.5) is easier than 18 vs. 24 (ratio of 0.75), more challenging than 17 vs. 68 (ratio 0.25) and equally as challenging as 23 vs. 46 (ratio of 0.5).

Thus far, it has been asserted that the semantic representations associated with numerals originate in the approximate, non-symbolic system for perceiving and representing numerical magnitude. An alternative hypothesis would be that two separate systems of representation exist (Cohen Kadosh & Walsh, 2009). In this theory, the non-symbolic system is employed by humans to make judgments about non-symbolic magnitudes. In contrast, a symbolic system of number representation would provide precise cardinal values of numerical magnitude. Superficially, this two-system explanation is compelling. While it is perceptually impossible to discriminate 437 from 438 dots, it is quite simple to discriminate the values using symbolic representations. However, psychophysical data suggest that even the symbolic representation of numerical magnitude suffers from imprecision. In tasks such as the numerical comparison task, human participants are asked to choose which of two simultaneously presented quantities are numerically larger. Consistent with evidence reported in animal models, the documented accuracy and latency profiles of the numerical comparison task in literate adults show that numerical decisions are slower and more inaccurate as numerical ratio between the to-be-compared numerals increases (Buckley & Gillman, 1974; Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999; Moyer & Landauer, 1967; Sekuler & Mierkiewicz, 1977). For example, Moyer and Landauer (1967) demonstrated that when adults compared which of two simultaneously presented numerals was numerically larger, the reaction time and error rate of the judgments decreased as numerical distance increased. The distance effect, they argued, demonstrates that the semantic representations underlying the numerical symbols are imprecise in nature. If, instead, the representations of the numerals were digital and precise, there would be no reason why the comparison of 7 vs. 9 should take significantly longer or be more inaccurate than the comparison of 3 vs. 9. Considering this evidence, it is clear that the semantic representations of numerals are constructed from and continue to be linked to the intrinsic non-symbolic representation of numerical magnitude.

While this evidence of links between the symbolic and non-symbolic representation of numerical magnitude is compelling, it should still be acknowledged that numerical symbols afford a representation of numerical magnitude that can be used to discriminate quantities far greater than those that can be discriminated non-symbolically. That is, when a symbol is linked with a numerical magnitude representation, it adds a degree of precision. Recent research has reported evidence that this sharpening of the magnitude representation occurs both in the human brain (Piazza, Pinel, Le Bihan, & Dehaene, 2007) as well as in neural network models of symbolic numeral representation (Verguts & Fias, 2004).

In summary, the semantic representation of numerals is characterized by imprecision inherited from the non-symbolic numerical magnitude representations on which they are mapped. This representational imprecision results in the numerical ratio effect, which can be used to study the semantic processing of numerals. Let us now turn to the other principal referent of numerical symbols: auditory number names.

1.1.2.2 Auditory referents of numerals

Relative to the semantic referents of numerals, very little is known about the nature of their auditory referents. The study of the cognitive and neural correlates of numerals has focused almost exclusively on the semantic level of representation. The dominant theory guiding the study of numerical cognition considers the auditory processing of numerals as a purely linguistic process (Dehaene, 1992). Yet, the degree to which the auditory processing of numerals is comparable to the auditory process of other types of verbal representations has not been empirically tested.

Although the auditory referents of numerals have been largely ignored, they nonetheless play a crucial role in the acquisition of the symbolic representation of number. This fact has been demonstrated clearly by studies of the acquisition of counting. Typically developing children know the names of numbers (what becomes the auditory referents of numerals) well before they understand what those numbers mean (Le Corre & Carey, 2007; Le Corre, Van de Walle, Brannon, & Carey, 2006; Wynn, 1990). Wynn (1990), for example, used the so-called "Give-a-Number" task with children 2 to 4 years of age. In this task, children are first asked to demonstrate their ability to count, typically by counting as high as they can. Following this, children are introduced to a stuffed animal that has forgotten how to count. They are asked to give the stuffed animal a certain quantity of objects from a large bowl of those objects placed near the child. Children younger than 3 ½ or 4 years of age show a peculiar pattern of performance such that they are able to recite the number sequence quite well, but are not able to utilize counting to enumerate the proper quantity of objects for the stuffed animal. For example, a child of 3 years might be able to count to 25, but when asked to give a stuffed toy 5 marbles the child does not understand that the auditory words in the counting sequence can be used to count out 5 marbles. Through a process that is still poorly understood, learning to count assists young children in associating the auditory number words with a semantic meaning. In other words, an asemantic auditory representation becomes associated with the representation of numerical magnitude. As children begin formal education, children learn the written numerical symbols that become connected with both the auditory and the numerical magnitude representations. Although the auditory referents of numerical symbols play an important scaffolding role in the acquisition of number symbols, little research has been conducted to specifically study them.

When the auditory number words are linked to visual representations such as numerals, an additional level of processing emerges—one in which the auditory and visual representations are integrated into a bimodal audiovisual percept. This audiovisual level of processing is crucial in reading alphabetic languages where the phonological information of speech sounds is associated with the visual information of letters (for review see Blomert, 2011). It can be assumed that a similar process of audiovisual integration is important for reading numerals. Unlike letters, however, numerals have an additional semantic content embedded in them. It, therefore, remains unclear whether comparable audiovisual processing exists in the reading of letters and numerals. Moreover, the interaction between the audiovisual and semantic representations of numerals has never been studied.

In summary, the number words are important for the initial acquisition of symbolic representations of numerical magnitude. Children learn number words and associate them with their pre-existing representations of numerical magnitude. In early elementary school, children then learn to read a special set of symbols (numerals) that can be used to stand in for the number words. The degree to which the verbal and audiovisual processing of numerals is similar to and divergent from the processing of words and letters remains to be determined.

Thus far, I have discussed numerals and their two principal referents. Next I turn to a brief overview of what is currently known about how numerical symbols are processed in the brain both in the semantic and the asemantic (auditory, visual, and audiovisual) domains.

1.2 Neural substrates of symbolic number processing

1.2.1 Semantic processing of numerals

The above discussion introduced the notion that the semantic representation of numerals is constructed from the intrinsic, approximate, non-symbolic representation of numerical magnitude. The basic evidence for this is the effect of numerical ratio on the processing of numerical symbols, which originates from the imprecise nature of numerical magnitude representations. Almost all of the neuroimaging research that has been conducted on the processing of numerical symbols has focused on testing this hypothesis. A growing number of studies have demonstrated a neural correlate that is common for the semantic processing of numerals (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon et al., 2009; Chochon, Cohen, van de Moortele, & Dehaene, 1999; Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Notebaert, Pesenti, & Reynvoet, 2010; Pesenti, Thioux, Seron, & De Volder, 2000; Pinel et al., 1999; Pinel, Dehaene, Rivière, & LeBihan, 2001) and the quantitative processing of non-symbolic stimuli, such as arrays of dots (Ansari & Dhital, 2006; Ansari, Dhital, & Siong, 2006; Cantlon et al., 2009; Cantlon, Brannon, Carter, & Pelphrey, 2006; Cappelletti, Lee, Freeman, & Price, 2010; Fias et al., 2003; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Piazza et al., 2007). This body of literature has converged on the intraparietal sulcus (IPS), which runs between the inferior and superior parietal lobes, as the brain region that houses the representation of numerical magnitude (see Figure 1.2).

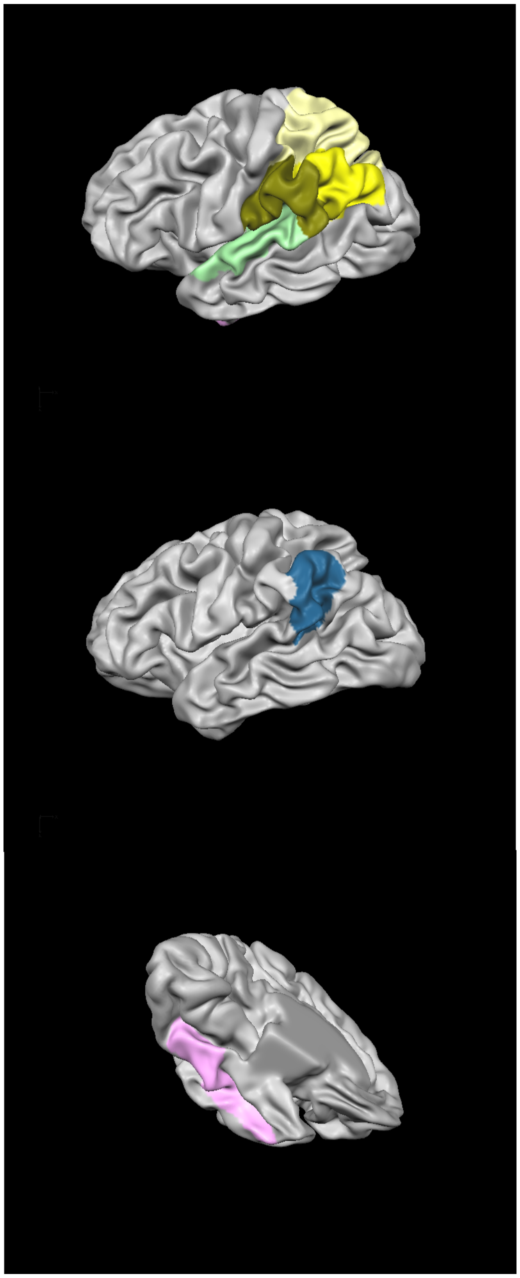

Figure 1.2 Brain regions commonly involved in number processing and referred to in the empirical chapters: superior parietal lobe (pale yellow), inferior parietal lobe (dark yellow), supramarginal gyrus (olive green), superior temporal gyrus (light green),

angular gyrus (blue), fusiform gyrus (pink). Note that the intraparietal sulcus runs between the superior and inferior parietal lobes.

In general, two different paradigms have been used to elicit the neural correlates of numerical magnitude processing. The first is the numerical comparison task, which was discussed above. In this task, participants are asked to compare two numerical magnitudes. The numerical ratio between these magnitudes is varied so that experimenters can identify brain regions whose response is modulated by numerical information. The IPS responds more strongly when numerical ratio is large (magnitudes are more similar) than when numerical ratio is small (magnitudes are less similar). This response is thought to reflect the greater reliance on the neural system of semantic representation to disambiguate two quantities whose representations are highly overlapping. In other words, the IPS must be brought online much more strongly to distinguish 32 from 42 dots relative to when it is asked to distinguish 32 from 12 dots. As aforementioned, this neural ratio effect is seen in the IPS regardless of whether the numerical comparison task uses symbolic or non-symbolic stimuli.

The other experimental paradigm used to study the semantic processing of numerals is called the numerical adaptation paradigm. In such paradigms, the repeated presentation of the same quantity (adaptation stimulus) will cause the neurons that encode numerical magnitude representation to reduce in the extent of their response (Cantlon et al., 2006; Piazza et al., 2004). When one presents a novel quantity (deviant stimulus), the size of the rebound is inversely proportional to the amount of overlap between the adaptation and deviant quantities. Therefore, as the IPS is adapted to the quantity "23," it will show a larger rebound when the deviant is 11 than when the deviant is 22. This is due to the fact that the quantities 22 and 23 are highly overlapping in their respective representations and, therefore, utilize many of the same neurons to encode the quantity. Thus, when deviant 22 is presented, most of the neurons that encode it have already been adapted. Presenting 22 would not result in the recruitment of many new neurons that were not involved in the previous response to 23. Presenting 11, on the other hand, would result in a much larger rebound effect as many of the representational neurons were not previously adapted to 23.

Recently published data has suggested that important differences in the representation of symbolic and non-symbolic numerical magnitudes may be detectable in the IPS. Piazza et al. (2007) used a numerical adaptation paradigm to examine the representation of symbolic and non-symbolic numerical magnitude in the parietal lobe. These authors demonstrated that the left IPS showed evidence of greater representational precision for numerical symbols relative to non-symbolic magnitudes. The right IPS showed no differences between formats. More evidence for the specialization of the left IPS for the representation of symbolic numerical magnitudes comes from a study published by Cohen Kadosh and colleagues (2007) who used an adaptation paradigm to demonstrate that the left IPS showed ratio-dependent adaptation to both numerals and number words, whereas the right IPS showed quantity adaptation only to numerals. Finally, Notebaert and colleagues showed that activity in the left, but not the right, IPS is correlated with the numerical ratio of both single- and double-digit Arabic numerals during a numerical adaptation task (2011). Taken together, these data are commensurate with a recently proposed hypothesis suggesting specialization of the left IPS for the representation of symbolic number (Ansari, 2007, 2008).

In summary, studies of the semantic processing of numerical symbols have demonstrated that the IPS underpins the numerical magnitude representations associated with the numerals. Recent research has begun to underscore the importance of the left IPS for the representation of symbolic numerical magnitudes. In the next section, I turn to a discussion of what is known about the asemantic processing of numerals in the brain, which can include processing numerals as an asemantic visual form, an asemantic auditory representation or an asemantic audiovisual percept.

1.2.2 Asemantic processing of numerals

The overwhelming majority of research studying the neurocognitive correlates of number processing have focused on understanding the representation of numerical magnitude, whether the representations are encoded in a non-symbolic or symbolic manner. This emphasis on numerical representation has resulted in a marked lack of research investigating any aspect of the asemantic processing of numerals in the human brain. Studies that have measured the neural responses to asemantic tasks such as Hindu-Arabic number naming have used these responses as a comparison with semantic processing (Chochon et al., 1999; Pesenti et al., 2000; Zago et al., 2001). The specific neural responses to these asemantic tasks were never reported.

One recent study has examined the neural correlates involved in the asemantic visual processing of Hindu-Arabic numerals (Price & Ansari, 2011). These authors presented participants with numerals, letters, and scrambled versions of the same. Relative to scrambled stimuli, a dorsal region of the left angular gyrus showed more activation for whole numerals and letters. In addition, a ventral region of the left angular gyrus showed more activation for numerals relative to letters. These results suggest that the left angular gyrus is involved in some aspect of the asemantic visual processing of numerals.

1.3 Open questions

The above review outlined what is currently known about the two main referents of numerals, followed by a description of the neural correlates underlying the semantic and asemantic processing of numerals. As demonstrated, the vast majority of research investigating numerical symbol processing has focused on the semantic level. The semantic representation of numerical magnitude has been well characterized on both the behavioral and the neural level. However, it must be noted that characterizing a representation of numerical magnitude that is common across all forms of number, including numerals, cannot yield any information specifically about the processing of numerical symbols. Thus, almost nothing is known about the neural correlates that are specific to the processing of Hindu-Arabic numerals. Against this background, a set of three inquiries that can begin to provide insights into the specific neural correlates underlying various aspects of numerical symbol processing is proposed.

1.4 The present studies

1.4.1 Similarities and differences in symbolic and non-symbolic processing

Assuming that a common representation of numerical magnitude exists for symbolic and non-symbolic formats, distinct brain regions must be involved in accessing the numerical information from the visual stimulus. Non-symbolic arrays encode numerical magnitude in a 1:1 fashion, whereas numerals encode numerical magnitude in a purely abstract way. If the numerical magnitude representation underlying symbolic and non-symbolic format is similar, a common substrate should be found in response to both formats. In addition, if the brain encodes this abstract representation in format-specific ways, then it should also be possible to identify neural correlates specific to each type of numerical stimulus format. In other words, what brain regions are common and divergent in the processing of symbolic and non-symbolic numerical magnitudes and what can they tell us about how the brain transforms numerical information into numerical representation?

To address this question, Experiment 1 was conducted. Adult participants performed symbolic and non-symbolic numerical comparisons while their neural responses were recorded using fMRI. The neural response to each format was contrasted to delineate the neural correlates related to each numerical stimulus format. A conjunction analysis was then conducted to identify regions that were significantly active during both symbolic and non-symbolic comparison. The details and results of this experiment can be found in Chapter 2.

1.4.2 Semantic versus asemantic processing of numerical symbols

While the nature of the semantic representation of numerical symbols has been relatively well characterized, it is currently unknown what regions come online as a symbol is changed from an arbitrary, asemantic shape to a quantitatively rich semantic entity. In other words, what brain regions respond when the arbitrary visual shape of a symbol is viewed asemantically relative to when it is viewed semantically? What regions in the cortex differentiate semantic processing from asemantic processing? Are they similar to the neural correlates that differentiate symbolic from non-symbolic numerical processing? Does the visual processing of numerals interact with the semantic processing of numerals?

To test this, two groups of participants were recruited: individuals who spoke and read either Cantonese or Mandarin and individuals who did not. Using an fMRI adaptation paradigm adapted from (Notebaert et al., 2011), the participants were presented with two different types of numerical symbols: Hindu-Arabic numerals and Chinese numerical ideographs. Since the Chinese readers knew the ideographs as a semantically rich symbol, but the control group did not, a between-group comparison of the neural response to ideographs distinguished semantic from asemantic processing of numerical symbols. A contrast of the Chinese readers' response to numerical ideographs with both groups' response to numerals was also conducted in order to detect any differences between the semantic processing of ideographs and numerals. The details and results of this experiment are documented in Chapter 3.

1.4.3 Visual, auditory, and audiovisual processing of numerical symbols

In addition to a semantic referent, the Hindu-Arabic numerals are associated with an auditory number name. Are these number names distinct from similar verbal stimuli such as letter names? How are these auditory referents integrated with the visual form of the numeral? If reading numerals is akin to reading letters, then the audiovisual integration of both should rely on common neural correlates. However, it is also possible that the reading of numerals is highly dissimilar from the reading of letters. If both commonalities and differences in numeral and letter processing can be identified, what can they tell us about the processes underlying the reading of these two types of symbols?

Chapter 4 holds a description of a study conducted to examine the audiovisual processing of numerical symbols. To accomplish this, a paradigm used in studies of the audiovisual processing of letters and speech sounds (van Atteveldt, Formisano, Goebel, & Blomert, 2004) was adapted. Participants passively viewed three different audiovisual pairs: letters and letter sounds, letters and letter names, and numerals and number names. The pairs could either be congruent, e.g., participants saw 3 and heard "three," or incongruent, e.g., participants saw 3 and heard "nine." Three contrasts were of central interest in this study. Firstly, what regions respond greater to the congruent relative to incongruent pairing of numerals and number names, i.e., what regions are involved in integrating the auditory and the visual information in numerals? Secondly, in numerals, does the semantic level of representation interact with the audiovisual response, i.e., are semantic and audiovisual processing parallel processes? Thirdly, do any differences exist between the audiovisual processing of numeral-number name pairs and the audiovisual processing of letter-letter name pairs or letter-letter sound pairs, i.e., is audiovisual integration general to letters and numerals? This experiment also afforded a test of whether the unimodal visual or the unimodal auditory response differed between letters and numerals.

1.5 Summary and Conclusion

In summary, the three empirical chapters that follow will present the first data to document the neural correlates underlying the processing of numerical symbols in the human brain. The data presented will address the three areas of inquiry described immediately above. Together, they will provide insight into the processes that are common between numerals and non-symbolic numerical stimuli, on the one hand, and numerals and non-numerical letter symbols, on the other hand. In addition, they will characterize differences between numerals, non-symbolic arrays, and letters, which, in turn, can be used to identify processes specific to reading and understanding Hindu-Arabic numerals.

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Chapter 2: Common and segregated neural pathways for the processing of symbolic and non-symbolic numerical magnitude: an fMRI study

2.1 Introduction

Because numerical magnitude is an abstract quality of a set, its meaning does not depend on the format in which that number is presented. In other words, whether one sees a numerical representation such as “6,” a verbal representation such as “six,” or a non-symbolic representation such as six goldfinches in a bush, the “sixness” of the number is the same in all cases.

This abstract quality of numerical magnitude has led to a substantial amount of research that has canvassed the brain in search of brain responses that reflect such an abstract representation of numerical magnitude. These empirical efforts have demonstrated that bilateral inferior parietal regions (most commonly the intraparietal sulcus (IPS)) respond to numerical magnitude across numerical stimulus formats. The IPS is modulated by numerical information when magnitudes are presented as numerals (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Chochon, Cohen, van de Moortele, & Dehaene, 1999; Pesenti, Thioux, Seron, & De Volder, 2000), words (Dehaene et al., 1996; Pinel, Dehaene, Rivière, & LeBihan, 2001), or non-symbolic arrays (Ansari & Dhital, 2006; Ansari, Dhital, & Siong, 2006; Cantlon, Brannon, Carter, & Pelphrey, 2006; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Venkatraman, Ansari, & Chee, 2005). In addition, numerical information evokes IPS activation in both the visual and the auditory domains (Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003). It has, therefore, been contended that the IPS is a region of the brain that supports the representation of abstract numerical information (Dehaene, Piazza, Pinel, & Cohen, 2003). However, it should be noted that the idea of abstract numerical representation has been challenged by recent behavioral and neuroimaging research (Cohen Kadosh & Walsh, 2009).

Irrespective of its validity, by focusing on the search for an abstract representation of numerical magnitude, the majority of existing research has deemphasized the importance of numerical stimulus format in the processing of numerical magnitude. Investigations designed to characterize similarities in the neural processing across all representations of numerical magnitude are an exploration of commonalities in the neural structures underlying the processing of all numerical stimulus formats and, therefore, treat differences between these formats as a variable of no interest.

Behavioral studies have begun to reveal important variations in numerical processing that depend upon differences in numerical stimulus format. For example, a study performed by Campbell has shown that stimulus format differences are crucial in the domain of calculation (Campbell, 1994). Specifically, these authors compared simple addition and multiplication problems presented as either Hindu–Arabic numerals or number words. The error profiles of the two problem types differed depending upon the numerical stimulus format in which the problems were presented. Format differences have also been shown to be important even for low-level numerical processing such as numerical comparison. For example, a recent behavioral study showed that children with developmental dyscalculia performed at the same level as matched controls on relative magnitude judgments of non-symbolic arrays, but performed much more poorly than their typically developing peers on judgments of Hindu–Arabic numerals (Rousselle & Noël, 2007). In addition, behavioral work by Holloway and Ansari demonstrated a similar effect in a sample of typically developing children (Holloway & Ansari, 2009). Specifically, these authors found that children's individual differences in the basic processing of symbolic, but not non-symbolic numerical magnitudes are related to individual differences in mathematics achievement.

In addition to behavioral research pointing to important format- related differences in number processing, recent brain imaging research has found hemispheric differences in numerical representation that are dependent on stimulus format. In a recent study, Cohen Kadosh et al., compared the neural representation of numerical magnitude for Hindu–Arabic numerals and written number words using an fMRI adaptation design. In fMRI adaptation experiments, the neural response to stimulus repetition is measured, with the assumption that neural regions involved in the processing of a particular stimulus dimension will decrease in their activation as a function of stimulus repetition. In their fMRI adaptation study, Cohen Kadosh et al.

found that while left IPS exhibited cross-format adaptation (decreased parietal response following repetition of number irrespective of the presentation format), the right IPS was only found to adapt its response to the repeated presentation of Arabic numerals, with no such pattern emerging for number words or cross-format pairs (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007). These data suggested that the left IPS is related to format-independent numerical magnitude representation, while the right IPS shows some specificity for the representation of Hindu–Arabic numerals. In a related experiment also employing an fMRI adaptation design, Piazza et al. demonstrated that the representation of Arabic numerals in the left IPS is more finely tuned than the representation of non-symbolic arrays in the left IPS (Piazza et al., 2007). These two sets of findings have led some to argue that the abstract representation of numerical magnitude in the left IPS could undergo important changes due to enculturation (Ansari, 2007) and moreover suggests that the IPS may contain both abstract and non-abstract representations of numerical quantity.

In a recent computational model Verguts and Fias have proposed a mechanism by which differences in the processing of symbolic (i.e., Hindu-Arabic numerals) and non-symbolic representations (i.e., arrays of dots) of numerical magnitude develop (Verguts & Fias, 2004). Using non-symbolic numerical input, these authors trained a neural network to represent discrete quantities. Their model included an “input field” in which the external representation of the number was presented, a “summation field” in which the external, non-symbolic representation was summed and recoded so that it could be represented on a place-coded “number field”. To explain, the “summation field” represents the items in the set through an additive process called summation coding. In summation coding the size of the representation monotonically increases with the size of the quantity being represented. In contrast to the “summation field,” the “number field” corresponds to the internal representation of number and is defined by place coding. Place coding is a way of representing the total number of items in a set by representing that quantity with a specific “place” on a number line. Verguts and Fias showed that with repeated trials, a neural network with a pre-existing ability to sum the items of a non-symbolic array could learn how to internally represent non-symbolic quantities using place coding.

Verguts and Fias then tested whether this model could be trained to process symbolic representations of numerical magnitude, such as the Hindu–Arabic numerals. Specifically, the authors tested the hypothesis that symbolic numerical representations can be learned through a process of association with pre-existing non-symbolic representations of numerical magnitude. Thus, they trained their model to associate symbolic numerals with the non-symbolic representations that the model had learned previously. In each trial the presentation of symbolic inputs was paired with the presentation of non-symbolic inputs. As a function of this training regime, the network eventually developed a so-called “symbolic field” which was used in place of the “summation field” to transform symbolic inputs into place-coded representations on the internal layer of the model. In other words, the network began representing a symbolic number by summing the associated non-symbolic array, but as a function of training time, ceased using summation coding and began mapping symbolic inputs directly onto the internal place coding representation common to symbolic and non-symbolic representations of numerical magnitude.

Based on the results, two testable predictions can be derived from this model. First, the model predicts that across different types of surface format, numerical magnitude is internally represented in a common, place-coded representation. Second, the model suggests that, within the adult human brain, one should find that symbolic and non-symbolic representations of numerical magnitude are processed with divergent encoding pathways.

In the present functional magnetic resonance imaging (fMRI) study, I tested these two predictions. To do so, I collected functional neuroimaging data while participants performed relative magnitude judgments on both symbolic (Hindu–Arabic numerals) and non-symbolic (arrays of squares) stimuli. A numerical comparison task was chosen for this study as such tasks require participants to process the stimuli semantically, while also allowing for differences in stimulus format. Therefore, this task could be used to measure both semantic and stimulus format-related processing. To test the first prediction of the Verguts and Fias model, I investigated which brain areas were associated with the conjunction of symbolic and non-symbolic numerical magnitude comparison. In this way, I was able to identify regions that showed common activation to both numerical stimulus formats. In accordance with the large corpus of research (for an overview see Dehaene et al., 2003) examining the neural correlates of numerical representation, I predicted that a conjunction of activation between symbolic and non-symbolic numerical processing would be found in inferior parietal regions. Although my hypothesis is convergent with the findings reviewed by Dehaene et al., my analysis includes important differences from these previous studies.

To test the second prediction, I statistically contrasted the neural responses to symbolic and non-symbolic numerical comparison. I expected to find differential regions involved in the processing of the two numerical stimulus formats. I hypothesized that regions of the superior parietal lobe would be particularly involved in non-symbolic numerical processing, while regions in the left temporoparietal junction would be implicated in symbolic numerical processing. Because a similar analysis has not been previously reported in the literature, I based my hypothesis on ancillary sources of evidence. With respect to non-symbolic comparison, recent work has shown that neurons found in the lateral intraparietal area (LIP) of macaque monkeys are involved in numerically summing an array of objects (Roitman, Brannon, & Platt, 2007). The existence of this type of summation coding in humans has been shown in a behavioral study (Roggeman, Verguts, & Fias, 2007). Importantly, a number of studies have suggested that the human homologue of the macaque LIP is found in the superior parietal lobe (Koyama et al., 2004; Sereno, Pitzalis, & Martinez, 2001). Consistent with these data from non-human primates, Santens, Roggeman, Fias, & Verguts (2010) have recently shown that the superior parietal cortex exhibits a pattern of increasing activation with increasing numerical size of non-symbolic arrays. Based on these findings, it is reasonable to predict that non-symbolic comparison will activate regions of the superior parietal cortex, potentially reflecting this region's involvement in the summation coding necessary for non-symbolic number processing.

To formulate my anatomical hypotheses for symbolic comparison, I looked to neuroimaging studies of reading. Against the background of data showing that left temporoparietal regions are involved in integrating orthographic, phonological and lexical–semantic dimensions of words during reading (Booth, Burman, Meyer, & Lei, 2003; C. J. Price, 2000; Pugh et al., 2001), I hypothesized that these regions may also play a role in symbolic number processing and, in particular, the association of numerical symbols with their quantitative referents.

2.2 Methods

2.2.1 Participants

Nineteen (10 females) adults (Mean age = 23.5 years, Range = 18.4–28.25 years) participated in this study. All participants were healthy, right-handed, and had normal or corrected-to-normal vision. Participants were recruited from graduate and undergraduate faculties at Dartmouth College, Hanover, NH, USA. All participants gave informed consent in accordance with the Committee for the Protection of Human Subjects at Dartmouth College. All fMRI scans took place at the Dartmouth College Brain Imaging Center.

To ensure that the fMRI data were not confounded by motion artifacts, I applied stringent criteria for the inclusion of functional data based on participants' motion. Specifically, only functional runs whose overall motion was less than one voxel (3 mm) across the entire run were included in the analysis. In addition, only functional runs with less than 2 mm motion between sequential functional volumes were included in the analysis. Participants were required to have at least one run for each condition that met these motion parameters to be included in the analysis. Every run from each participant met these criteria and thus no runs were removed from the analysis.

2.2.2 Task Design and Stimuli

2.2.2.1 General Features of Stimuli

The stimuli for each of the four tasks described immediately below were created using Adobe PhotoShop software and presented using SuperLab software (Cedrus Corporation, San Pedro, CA). All stimuli were white presented on a black background measuring 600 × 800 pixels. Stimuli were presented equidistant from a fixation dot that appeared between individual trials. See Figure 2.1 for an example of each stimuli type.

2.2.2.2 Symbolic Task

In the symbolic task, Arabic numerals 1–9 were presented measuring 200 pixels in height. Participants were asked to choose which side of the screen contained the larger number. The stimuli pairs used were: 1–6, 1–7, 1–8, 2–3, 2–4, 2–7, 2–8, 2–9, 3–4, 3–5, 3–6, 3–9, 4–6, 4–7, 4–9, 5–2, 5–4, 5–8, 6–5, 7–1, 7–2, 7–4, 7–5, 7–6, 7–8, 8–1, 8–

2, 8–3, 8–6, 9–2, 9–3, 9–6, and 9–7. The pairs 2–9, 8–1, and 8–3 were used twice resulting in a total of 36 stimulus pairs laterally counterbalanced across the three runs of the experiment for a total of 72 trials per condition. Blocks of trials consisted exclusively of either small numerical distances (1–3) or large numerical distances (5–7).

2.2.2.3 Non-symbolic Task

In the non-symbolic comparison condition, the same stimuli were used as those reported in three recently published studies (Holloway & Ansari, 2009; Price, Holloway, Räsänen, Vesterinen, & Ansari, 2007). Specifically, in this task, participants were asked to determine which of two arrays of white squares contained the larger numerosity. Each non-symbolic trial matched the number-pair parameters of a corresponding symbolic trial, e.g., a symbolic number comparison of 3 vs. 7 would correspond to a non-symbolic comparison of 3 squares vs. 7 squares. To control for the possible confound of continuous variables, the density, individual square size, and total area of each array was systematically varied across trials to ensure that numerosity could not be reliably predicted from variables continuous with it. Specifically, I first divided the 24 stimulus pairs into two groups of 12. In one of these groups, the larger numerosity had a larger overall area than the smaller numerosity. This pattern was reversed in the other group. Then, each group of 12 stimuli was further divided into two additional groups of 6 such that within each group of twelve, six of the stimuli with a greater overall area also had the greater density and six of the stimuli with a smaller overall area had the greater density. In addition to these controls, individual square size was also varied in each array. In this way, numerosity could not be reliably predicted from variables continuous with it.

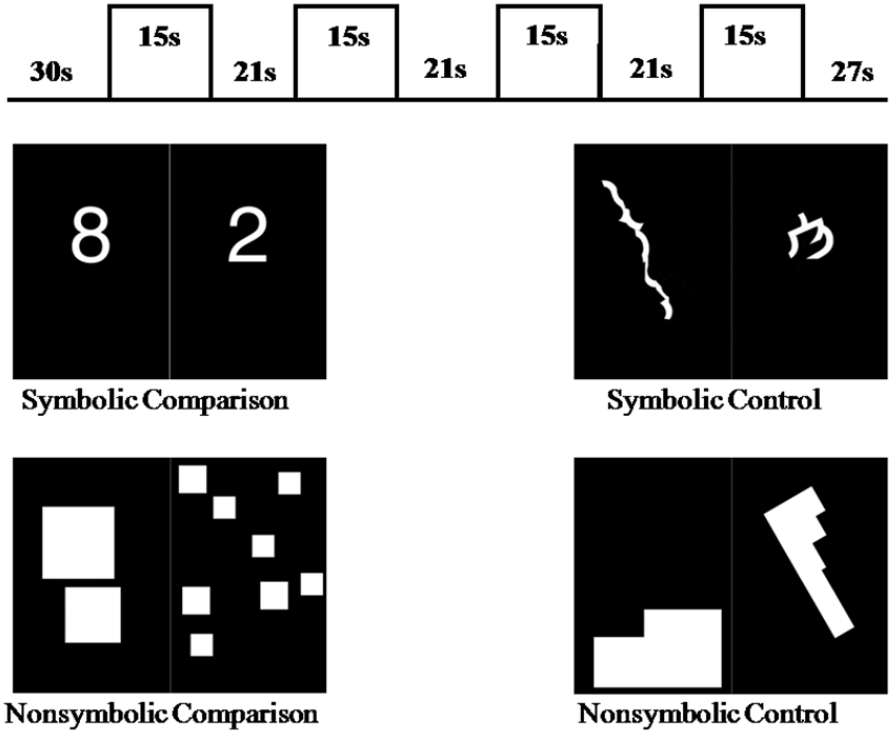

Figure 2.1 Experimental timing information and examples of stimuli. During symbolic comparison, participants chose which of two Arabic numerals was numerically larger. During non-symbolic comparison, participants chose which side of the screen contained more squares. The control tasks recombined the numerical comparison tasks into shapes and participants were asked to choose which of two shapes more closely resembled a diagonal line.

2.2.2.4 Control Tasks

The control tasks for both the symbolic and non-symbolic comparison tasks involved judging which of two stimuli more closely resembled a diagonal line. In this way, the control task, like the experimental task, involved making a selection between the two sides of the display. For the symbolic control task, the stimuli were created by dividing the Arabic numerals into segments which were then rotated and reconnected in arbitrary shapes that either unambiguously approximated a diagonal line or did not (see Figure 2.1 for an example of this). My symbolic control stimuli were thus very similar to stimuli used by Göbel et al. (2004). Using a similar procedure, the non-symbolic control task was created by combining the separate squares into either a shape that resembled a diagonal line or a shape that did not. The line-like stimuli were all constructed from the larger numerosity. In other words, when a participant was presented with a trial pairing 8 and 2 in the numerosity comparison tasks, a corresponding control task was created such that 8 was transformed into a line-like shape and 2 was transformed into a non-line-like shape. No visual information was added or subtracted from the stimuli. Thus the overall visual stimulation (the amount of white color in the display) in the control tasks is equivalent to the experimental tasks

2.2.3 Task Timing Parameters

A total of 12 functional runs was collected for each participant, three runs for each of the four conditions (see Figure 2.1). Each functional run contained blocks of only one type of comparison task. Functional runs began with 30s of fixation followed by four 15-second blocks of trials made up of 6 trials each. Each trial was 2.5s in length. The trials were further divided into 1200ms of stimulus presentation followed by 1300ms of fixation. Participants were instructed to choose which of the two sides of the screen corresponded to the correct answer. Subjects were asked to make the appropriate responses as quickly and accurately as possible by depressing the response button placed in their right hand if the correct answer was located on the right side of the screen and the response button placed in their left hand if the correct answer was located on the left side of the screen. The blocks of trials were separated by 21-second blocks of rest during which subjects were presented with a fixation dot and were not required to make any responses. After the final block of trials a block of rest was presented for 27 s before the run terminated. Thus, the total duration of each run was 3 min. Small and large distance blocks were alternated within a functional run.

2.2.4 Data Acquisition

Functional and structural images were acquired in a 3T Phillips Intera Allegra whole-body MRI scanner (Phillips Medical Systems, The Netherlands) using an 8-Channel Phillips Sense head-coil. A gradient echo-planar imaging $T2^*$ sequence sensitive to blood-oxygenation level-dependent (BOLD) contrast was used to acquire functional images. Functional images consisting of 30 non-contiguous slices were acquired in an interleaved order (4 mm thickness, 0.5 mm gap, 80 × 80 matrix, repetition time (TR): 3000 ms, echo time: 35 ms, flip angle: 90°, field of view 240 × 240 mm) covering the whole brain. For each functional run, 58 volumes were acquired. Each volume was collected using a standard Phillips MPRage 3-D sequence. Volumes consisted of 160 three-dimensional whole-brain high-resolution T1- weighted images collected in the sagittal plane and measuring 1 mm × 0.94 mm × 0.94 mm.

2.2.5 Data Analysis

Both structural and functional images were analyzed using Brain Voyager QX 2.0.7 (Brain Innovation, Maastricht, Netherlands). The functional images were corrected for differences in slice time acquisition, head motion, and linear trends. In addition, functional images were spatially smoothed with a 6-mm full width at half maximum Gaussian smoothing kernel. Following initial automatic alignment, the alignment of functional images to the high-resolution T1 structural images was manually fine-tuned. The realigned functional data set was then transformed into Talairach space (Talairach & Tournoux, 1988). A two-gamma hemodynamic response function was used to model the expected BOLD signal (Friston et al., 1998).

An initial whole-brain, random-effects conjunction analysis was conducted to reveal regions that responded to both numerical stimulus formats greater than their control conditions (symbolic − symbolic control) ∩ (non-symbolic − non-symbolic control). That is, this conjunction revealed regions that were significantly more activated in the numerical than the control task for both types of stimulus format. Following the conjunction, I conducted a whole-brain random-effects analysis, which examined differences in BOLD response to the two numerical formats (i.e., symbolic and non-symbolic). Before contrasting the two numerical formats with one another, I first subtracted out neural activation of the corresponding control tasks. Thus, this analysis revealed regions sensitive to differences in numerical stimulus format (symbolic − symbolic control) − (non-symbolic − non-symbolic control) after controlling for response selection and aspects of visual processing common to numerical and control tasks.

The conjunction analysis and contrast of numerical stimulus format were initially calculated using an uncorrected statistical threshold of $p < .005$ and $p < .001$, respectively. For the conjunction analysis, the lower statistical threshold was chosen since in a conjunction analysis two contrasts of interest must both significantly modulate the fMRI activation in a given region. For a conjunction analysis, the effective p-value is the square of the p-values for each component (in my case 0.005^2). Therefore, a more liberal threshold for such a conservative statistical procedure is justified. Both of the resulting statistical maps were subsequently corrected for multiple comparisons using cluster-size thresholding (Forman et al., 1995; Goebel et al., 2006). In this method, an initial voxel-level (uncorrected) threshold is set. Then, thresholded maps are submitted to a whole-slab correction criterion based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster-size that yielded a cluster-level false-positive rate ($\propto$) of 0.05 (1%) was used to threshold the statistical maps. Put another way, this method calculates the size that a cluster would need to be (the cluster threshold) to survive a correction for multiple comparisons at a given statistical level. Only activations whose sizes meet or exceed the cluster threshold are allowed to remain in the statistical maps.

Region of interest (ROI) analyses were conducted for the sole purpose of extracting parameter estimates from regions showing significant whole-brain effects. For each ROI analysis described below, the region was first defined from areas that showed significant activations in the whole-brain analysis. In other words, my regions of interest were not defined a priori, but instead were defined by my actual data and intended simply as further explorations of the whole- brain effects. A general linear model (GLM) was performed across all of the voxels that comprised a given ROI, leading to an average activation of voxels within the region of interest for each condition and subject. The resulting parameter estimates (beta weights) are standardized scores (*z*-scores). In each ROI analysis therefore, each subject has a beta weight from the GLM for each condition, which represents this average *z*-scored magnitude of the activation for all voxels in a given ROI for each condition.

I performed two specific types of ROI analysis. For both the conjunction and the contrast of stimulus format, I extracted beta weights for the four experimental conditions (symbolic, symbolic control, non-symbolic, and non-symbolic control). This afforded further offline statistical analysis of the relative differences in BOLD response for each of these conditions in each region and allowed my to assess to what extent format differences are differences in activation or deactivation of brain regions.

The second ROI analysis examined the effect of numerical distance on the regions found in the conjunction analyses. I did not perform the analysis of distance on the regions elicited by differences in numerical stimulus format as numerical distance was not the primary focus of my stimulus-format analysis. I included the analysis of numerical distance to investigate whether regions elicited by the conjunction analysis were sensitive to the semantic dimension of numerical magnitude for both stimulus formats. The blocks of trials in the numerical comparison tasks were separated into small and large distances (see above), which allowed my to model the effect of symbolic and non-symbolic numerical distance on the hemodynamic response. Accordingly, my second ROI extracted beta weights for the effect of symbolic and non-symbolic numerical distance from the areas implicated in the conjunction analyses. Both the effects of symbolic and non-symbolic distance were examined.

Finally, I performed a series of correlational analyses to rule out the possibility that the modulation of brain regions was due simply to differences in task difficulty between conditions. Specifically, I examined whether the magnitude of differences in BOLD activity in regions showing differences between numerical notations correlated with differences in accuracy and response time between numerical notations. I reasoned that if the difference between the neural response to symbolic and non-symbolic numerical processing in a given region was related to differences between reaction time and accuracy for symbolic and non-symbolic numerical processing, then the neural activation could be related to a general feature of the tasks rather than to numerical processing per se. However, if no correlation exists between BOLD activity and task performance, then I can be reasonably more certain that my findings reflect numerical processing rather than general task performance.

2.3 Results

2.3.1 Behavioural Results

Format differences in reaction time and accuracy of the *numerical* comparison tasks were analyzed in separate 2 (format: symbolic vs. non-symbolic) by 2 (task: numerical vs. control) repeated measures analyses of variance. The effect of numerical distance on reaction time and accuracy was analyzed in a similar way using separate 2 (format: symbolic vs. non-symbolic) by 2 (distance: small vs. large) repeated measures analyses of variance. For the distance effect analyses, the small distance level was created by averaging behavioral responses to distance 1–3 while the large distance level was formed by an average of behavioral responses to distance 5–7. For all analyses, significant interactions were further analyzed using Bonferroni-corrected *t*-tests. Because the accuracy data were skewed, I applied a logarithmic transformation to the data before submitting them to the analyses of variance and any follow-up *t*-tests.

2.3.1.1 Effect of Format Differences on Reaction Time

The analysis revealed a main effect of format in which the reaction times required for non-symbolic comparison (*M* = 548.1, *SD* = 128.8) were found to be higher than those required for symbolic number comparison (*M* =493.1, *SD* = 109.5), *F* (1, 18) = 25.4, $p < .001$, $\eta^2 = 0.59$. A main effect of task was also revealed by this analysis, such that the numerical comparison tasks (*M* = 577.6, *SD* = 121) required more time than the control tasks (*M* = 463.6, *SD* = 121.2), *F* (1, 18) = 65.2, $p < .001$, $\eta^2 = 0.78$. In addition, the effect of format differed by task *F* (1, 18) = 30.0, $p < .001$, $\eta^2 = 0.62$. In the numerical task, reaction times during symbolic comparison (*M* = 525.9, *SD* = 104.7) were significantly shorter than reaction times during non-symbolic comparison (*M* = 629.4.1, *SD* = 146.6), *t* (18) = − 5.7, $p < .001$ corrected. In contrast, the reaction times of the control tasks did not differ by format *t* (18) = − 0.8, *ns*.

2.3.1.2 Effect of Format Differences on Accuracy

Accuracy for all of the comparison tasks was all above 95%. Overall, more errors were made in the numerical tasks (*M* = 0.97, *SD* = 0.02) than the control tasks (*M* = 0.99, *SD* = 0.01), *F* (1, 18) = 16.9, $p < .01$, $\eta^2 = 0.48$. In addition, more errors were committed during the non-symbolic condition (*M* = 0.97, *SD* = 0.02) than the symbolic condition (*M* = 0.99, *SD* = 0.01), *F* (1, 18) = 19.9, $p < .001$, $\eta^2 = 0.53$. Bonferroni-corrected post-hoc analyses of the significant interaction between task and format, *F* (1, 18) = 13.4, $p < .01$, $\eta^2 = 0.43$, suggested that the lower accuracy in the non-symbolic (*M* = 0.95, *SD* = 0.03) compared with the symbolic condition (*M* = 0.99, *SD* = 0.02) was present in the numerical tasks, *t* (18) = 4.7, $p < .001$ corrected, but not the control tasks, *t* (18) = 2.3, *ns*.

2.3.1.3 Effect of Distance on Reaction Time

Reaction time for performing symbolic comparison (*M* = 525.9, *SD* = 104.7) was lower than that required for non-symbolic comparison (*M* = 629.4.1, *SD* = 146.6), *F* (1, 18) = 32.1, $p < .001$, $\eta^2 = 0.64$. In addition, numerical distance had a main effect on reaction time, *F* (1, 18) = 117.6, $p < .001$, $\eta^2 = 0.87$, with small distances (*M* = 651.6, *SD* = 138.3) requiring longer reaction times than large distances (*M* = 503.6, *SD* = 109.1). The effect of numerical distance on reaction time also depended upon the stimulus format, *F* (1, 18) = 49.5, $p < .001$, $\eta^2 = 0.73$. Specifically, reaction times to small distances were significantly longer in the non-symbolic condition (*M* = 743.9, *SD* = 183.3) compared with the symbolic condition (*M* = 559.3, *SD* = 109.4), *t* (18) = 6.7, $p < .001$ corrected, whereas large distances did not differ between stimulus formats, *t* (18) = 1.7, *ns*.

2.3.1.4 Effect of Distance on Accuracy

The analysis of the accuracy data revealed results very similar to those of the reaction time data. A main effect of format was found, *F* (1, 18) = 22.1, $p < .001$, $\eta^2 = 0.55$. More errors were made in the non-symbolic format (*M* = 0.95, *SD* = 0.03) than the symbolic format (*M* = 0.99, *SD* = 0.02). A main effect of distance was found such that more errors were made for small numerical distances (*M* = 0.95, *SD* = 0.03) than for large distances (*M* = 0.99, *SD* = 0.01), *F* (1, 18) = 30.3, $p < .001$, $\eta^2 = 0.62$. In addition, an interaction was found between distance and format, *F* (1, 18) = 20.6, $p < .001$, $\eta^2 =$

0.53. For small distances, significantly more errors were made for the non-symbolic stimuli (*M* = 0.92, *SD* = 0.05) than the symbolic stimuli (*M* = 0.98, *SD* = 0.03), *t* (18) = 4.9, *p* < .001. No difference between symbolic and non-symbolic formats was found for the large distances, *t* (18) = 0.1, *ns*.

2.3.2 Imaging Results

2.3.2.1 Conjunction Analysis

In a first analysis, the conjunction of numerical stimulus format was analyzed by conducting a voxel-wise *t*-test to examine which areas were significantly modulated by both symbolic and non-symbolic comparison relative to their control conditions (see Figures 2.2 and 2.3 and Table 2.1). Results from the conjunction analysis revealed several distinct regions whose activity was significantly greater than their controls. Of particular note, two of the regions revealed by the conjunction analysis were the right inferior parietal lobule (IPL) and right superior parietal lobule (SPL). In addition, the conjunction analysis revealed several additional regions including the inferior frontal gyrus extending up into the middle frontal gyrus, a region of the right anterior insula, the anterior cingulate, and the right superior frontal gyrus extending ventro-laterally into the middle frontal gyrus.

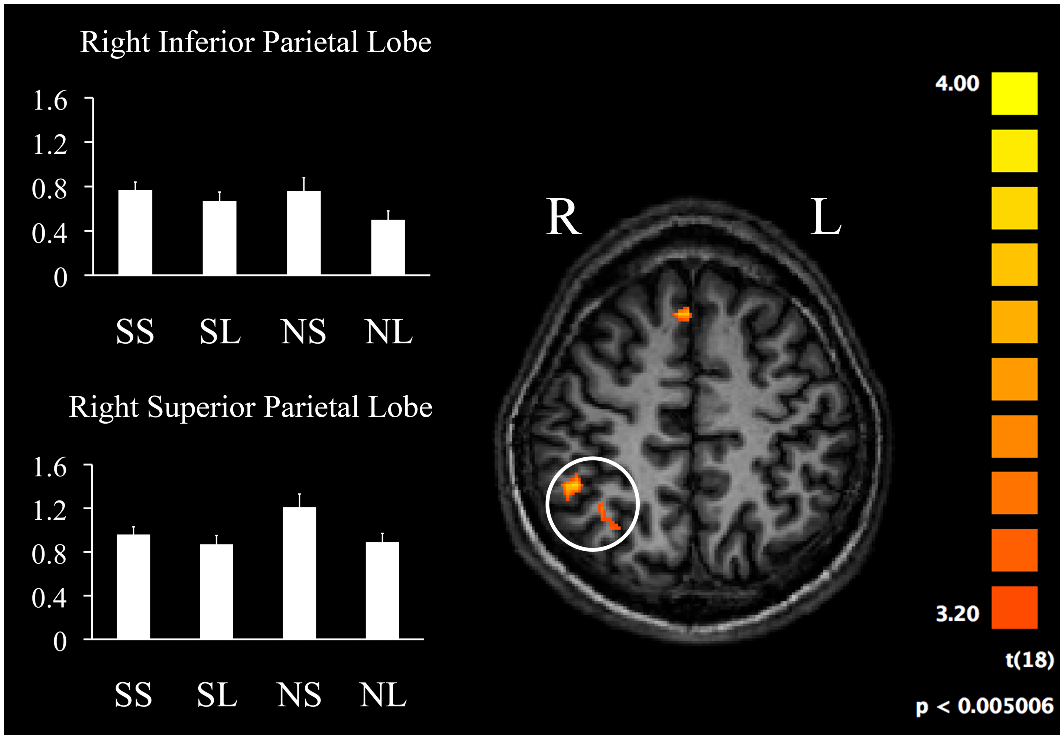

Figure 2.2 Statistical map illustrating activation elicited by conjunction of symbolic and non-symbolic comparison. Bar charts represent mean parameter estimates of activation across all participants in the inferior parietal lobe (above) and superior parietal lobe (below). Y-axis depicts BOLD signal represented in *z*-scores. Error bars represent standard error of the mean.

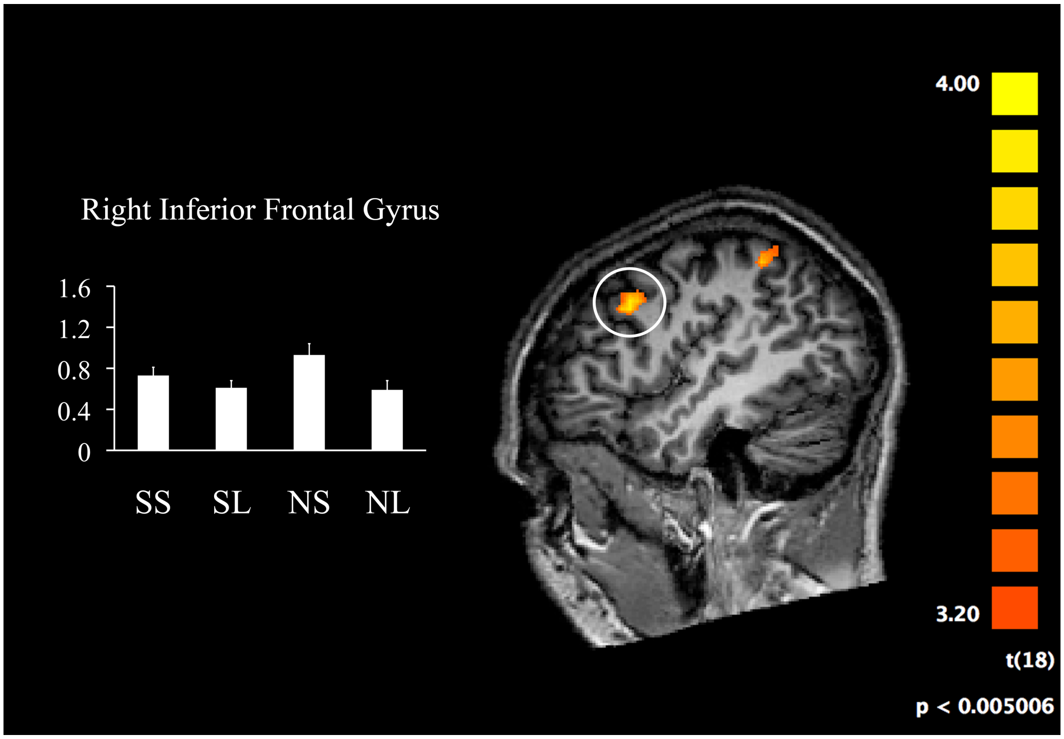

Figure 2.3 Statistical map illustrating activation elicited by conjunction of symbolic and non-symbolic comparison. Bar charts represent mean parameter estimates of activation across all participants in the right inferior frontal gyrus for symbolic small distance (SS), symbolic large distance (SL), non-symbolic small distance (NS) and non-symbolic large distance (NL). Y-axis depicts BOLD signal represented in *z*-scores. Error bars represent standard error of the mean.

2.3.2.2 Analysis of distance contrast in conjunction-defined regions

To examine the effect of numerical distance on these regions, I conducted a 2 (format: symbolic and non-symbolic) by 2 (distance: small and large) repeated measures ANOVA on each of the six regions implicated in the conjunction analysis. After applying a Bonferroni correction to control for type I error inflation due to multiple comparisons, four of the six regions showed a significant main effect of numerical distance. These included both the inferior parietal lobe, F (1, 18) = 10.0, $p < .05$, $\eta^2 = 0.36$ and the superior parietal lobe, F (1, 18) = 12.9, $p < .05$, $\eta^2 = 0.42$ (see Table 1). In addition, the activation of the anterior insula, F (1, 18) = 12.8, $p < .05$, $\eta^2 = 0.42$ and the inferior frontal gyrus, F (1, 18) = 14.1, $p < .05$, $\eta^2 = 0.44$ also reflected significant modulation by numerical distance. Importantly, none of these regions showed a significant format × distance interaction, which suggests that effect of numerical distance on the hemodynamic response was comparable in both symbolic and non-symbolic comparison. The anterior cingulate, on the other hand, showed no main effect of distance, but a significant format × distance interaction, F (1, 18) = 9.5, $p < .05$, $\eta^2 = 0.35$. Bonferroni-corrected *t*-tests indicated that this interaction is characterized by a significant effect of distance in the non-symbolic condition, t (18) = 3.2, $p < .05$, but not the symbolic condition, t (18) = 1.0, *ns*. The superior frontal gyrus showed no significant effect of distance or a significant format × distance interaction.

Table 2.1 Activations from conjunction analysis

	x	y	z	*k*	*t*	S	SC	N	NC	SS	SL	NS	NL
R inferior frontal gyrus	48	13	31	1322	3.7	0.7	0.5	0.8	0.4	0.7	0.6	0.9	0.6

R inferior parietal lobe	45	-41	49	254	3.4	0.7	0.5	0.6	0.4	0.8	0.7	0.8	0.5
R anterior insula	32	20	4	1678	3.5	0.7	0.4	0.8	0.5	0.8	0.6	0.9	0.6
R superior parietal lobe	30	-51	44	333	3.4	0.9	0.8	1.1	0.8	1.0	0.9	1.2	0.9
R superior frontal gyrus	20	11	58	504	3.5	0.4	0.3	0.6	0.3	0.5	0.3	0.7	0.5
R anterior cingulate	5	23	38	1373	3.5	0.7	0.5	0.8	0.5	0.8	0.6	1.1	0.5

Notes: List of the anatomical localization of the peak voxel for each activation, its coordinates, the number of voxels in each activated region, and the average *t*-statistic for each distinct activation elicited by the conjunction of stimulus format (symbolic − control) + (non-symbolic − control). The right side of the table lists the average parameter estimate for the symbolic (S), symbolic control (SC), non-symbolic (N), non-symbolic control (NC), symbolic small distance (SS), symbolic large distance (SL), non-symbolic small distance (NS), and non-symbolic large distance (NL) conditions.

2.3.2.3 Contrast of Stimulus Format

To examine the effect of numerical stimulus format, I conducted a voxel-wise *t*-test to examine the brain for regions which showed significant differences in activation between the symbolic and non-symbolic stimulus formats after subtracting out activity associated with the control tasks (see Figures 2.4 and 2.5 and Table 2.2). Nine regions were found. Seven of these areas showed greater activation in the non-symbolic condition relative to the symbolic condition. These included the posterior portion of the right superior parietal lobe, the anterior portion of the right inferior occipital gyrus, the right cuneus, the posterior aspect of the left occipital gyrus extending ventrally into inferior occipital gyrus, the left superior occipital gyrus extending down into the middle occipital gyrus, and the left middle occipital gyrus extending ventrally into inferior occipital gyrus. In addition, one very large region was found centered on the right superior occipital gyrus, which extended into the middle occipital gyrus and, at its extremes, to ventral aspects of the cuneus and very posterior aspects of the inferior parietal lobe. Note that the posterior right superior parietal lobe found in this contrast did not overlap with the more anterior portion of the superior parietal lobe elicited by the conjunction analysis (see Tables 2.1 and 2.2). Two regions showed greater modulation during the symbolic compared to the non-symbolic comparison task. They include the left angular gyrus and the left superior and middle temporal gyrus near their border with the supramarginal gyrus.

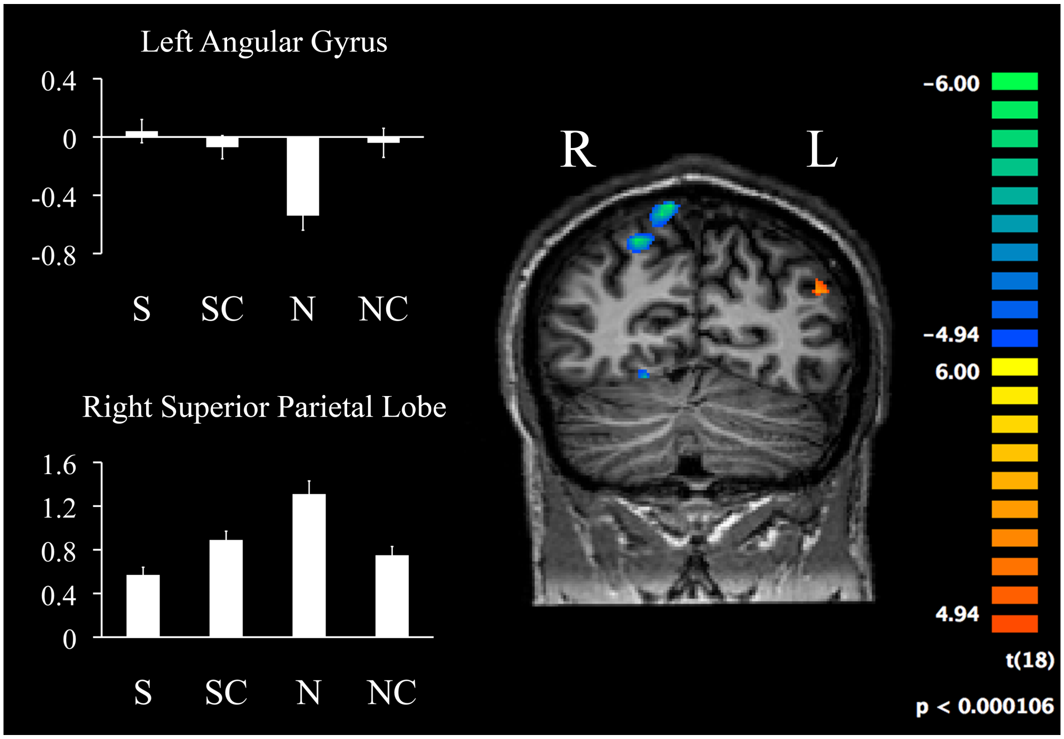

Figure 2.4 Statistical map illustrating activations elicited by contrast of stimulus format. Activations in blue areas that were modulated more by the non-symbolic compared with the symbolic tasks (after subtraction of the control tasks), while activations in orange represent regions showing relatively greater activation for symbolic compared to non-symbolic comparisons (after subtraction of the control tasks). Bar charts represent mean parameter estimates of activation across all participants in the left angular gyrus (above) and superior parietal lobe (below) for the symbolic condition (S), symbolic control condition (SC), non-symbolic condition (N) and non-symbolic control condition (NC). Y-axis depicts BOLD signal represented in *z*-scores. Error bars represent standard error of the mean.

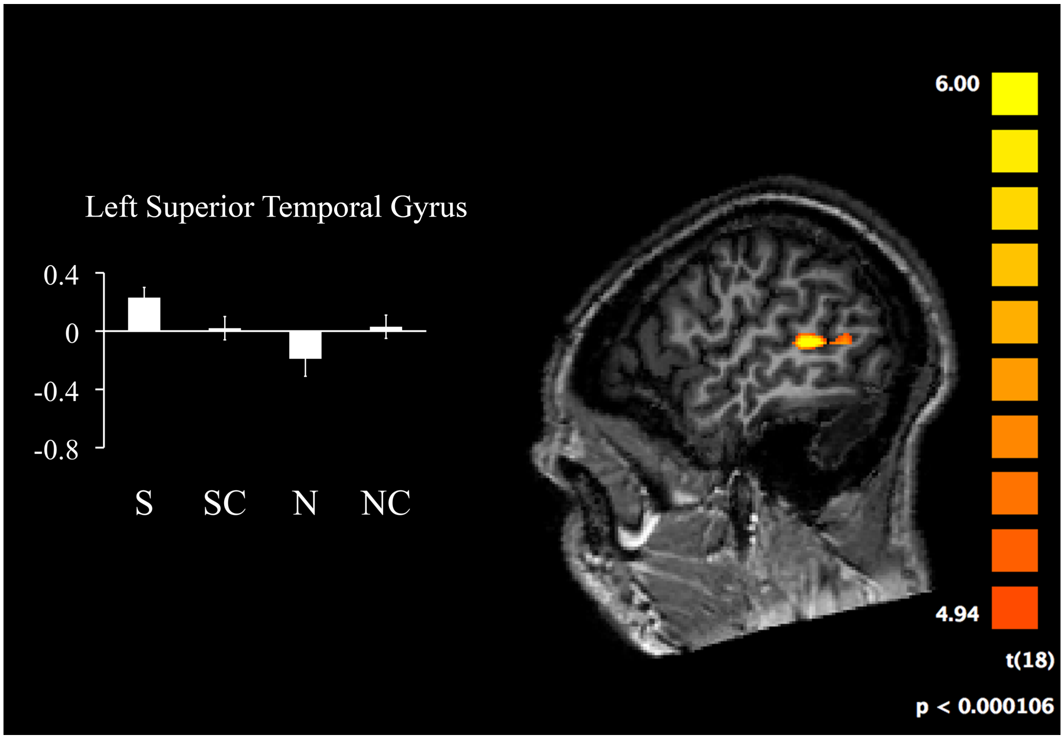

Figure 2.5 Statistical map illustrating activations elicited by contrast of stimulus format. Orange represent regions showing greater activation for symbolic compared to non-symbolic comparisons (after subtraction of the control tasks). Bar charts represent mean parameter estimates of activation across all participants in the left superior temporal gyrus for the symbolic condition (S), symbolic control condition (SC), non-symbolic condition (N) and non-symbolic control condition (NC). Y-axis depicts BOLD signal represented in *z*-scores. Error bars represent standard error of the mean.

Table 2.2 Activations from contrast of stimulus format

	x	y	z	voxels	t	S	SC	N	NC
R inferior occipital gyrus	49	-54	-2	122	-5.4	0.5	0.7	0.8	0.7
R superior occipital gyrus	29	-79	19	5183	-5.7	0.8	1.2	1.7	1.2
R superior parietal lobe	18	-64	53	2527	-5.5	0.6	0.9	1.3	0.8
R cuneus	9	-89	20	1294	-5.8	0.4	0.7	1.6	1.1
L superior occipital gyrus	-27	-77	23	1651	-5.5	0.8	1.2	1.6	1.1
L posterior superior occipital gyrus	-23	-91	18	161	-5.3	0.6	1.0	1.4	0.9
L middle occipital gyrus	-32	-84	6	252	-5.3	0.8	1.2	1.3	1.0
L angular gyrus	-43	-67	30	85	5.1	0.0	-0.1	-0.5	0.0
L superior temporal gyrus	-52	-44	11	496	5.5	0.2	0.0	-0.2	0.0

Notes: list of the anatomical localization of the peak voxel for each activation, its coordinates, the number of voxels in the activation, and the average *t*-statistic for each distinct activation elicited by the contrast of stimulus format (symbolic − control) − (non-symbolic − control). Right side of the table lists the average parameter estimate for the symbolic (S), symbolic control (SC), non-symbolic (N), and non-symbolic control (NC) conditions.

2.3.2.4 Analysis of Directionality of Effects in Contrast-defined Regions

In previous studies, some of the activations found in temporoparietal regions such as the angular gyrus have been shown to be reflective of relative deactivation in this region (Ischebeck et al., 2006; Shulman, Astafiev, McAvoy, D'Avossa, & Corbetta, 2007). I, therefore, examined the beta weights from each of the regions elicited by my contrast of stimulus format to determine the directionality of the effects. Of the nine regions found, only two of these involved relative deactivations. I examined the effects of task and format more closely in these two regions using separate 2 (format: symbolic vs. non-symbolic) by 2 (task: numerical vs. control) repeated measures analyses of variance, corrected for multiple comparisons using the Bonferroni method. In the angular gyrus, my analysis revealed both a significant main effect of format, $F\ (1, 18) = 16.0$, $p < .01$, $\eta^2 = 0.47$, and a significant main effect of task, $F\ (1, 18) = 10.3$, $p < .01$, $\eta^2 = 0.36$. These effects were not interpreted in light of the significant interaction between task and format $F\ (1, 18) = 36.2$, $p < .01$, $\eta^2 = 0.69$. Bonferroni correct *t*-tests indicated that the interaction was characterized by a significant difference between symbolic and non-symbolic numerical comparison, $t\ (18) = -\ 7.1$, $p < .01$, but no difference between the control conditions, $t\ (18) = -\ 0.307$, *ns*. In addition, a one-sample *t*-test revealed that the difference between the symbolic and non-symbolic numerical tasks was characterized by a significant deactivation of the angular gyrus during the non-symbolic condition, $t\ (18) = -\ 5.1$, $p < .001$ and no significant modulation in the symbolic condition, $t\ (18) = 0.52$, *ns* (for a visual representation of this see Figure 2.4). Thus, the interaction was characterized by a significant difference in numerical conditions (i.e., deactivation during non-symbolic and no significant modulation during symbolic) and no difference in modulation of the angular gyrus during the control conditions.

An identical analysis was conducted on the parameter estimates from the superior temporal gyrus. Neural activity in this region was characterized by a significant effect of format F (1, 18) = 21.9, $p < .001$, $\eta^2 = 0.55$ and a significant interaction between format and task, F (1, 18) = 64.9, $p < .01$, $\eta^2 = 0.78$. Bonferroni-corrected *t*-tests indicated that the interaction was defined by a significant difference between the numerical comparison conditions, t (18) = − 7.0, $p < .01$, but no difference between the control conditions, t (18) = − 0.079, *ns*. One-sample *t*-tests revealed that the difference in activation between the symbolic and non-symbolic numerical tasks was due to a significant deactivation during the non-symbolic numerical comparison, t (18) = − 2.8, $p < .05$ and a significant activation in the symbolic condition, t (18) = 3.5, $p < .01$ (for a visual representation of this see Figure 2.5). In the superior temporal gyrus, the interaction was defined by a significant difference in numerical conditions (i.e., deactivation during non-symbolic and significant activation during symbolic) and no significant modulation of this region during the control conditions.

2.3.2.5 Tests of Correlation between Parameter Estimates and Behavioral Measures

The behavioral data above revealed a difference in reaction time and accuracy between the symbolic and non-symbolic numerical tasks. The behavioral data above revealed a difference in reaction time and accuracy between the symbolic and non-symbolic numerical tasks. To rule out the possibility that format-related differences in brain activation were solely related to differences in general task performance, I performed a series of correlational analyses. Thus, for each subject I calculated two performance scores that reflected the difference in reaction time and accuracy between the symbolic and non-symbolic numerical conditions. I also calculated scores reflecting the difference in BOLD activity between the symbolic and non-symbolic numerical conditions for each region that showed a significant effect of stimulus format. No significant correlations were found between BOLD activity and performance, which suggests that the brain activation differences cannot be entirely explained by differences in task performance.

2.4 Discussion

In this study, I investigated the neural correlates of symbolic and non-symbolic numerical processing to elucidate commonalities and differences between the processing of numerical stimulus formats in the adult human brain. To examine which brain regions responded to both symbolic and non-symbolic formats of stimulus presentation, I investigated the conjunction of neural response to symbolic and non-symbolic comparison. This was followed by a contrast of numerical stimulus format to identify regions that responded differentially to symbolic and non-symbolic numerical processing. Below I discuss the results from these analyses in turn.

2.4.1 Conjunction of stimulus format

The conjunction of symbolic and non-symbolic stimulus formats revealed several areas previously shown to be engaged by numerical comparison including the right superior parietal lobe (Chochon et al., 1999; Eger et al., 2003; Pesenti et al., 2000), the right superior frontal gyrus (Chochon et al., 1999; Pinel et al., 1999), the inferior frontal gyrus (Pinel et al., 1999), and the right anterior cingulate (Chochon et al., 1999; Pinel et al., 1999). Most notably, this analysis supported my prediction that inferior parietal regions would be activated by the conjunction of symbolic and non-symbolic numerical comparison. This result is commensurate with a growing body of neuroimaging studies showing that this region is engaged by numerical processing tasks in symbolic formats (Ansari et al., 2005; Chochon et al., 1999; Eger et al., 2003; Pesenti et al., 2000; Pinel et al., 1999, 2001), non-symbolic formats (Ansari & Dhital, 2006; Ansari et al., 2006; Cantlon et al., 2006; Piazza et al., 2004, 2007), and both (Venkatraman et al., 2005). My findings also converge with previous research by Fias et al. who demonstrated the IPL to be involved in the processing of both numerical (Hindu–Arabic numerals) and non- numerical (line length and angle size) magnitudes (Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003).

However, the notion that parietal responses during number comparison are specifically related to the processing of numerical magnitude has not been uncontroversial. In particular, Göbel et al. have challenged the findings of previous numerical comparison studies implicating the parietal cortex in the processing and representation of numerical magnitude by demonstrating that inferior parietal regions (in particular the intraparietal sulcus) are engaged to an equal extent when participants are required to select one of two non-numerical stimuli (Göbel et al., 2004). Since all numerical comparison tasks contain a response selection component, it is difficult to determine whether the activation in response to numerical comparison is reflective of numerical processing or response selection. However, by using control stimuli very similar to the stimuli used by Göbel et al., I was able to avoid this confound. The activations shown in the present study were present even after controlling for response selection components of the tasks (selecting one of two sides of the display by means of a button press).

The results of the conjunction analysis revealed inferior parietal activation that was found to be right lateralized. Similar lateralization has been demonstrated in other neuroimaging research of numerical processing. In particular, Chochon et al. compared numerical comparison to arithmetic tasks. They showed that the right, but not left, parietal cortex is modulated by nonverbal numerical processing and thus concluded that the right parietal lobe houses an analog representation of numerical magnitude (Chochon et al., 1999). This conclusion was later supported by Piazza et al. who demonstrated format-general representation of numerical magnitude only in the right parietal lobe (Piazza et al., 2007). The present data converge with these previous data and implicate the right parietal lobe in format-general numerical representation.

Recently, Cantlon et al. (2009) published a report documenting the ontogenetic development of a format-independent representation of numerical magnitude. In this study, the authors used comparison tasks that were highly similar to the ones used in this study. Using a conjunction analysis between symbolic and non-symbolic numerical comparison, the authors showed that adults show stronger activation relative to children in the left superior parietal cortex. However, when these authors examined only the adult participants, they found that adults recruited bilateral parietal regions extending along the intraparietal sulcus from the superior to the inferior parietal lobules. Thus, my data are commensurate with those reported by Cantlon and colleagues in that both studies implicate parietal regions in the format-independent processing of numerical magnitude. The specific regions revealed in these two studies (right lateralized intraparietal suclus in my study and bilateral IPS in Cantlon et al.'s study) are, overall, quite similar. The differences in the parietal activation between the two studies are likely due to my use of a control task in addition to the numerical comparison tasks. It will be important for future studies of the development of numerical representation to include appropriate control tasks to distinguish developmental differences in number-related activation from developmental differences in task-specific and domain-general response selection mechanisms.

In addition to parietal regions, the conjunction analysis also revealed that the right inferior frontal gyrus was significantly activated by both symbolic and non-symbolic representations of numerical magnitude. While the precise role of this region in numerical magnitude processing is unclear, recent research has suggested that this region might be mediating a connection between symbolic and non-symbolic representations that is crucial for the establishment of connections between numerals and their semantic referents (Cantlon et al., 2009; Diester & Nieder, 2007). My data are commensurate with this hypothesis in that both symbolic and non-symbolic representations activate this region.

2.4.2 Contrast of stimulus format

2.4.2.1 Regions responding to non-symbolic numerical processing

The contrast of numerical stimulus format revealed regions that were differentially activated by the surface format in which quantities were represented. It should be noted that these format-related differences emerged after subtracting away the variance related to the control tasks. These control tasks included a response selection component (depressing a button underneath the side of the display that most closely resembled a line) and were equated with the experimental tasks in terms of the number of white pixels that were visually presented.

The contrast of non-symbolic vs. symbolic number comparison revealed a large area of the visual cortex, which reflects the greater visual demands of the non-symbolic condition. This activation could reflect aspects of visual processing that were not accounted for by the control task such as processing the density of an array. However, it is also possible that some of the activation in the visual cortex reflects visual processing necessary for non-symbolic numerical processes such as the individuation and summation of the white squares. Future studies specifically targeting the role of visual aspects in non-symbolic numerical processing are needed to clarify this issue further. In addition to these visual regions, the non-symbolic condition also activated a region of the right posterior superior parietal lobe—an area that has previously been implicated in non-symbolic number processing by several other studies (Ansari et al., 2006; Cantlon et al., 2006; Piazza et al., 2004, 2007).

The involvement of the posterior superior parietal lobe in non-symbolic numerical processing confirms my prediction put forward in the introduction. Specifically, at the outset of this paper I proposed that this region would be involved in non-symbolic numerical processing due to its role in the summation coding necessary for processing non-symbolic quantities. Indirect support for the role of the posterior superior parietal lobe in summation coding can be found in recent research in monkeys and humans. Roitman et al. recently demonstrated that the LIP of macaque monkeys contains neurons whose firing rate increases monotonically with the number of non-symbolic items presented (Roitman et al., 2007). Thus, the behavior of these neurons reflects a summing of the objects (summation coding) in a visually presented non-symbolic array. Behavioral research has demonstrated the existence of summation coding in humans (Roggeman et al., 2007). Furthermore, recent neuroimaging work has demonstrated that the superior parietal lobe (Talairach coordinates: 21, − 67, 57) is involved in non-symbolic, but not symbolic, numerical processing and, consistent with the summation coding, is modulated by the set size of non-symbolic numerical magnitudes (Santens et al., 2010). Other neuroimaging work has provided evidence that the superior parietal lobe in humans is the homologue to the LIP of macaque monkeys (Koyama et al., 2004; Sereno et al., 2001). More specifically, Koyama and colleagues elicited LIP activation in macaque monkeys and SPL activity in humans using identical visually-guided saccade tasks. The authors reported bilateral activity in the human SPL that was homologous to the LIP activation in macaques. The Talairach coordinates of the peak voxel for the right SPL in that study were reported as 19, − 63, 49. To quantify the proximity of that activation with the SPL activation elicited by my contrast of stimulus format, I calculated the Euclidean distance between them. The activations reported by Santens et al. and Koyama and colleagues are quite close ($d = 4.69$ and 4.24, respectively) to the peak voxel of my SPL: 18, − 64, 53. Taken together, these data support my claim that the activity of the superior parietal lobe in non-symbolic comparison may reflect this region's role in summation coding.

This explanation is also consistent with the predictions put forward in the Verguts and Fias (2004) model. This model predicts that non-symbolic quantities initially undergo a format-specific summation process and are subsequently represented in a format-general, place-coded manner. Against the background of this model, my data suggest that the posterior superior parietal lobe is involved in the summation coding necessary for enumerating a non-symbolic array.

Importantly, the right superior parietal activation elicited by the contrast of stimulus format did not overlap with the right superior parietal activation elicited by the conjunction analysis, *d* = 19.8. Specifically, the region from the conjunction analysis (peaking at 30, − 51, 44) was more ventral, lateral and anterior relative to the region from the contrast of stimulus format peaking at (18, − 64, 53). In addition, this region from the conjunction analysis, was much further removed, relative to the superior parietal lobe elicited by the contrast of stimulus format, from the purported homologue of the LIP reported by Koyama and colleagues, *d* = 17.0. Further research should clarify how the involvement of the posterior superior parietal lobe in non-symbolic processing is related to other processes associated with this region such as saccadic eye movements (Koyama et al., 2004) or visual attention (Corbetta & Shulman, 2002; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002). Indeed, because my study did not control for participants' eye movements, it is impossible to completely disambiguate eye movements from summation coding in the superior parietal lobe using the current data. It is therefore possible that the activation I show in the superior parietal lobe is related to saccadic eye movements. However, it should be kept in mind that eye movements are an integral part of the process underlying the enumeration of arrays of items. One possibility is that over the course of evolution, domain-general competencies such as visual attention and saccades served as a foundation upon which a summation system was built.

2.4.2.2 Regions involved in symbolic number processing

The contrast of stimulus format revealed two regions in the left hemisphere which showed statistically greater modulation in response to symbolic relative to non-symbolic comparison: the left angular and the left superior temporal gyri. The left angular gyrus has long been associated with numerical processing. For example, damage to this region is associated with a variety of symptoms including impairments in calculation (Gerstmann, 1940). Several neuroimaging studies have demonstrated empirically that the left angular gyrus is important for calculation (Burbaud et al., 1999; Roland & Friberg, 1985; Rueckert et al., 1996), may be more involved in exact than approximate calculation (Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999; Venkatraman et al., 2005), and is likely involved in arithmetic fact retrieval (Delazer, 2003; Delazer et al., 2005; Grabner et al., 2009). The present study is the first to demonstrate the role of the left angular gyrus in basic numerical processing in the absence of calculation. My data suggests that this region is not restricted to the retrieval of arithmetic facts, but instead, with the superior temporal gyrus, may play a more general role in symbolic numerical processing.

Convergent evidence for the left angular gyrus' specific involvement in basic symbolic numerical processing can be found in a recent study examining the neural correlates of calculation in adults (Grabner et al., 2007). Specifically, this study compared the effect of individual differences in mathematical competence on brain activation patterns during single and multi-digit multiplication as well as a control task where participants judged whether three Hindu–Arabic numerals were identical or not. Interestingly, the authors showed that even in the control task, which involved absolutely no calculation, but merely asemantic processing of Arabic numerals, mathematical competence modulated activation of the left angular gyrus in a similar way as for calculation. Against the background of these results, the authors argued that the differences in angular gyrus activation could reflect group differences in the amount of stimulus-driven access to the semantic information represented by the symbolic numerals.

Another region directly adjacent to both of the neural loci found in my study, the left supramarginal gyrus, has also been implicated in symbolic numerical processing. Roux et al. showed that direct electrostimulation of the cortex disrupted reading of numerical symbols in the supramarginal gyrus of the dominant hemisphere (Roux, Lubrano, Lauwers-Cances, Giussani, & Démonet, 2008). Further evidence to implicate the left temporoparietal cortex in the processing of numerical symbols comes from a neuropsychological study. In their study of a patient with a focal lesion of white matter directly beneath the left anterior supramarginal gyrus, Polk et al. presented evidence for a specific role of the supramarginal gyrus in symbolic but not non-symbolic number processing (Polk, Reed, Keenan, Hogarth, & Anderson, 2001). As a result of the lesion, the patient presented with a severe deficit in the processing of numerical symbols, while retaining intact non-symbolic numerical processing.

Together with these findings, my study could suggest a broader role of the left temporoparietal junction (composed of the angular, supramarginal gyri and the posterior aspect of the superior temporal gyrus) in symbolic number processing. While the exact role of the left angular and superior temporal gyri in symbolic number processing cannot be directly addressed by my data, a review of neuroimaging studies of reading yields an interesting possibility for how they may be involved in processing numerical symbols. Neuroimaging research has found the left angular gyrus (Booth et al., 2003; Joseph, Cerullo, Farley, Steinmetz, & Mier, 2006; McDermott, Petersen, Watson, & Ojemann, 2003; Pugh et al., 2001) and left superior temporal regions (Raij, Uutela, & Hari, 2000; van Atteveldt, Formisano, Goebel, & Blomert, 2004) to be involved in the integration of letters (graphemes) with speech sounds (phonemes). I propose that my results may reflect similar roles for these regions in the numerical domain. The greater involvement of the left angular and superior temporal gyri in symbolic relative to non-symbolic processing could reflect this region's role in processing the connection between numerical symbols and their quantitative referents (numerical magnitude). In the case of the left angular gyrus, the symbol-to-referent mapping hypothesis can explain both my findings and previous work implicating this site in calculation. The association between an arithmetic equation and its result, on the one hand, and the mapping between a numerical symbol and its numerical magnitude, on the other hand, could both involve the angular gyrus. Here the common denominator is the role it may play in mapping between a visual form and its semantic referent. This hypothesis is directly in line with the one put forth by Grabner and colleagues, suggesting that “in addition to being involved in the automatic retrieval of arithmetic facts, the angular gyrus also mediates the mapping between symbols and numerical magnitudes" (p. 354).

Compared to the non-symbolic condition, the degree to which my symbolic findings converge with the model put forth by Verguts and Fias is less straightforward. While these authors predicted that non-symbolic processing would require summation coding, the nature of the "symbolic field" in their model was described in much less detail. However, one feature must be present in order for this input field to be truly symbolic. A symbolic relationship requires there to be an integration of at least two distinct types of representation. For example, the symbolic relationship embedded in a written word requires the reader to integrate a visual representation with an auditory representation which is itself symbolically related to a semantic representation. Thus, a given symbolic relationship involves distinct representations and the connection between them. Therefore, although not explicitly stated by Verguts and Fias, the processing underlying the "symbolic (number) field" should be characterized by similar properties. Put most simply, such symbolic processing would involve a visual external representation of the numeral, a semantic internal representation of numerical magnitude (shown in this study to be housed in the right parietal lobe) and a connection between these. As these brain regions have not been associated with basic visual processing, I contend that the angular and superior temporal gyri are not involved in the processing of the visual features of the symbolic (Hindu–Arabic) numerals. Instead, and especially given their involvement in cross-modal integration in reading, I suggest that these regions support the processing of the symbolic relationship between the visual and numerical representations of symbolic numerals.

An alternate explanation of the activity of the temporoparietal junction in my study is that it reflects the processing of verbal number words associated with numerical symbols rather than a connection between symbols and their semantic referents. In his influential “Triple Code Model,” Dehaene suggests that one aspect of numerical information is verbal in nature (Dehaene, 1992) and that this verbal code is localized in the left angular gyrus (Dehaene et al., 2003). It is possible that the participants in my study were covertly saying the names of the Arabic numerals during symbolic numerical comparison. Thus, my data are commensurate either with the verbal hypothesis of Dehaene or with the symbol-to-referent mapping hypothesis put forth by Grabner and colleagues. To distinguish between these hypotheses, future studies must be designed that decompose symbolic number processing into its verbal and non-verbal components.

It should be mentioned that other recent data suggest that the prefrontal cortex is important for the creation of neural associations between numerical symbols and parietally-mediated numerical representations in monkeys (Diester & Nieder, 2007). In a training study, these authors trained monkeys to associate symbolic numerals with non-symbolic numerical arrays. The authors found neurons in the prefrontal cortex that respond preferentially to symbolic and non-symbolic numbers as well as neurons that respond to both stimulus formats and suggested that this region is involved in forming the connection between a numerical symbol and numerical representations. These data do not necessarily conflict with ours. Indeed, my conjunction analysis revealed right inferior frontal gyrus activation during the processing of both symbolically and non-symbolically presented numerical information. Unlike Diester and Nieder, however, I found no evidence of prefrontal activation that reflects preferential processing of symbolic or non-symbolic numerical processing alone. Taken together with the results presented by Diester and Nieder, my findings could suggest that while prefrontal areas are involved in the initial establishment of associations between numerical symbols and quantitative referents, the temporoparietal region revealed in my data reflects development of efficient activation and retrieval of those associations. However, this explanation does not completely account for why the prefrontal cortex is activated by both symbolic and non-symbolic numerical magnitudes. Future research must clarify the role of the prefrontal cortex in the numerical magnitude processing of both children and adults.

It is important to note that the activity in the angular gyrus is defined by deactivations relative to baseline. Although relatively common (Dehaene et al., 1996; Grabner et al., 2007; Ischebeck et al., 2006; Rickard et al., 2000; Shulman et al., 2007; Venkatraman, Siong, Chee, & Ansari, 2006; Zago et al., 2001), the nature of such deactivations is currently unresolved in the literature. One possibility is that the deactivations in the angular gyrus relate to task difficulty. Two of the above studies observed that greater deactivation was found in response to increased difficulty of the tasks being performed (Ischebeck et al., 2006; Zago et al., 2001). However, the deactivation in my study cannot be explained through a similar appeal to task difficulty. My pattern of reaction times showed that the non-symbolic comparison was more difficult than symbolic comparison, which in turn, was more difficult than either control task. If activity in this region were defined solely by task difficulty, one would expect to see greater deactivation in the more demanding symbolic condition than the control tasks. However, inspection of the beta weights suggest that the activity in response to the symbolic condition in the left angular gyrus was actually slightly, non-significantly higher than the activation related to the control tasks. Thus a pure task difficulty explanation cannot hold, as it should generalize to differences between the symbolic and control tasks, where a reaction time difference was also found.

A different explanation for neural deactivation has been put forth by Shulman et al. in a study of visual attention (Shulman et al., 2007). These authors showed that when participants searched presentations of distracter objects for a visual target, the right supramarginal gyrus (a region adjacent to the angular and superior temporal gyri) was significantly deactivated until the target was detected. Shulman et al. suggested that deactivation of this region inhibits stimulus-driven reorientation of attention to inappropriate stimuli and, in this way, acts as a neural stimulus filter. In this view, deactivation can serve a functional role in the performance of cognitive tasks.

I have proposed that the left temporoparietal areas found in my study are a network of brain regions that serve to process the connection between numerical symbols and their quantitative referents. Against the background of the Shulman et al.

findings, I tentatively hypothesize that deactivation of the left TPJ may serve a key function in the symbol-to-referent mapping attributed to this region. Specifically, the deactivation of the TPJ in response to non-symbolic stimuli, in concert with its activation in response to symbolic stimuli (in the superior temporal gyrus), could reflect these regions' joint role as a stimulus filter or gateway that allows differential access to numerical representations dependent upon the stimulus format of the number being presented. When individuals are presented with a non-symbolic numerical array, access to the quantity represented by the array may be indirect and mediated through the summation coding of the right superior parietal lobe. In contrast, presentation of an Arabic numeral could trigger a more direct access to the numerical representation with which it is associated and, hence, an absence of suppression (relative to baseline). Thus, the filter would not be engaged when representations can be mapped onto their semantic referents without further processing. This hypothesis should be explored using functional connectivity analysis in the context of an event-related fMRI study. It should be acknowledged that in the presence of significant deactivation in the left AG during non-symbolic comparison and no significant activation during symbolic comparison, it is difficult to ascertain, from the present findings, whether the pattern of relative deactivation of the left AG in the present study indicates anything about the processing of the symbolic stimuli or whether it merely reflects a function relevant to the processing of the non-symbolic stimuli. Thus the present hypothesis of a filtering mechanism is speculative and requires follow-up research. In contrast the pattern of activation from the left STG is much clearer, where significant activation during symbolic but neither non-symbolic nor control conditions is observed. Thus, my data provide clearer support for the involvement of the left STG in symbolic number processing than they do for the left AG.

In sum, the present study revealed brain regions involved in processing different numerical stimulus formats. I have shown a pattern of results that fits into the model of stimulus format processing put forth by Verguts and Fias (2004). These authors predicted that differential pathways are responsible for encoding a quantity from either symbolically or non-symbolically represented numbers. These differential pathways were then predicted to converge on a format- general representation of numerical magnitude. My data provide support for these predictions and identify key regions that might mediate different functions predicted by the Verguts and Fias model. In particular, a comparison of symbolic and non-symbolic numerical processing reveals different regions involved in these numerical stimulus formats in the left temporoparietal regions and the right posterior superior parietal lobe, respectively. In addition, I demonstrated that a conjunction between symbolic and non-symbolic numerical processing reveals regions in the right inferior parietal lobe and anterior superior parietal lobe, regions long associated with numerical representation. Thus, this study starts to map out the pathways that mediate numerical stimulus format processing in the human brain. I have demonstrated that while there is evidence for a common abstract representation of numerical magnitude, there are also important differences in the pathways mediating the mapping from external representations to internal ones. These mappings should be investigated developmentally to clarify more precisely how this mapping emerges through interplay of education and brain maturation.

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Interim Summary

In the previous chapter, I report evidence for common and distinct neural correlates underlying symbolic and non-symbolic numerical magnitude processing. These data revealed that numerical symbols are associated with activation in the left superior temporal gyrus and the left angular gyrus. In addition, the right intraparietal sulcus (IPS) was activated by both the symbolic and non-symbolic formats, presumably due to its role in representing and processing the numerical magnitude embedded in numerical stimulus formats at an abstract level. These activations yield questions that will be addressed in the next two chapters of the thesis.

One of the goals of this thesis was to investigate the semantic processing of numerals. Chapter 2 indicates that the right IPS was recruited when participants made symbolic and non-symbolic numerical comparisons, which implies that this region is involved in representing the numerical magnitude of number symbols. However, this conjunction analysis, which is designed to identify commonalities, cannot provide any information about the neural correlates that are specific to numerals and their semantic representation in the brain. The contrast of symbolic and non-symbolic comparison is not ideally suited to identify regions specifically involved in the semantic processing of numerical symbols. Regions emerging from a symbolic vs. non-symbolic contrast could reflect differences in input-to-representation mechanisms, differences in representational mechanisms, differences in mechanisms needed to complete the tasks, or any combination of the three. A more elegant way to identify regions involved in the semantic processing of numerals is to compare numerical symbols that have a semantic referent with those that do not. Such an analysis can, in principle, reveal cortical sites that are specifically involved in the semantic processing of numerals. This reasoning inspires Chapter 3, which compares the semantic and asemantic processing of numerical symbols.

Chapter 3: Semantic and perceptual processing of number symbols: evidence from a cross-linguistic fMRI adaptation study

3.1 Introduction

The ability to understand and use numerical symbols is a culturally transmitted skill. Like literacy, symbolic numeracy only exists in cultures where it is explicitly instructed. The theoretical foundation (Dehaene, 1997) guiding the study of numerical cognition posits that symbolic numerical processing is scaffolded by a system of non-symbolic numerical representation—one that is phylogenetically continuous (Brannon, 2006), ontogenetically foundational (Libertus & Brannon, 2009), and culturally universal (Gordon, 2004; Pica, Lemer, Izard, & Dehaene, 2004; Zebian & Ansari, 2012). This non-symbolic system of numerical magnitude, often called the Analog Number System (ANS), is populated by neural representations of quantity that are imprecise in nature (Nieder & Dehaene, 2009). The representational imprecision can also be seen in symbolic representations of number, which suggests that numerical symbols are associated with the approximate magnitude representations of the ANS (Dehaene, 1989; Dehaene, Dupoux, & Mehler, 1990; Duncan & McFarland, 1980; Hinrichs, Yurko, & Hu, 1981; Moyer & Landauer, 1967; Restle, 1970; Sekuler & Mierkiewicz, 1977). To date, little is known about how this process of associating numerical symbols occurs in the human brain or what effect the "symbolization" of numerical magnitude has on the intrinsic representations of quantity. Extant research has utilized three strategies to examine the neural correlates underlying acquired brain representations for numerical symbols: 1) comparison of symbolic with non-symbolic numerical processing; 2) examination of ontogenetic changes in symbolic number processing; 3) training individuals to associate numerical magnitudes with novel symbols. Below, I briefly outline each of these approaches and their associated findings before introducing a novel approach to understanding the neural representations of numerical symbols, which is the focus of this report.

Following the first approach, a growing body of research comparing symbolic with non-symbolic processing (Chochon, Cohen, van de Moortele, & Dehaene, 1999; Holloway, Price, & Ansari, 2010; Piazza, Pinel, Le Bihan, & Dehaene, 2007) has suggested that processing numerical symbols is associated with activation of the parietal cortex. When comparing symbolic and non-symbolic numerical magnitude processing, hemispheric differences in the parietal cortex have been observed. While the non-symbolic representation of number has been associated with activity in the bilateral intraparietal sulcus (Dehaene et al. 2003), data from investigations using symbolic stimuli have converged to suggest that the left IPS may become specialized for the processing of numerical symbols (Ansari 2008). While these results are promising, it must also be acknowledged that symbolic and non-symbolic numerical stimulus formats are, perceptually, quite different. Indeed, previous research has suggested that the processes involved in encoding numerical magnitude from symbolic and non-symbolic formats are underpinned by distinct neural circuits (Holloway et al. 2010). In view of this, any differences between symbolic and non-symbolic processing may represent encoding, representation or both. Therefore, while comparisons of symbolic and non-symbolic processing can provide a broad understanding of the neural processing of numerical symbols, they cannot specifically address the brain changes that occur when an arbitrary shape becomes a semantically-rich numerical symbol.

The second approach investigates the effects of learning symbolic number representations by comparing age-related differences in the neural representation of numerical symbols. This approach has been taken by several studies. These studies have shown that the processing of numerical symbols undergoes an age-related shift in locus of activity from prefrontal regions earlier in development to inferior parietal regions later in development. Together, they suggest that the parietal lobe becomes tuned to numerical symbols over time (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon et al., 2009; Holloway & Ansari, 2010; Houdé, Rossi, Lubin, & Joliot, 2010; Kaufmann et al., 2006). Using developmental time as an independent variable affords a more direct way of investigating how numerical symbols come to be associated with internal representations of numerical magnitude. However, as with all developmental research, it remains unclear whether the shift from frontal to parietal regions reflects enculturation processes, brain maturation, or both.

One neuroimaging study has used the third approach to investigate the neural consequences of training individuals to associate numerical magnitude with novel symbols (Lyons & Ansari, 2009). These authors trained a group of adults to associate novel symbols with non-symbolically presented numerosities (dot arrays) while fMRI data were recorded. Activity in the left inferior parietal cortex was systematically-related to individual differences in how well novel symbols were connected to their semantic referents, giving further credence to the notion that left parietal regions become attuned to the semantic information associated with numerical symbols. Because this study was conducted with adult participants, the findings can be linked to learning-related processes independent of brain maturation. However, it is unclear exactly how the association of novel symbols with non-symbolic quantities is related to the learning of numerical symbols that occurs through enculturation, which involves a highly complex and developmentally-protracted interplay of representations (verbal, semantic, and visual) and skills (subitizing, counting, and ordering). Indeed, a moment of introspection reveals that the visual form “31” does not elicit an imprecise image of approximately 31 dots, but rather calls forth a variety of mental representations including a distinct verbal tag, the knowledge of where 31 falls on a number line, and a quantitative understanding of “31-ness.” Thus, while providing important clues to the neural processes underlying numerical symbol-to-referent mapping, the neural correlates elicited by such a training study should be considered as suggestive of, rather than equivalent to, the neural correlates of numerical enculturation.

In the present study, I propose an alternative to the three approaches described above. An ecologically valid way to examine symbolic number processing is to study differences in the neural responses to known and unknown symbolic representations of numerical magnitude. For example, individuals who are raised reading Chinese learn two different symbolic number systems: the Hindu-Arabic numerals and the logographic system of Chinese numerical ideographs. In contrast, individuals who learn to read languages such as English or Polish become fluent in using the Hindu-Arabic numeral system, but have no knowledge of Chinese ideographs. It is possible, therefore, to utilize these naturally occurring groups to create an experimental scenario in which one group of participants has a semantic representation of a symbol while the other group does not.

Against the background of the evidence reviewed above, I used this cross-linguistic approach to investigate the neural correlates involved in the semantic processing of numerical symbols that overcomes some of the limitations of the three methods discussed above. Specifically, I analyzed similarities and differences in brain activation associated with Hindu-Arabic numerals and Chinese numerical ideographs in participants who knew the semantic referents (numerical magnitude) of both types of symbols or only the Hindu-Arabic numerals. I reasoned that a comparison of the two symbol types would reveal the neural differences between semantic and non-semantic processing of numerical symbols. In response to numerals, which can be semantically processed by both groups of participants, the IPS should show an activation pattern reflective of this common cultural knowledge. In contrast to numerals, numerical ideographs can be semantically processed by the Chinese readers, whilst in controls ideographs can only be processed as arbitrary shapes. Thus, a comparison between

Chinese readers and controls should isolate regions recruited for the semantic processing of numerical symbols in a more direct fashion than was possible using the previous, above discussed, approaches.

To collect my data, I employed an fMRI adaptation paradigm, which takes advantage of a particular feature of the hemodynamic response measured by fMRI (Grill-Spector et al. 2006). Specifically, if a particular aspect of a stimulus is presented repeatedly, the region or regions that respond to that feature will show a reduction in their hemodynamic response with repeated exposure (adaptation). A region that exhibits adaptation effects will also show a rebound response when the feature it encodes is changed. To put this in the present context: if a region encodes the semantic meaning of a specific numeral (hereafter referred to as the adaptation number), this region will adapt (decrease in response) to repeated exposure to the numeral. In addition, this region will rebound (increase in activation) when a novel numeral is presented (hereafter referred to as a deviant number). Most importantly, the extent of the rebound is a function of the numerical difference between the adapted number and the deviant in such a way that deviants that are further away on the 'number line' from the adaptation number will lead to a relatively larger rebound response. This occurs because the internal representation of numerical magnitude is ratio-dependent. Numbers that are close together on the 'number line' (e.g., 6 and 8, ratio 0.75) have a higher ratio and therefore share more representational overlap than numbers that are further apart (e.g., 6 and 12, ratio: 0.5). Ratio-dependent representation implies that if a region were responding to the semantic information embedded in a numerical symbol, the rebound in activation to a deviant should increase as the ratio between the adaptation and deviant numbers decreases (Piazza et al. 2004).

My use of fMRI adaptation affords me the confidence to compare the neural response to ideographs between the groups. If one uses an active task to compare the neuroanatomical correlates of different groups, one risks conflating group differences in competence with group differences in performance. In the present context, the aim is to isolate group differences in the semantic representation of numerical ideographs. By using an adaptation paradigm, I will be able to probe the neural representation of ideographs while avoiding confounding group differences in task performance.

However my use of an adaptation design also faces a significant challenge. The question of semantic vs. asemantic processing of numerical symbols was recently cast into sharp relief by Cohen (2009). This investigator reported data that decidedly showed that behavioral correlates previously assumed to reflect the semantic processing of Hindu-Arabic numerals in a particular cognitive task actually reflected the processing of the visual similarity (i.e., shape) of the numerals. Specifically, when visual similarity was pitted against numerical distance it was found to account for unique variance in response time data. While it could be argued that Cohen’s findings were specific to the task he used, his data hinge upon a broader point: the visual similarity of the single digit Hindu-Arabic numerals is highly correlated with the semantic similarity of the single digit Hindu-Arabic numerals. Thus, data collected in an experimental design such as fMRI adaptation, which does not specifically direct attention to the semantics of numerals, faces the possibility that neural correlates evoked by semantic features of the numerals will be conflated with those that are evoked by visual features. I addressed this issue in two ways. Using similarity values adapted from Cohen's physical similarity function, I created a predictor to test for brain regions that respond to visual features of the numerals. In addition, my cross-linguistic design affords my another source of methodological traction on this issue. A comparison of the Chinese readers and the control group during ideograph processing could yield some important insights into the differences between the neuroanatomical correlates of ratio-dependent (semantic) and shape-dependent (visual) processing, because while Chinese readers can process both the semantic and visual dimensions of the ideographs, the control group can only be sensitive to visual aspects of the ideographs.

Because the central question of this study focuses upon group similarities and differences in the semantic tuning of symbolic numerical magnitudes, it is crucial to verify that any potential group differences I report are specific to having acquired a symbolic representation and not due to group differences in the more basic non-symbolic representations of the ANS. Therefore, I collected neuroimaging data while participants performed a non-symbolic comparison task on three different numerical ratios. I then tested whether the effect of numerical ratio on non-symbolic comparison differed between the groups.

In summary, I presented two types of numerical symbols: 1) the standard Hindu-Arabic numerals and 2) simplified Chinese ideographs to two groups of participants: 1) Chinese/English bilinguals who could read the ideographs and 2) English/Other bilinguals who could not read the ideographs, nor any related ideographs from other east Asian writing systems. I hypothesized that if the neural signal in the IPS is tuned to cultural symbols of numerical magnitude, then I should demonstrate a ratio-dependent rebound response to the numerals, in both groups, but only see a rebound response to ideographs in the Chinese readers.

3.2 Methods

3.2.1 Participants

Twenty-six adults from undergraduate and graduate faculties at Western University were recruited into two groups of thirteen participants. The first group was comprised of individuals who reported the ability to read both Chinese and English fluently (Age: 20-29 years, mean 25; 4 males). The other group consisted of individuals who reported fluent reading in English and another non-East-Asian language (18-34 years, mean 25; 4 males). After viewing the ideographs, participants were asked whether they recognized the symbols. All Chinese readers were able to indicate the correct numerical value for each ideograph. In contrast, none of the control group participants were able to indicate the meaning of the ideographs. All participants gave informed consent consistent with the policies of the Human Subjects Research Ethics Board at Western University.

The English language abilities of the participants in each group were measured in two ways. All individuals were students enrolled in the University of Western Ontario and, as such, were either native English speakers or demonstrated English proficiency in accordance with admissions policies at the University. Both groups completed the Reading Fluency, Word Attack, Math Fluency, and Calculation subtests of the Woodcock Johnson III Tests of Achievement. The control group showed significantly higher reading scores than the Chinese readers on both the Reading Fluency (M = 99.7, SE = 4.16, M = 89.42, SE = 2.70, t (20) = 2.14, p = 0.045) and the Word Attack subtests (M = 102.20, SE = 3.28, M = 90.75, SE = 2.74, t (20) = 2.70, p = 0.014). Relative to the control group, the Chinese Readers exhibited significantly higher scores on both the Math Fluency (M = 129.17, SE = 1.46, M = 98.60, SE = 6.23, t (20) = 5.20, $p < .001$) and Calculation tests relative to the control group (M = 126.17, SE = 3.68, M = 96.40, SE = 4.53, t (20) = 5.78, $p < .001$). Note that, while the groups differed in reading, both groups showed scores well within the normal range (85-115). This was not the case in mathematics; the control group scored within the normal range, while the Chinese readers scored above the normal range. Due to attrition, 4 individuals (3 from the control group and 1 from the Chinese readers) did not complete the standardized tests.

3.2.2 Stimuli

Parameters for stimuli were based on a recently published study investigating the neural correlates of numeral processing using fMRI adaptation (Notebaert et al. 2011). The adaptation number (6) as well as the deviants (3, 4, 5, 8, 9, and 12) were presented in black on a gray background (color values: 211, 211, 211) using E-Prime 1.2 software. These quantities were presented as Hindu-Arabic numerals and simplified ideographs. To control for low-level perceptual effects that could confound the adaptation/rebound signal, both the font and the location of the stimuli were varied across trials. In the Numeral condition, stimuli were presented in either Times New Roman (40pt) or Courier New (40pt). In the ideograph condition, stimuli were presented in either SimSun (40pt) or STHeiti (40pt). Font was randomized across trials such that each font appeared an equal number of times for both the adaptation and deviant quantities over the course of an experimental run. In addition to variations in font, the stimuli were presented in one of six locations 2 degrees from the center of the display. The variation in location was pseudo-randomized such that stimuli did not appear in the same location twice in a row.

3.2.3 Experimental Procedure

3.2.3.1 Adaptation Task

Numerals and ideographs were presented in four separate runs, each of which consisted of a stream of symbols punctuated by blank screens. Each stream of symbols appeared for 200ms. Each of the blank screens appeared for 1200ms. The background color of the screen was the same when the screen was blank and when it contained a symbol. The stream of symbols consisted of a series of adaptation trials followed by either a deviant trial (36 total), a catch trial (12 total) or a null trial (12 total).

Adaptation trials consisted of repeated presentations of the numeral 6 between 5 and 9 times (average of 7 repeats). During a deviant trial, a quantity that deviated from the adaptation number was presented. Deviants included 3, 4, 5, 8, 9, and 12. For analysis purposes, deviants were binned by ratio: large ratio, 2.0 (deviants 3 and 12), medium ratio 1.5 (deviants 4 and 9), and small ratio, 1.25 (deviants 5 and 8). Each deviant quantity was randomly dispersed through the run, resulting in twelve trials for each ratio over the course of a run. For the 12 catch trials, the adaptation number (6) was presented in red font. Participants were asked to press a button any time they saw a red symbol. The catch trials were randomly dispersed through the run. The 12 null trials consisted of the presentation of a numeral 6 in the same font as the adaptation trials. Thus, to the participant, a null trial looked identical to an adaptation trial. An illustration of the adaptation, deviant, null, and catch trials can be seen in Figure 3.1.

Each participant first completed the two ideograph runs followed by the two numeral runs. This fixed order was used to ensure that the control participants did not use the numerical information from the numeral task to guess what the ideographs meant. Because the trial duration (1400 ms) was not a multiple of the scan repetition time (TR = 2000 ms), a natural jitter (oversampling) was created in the time course of data acquisition.

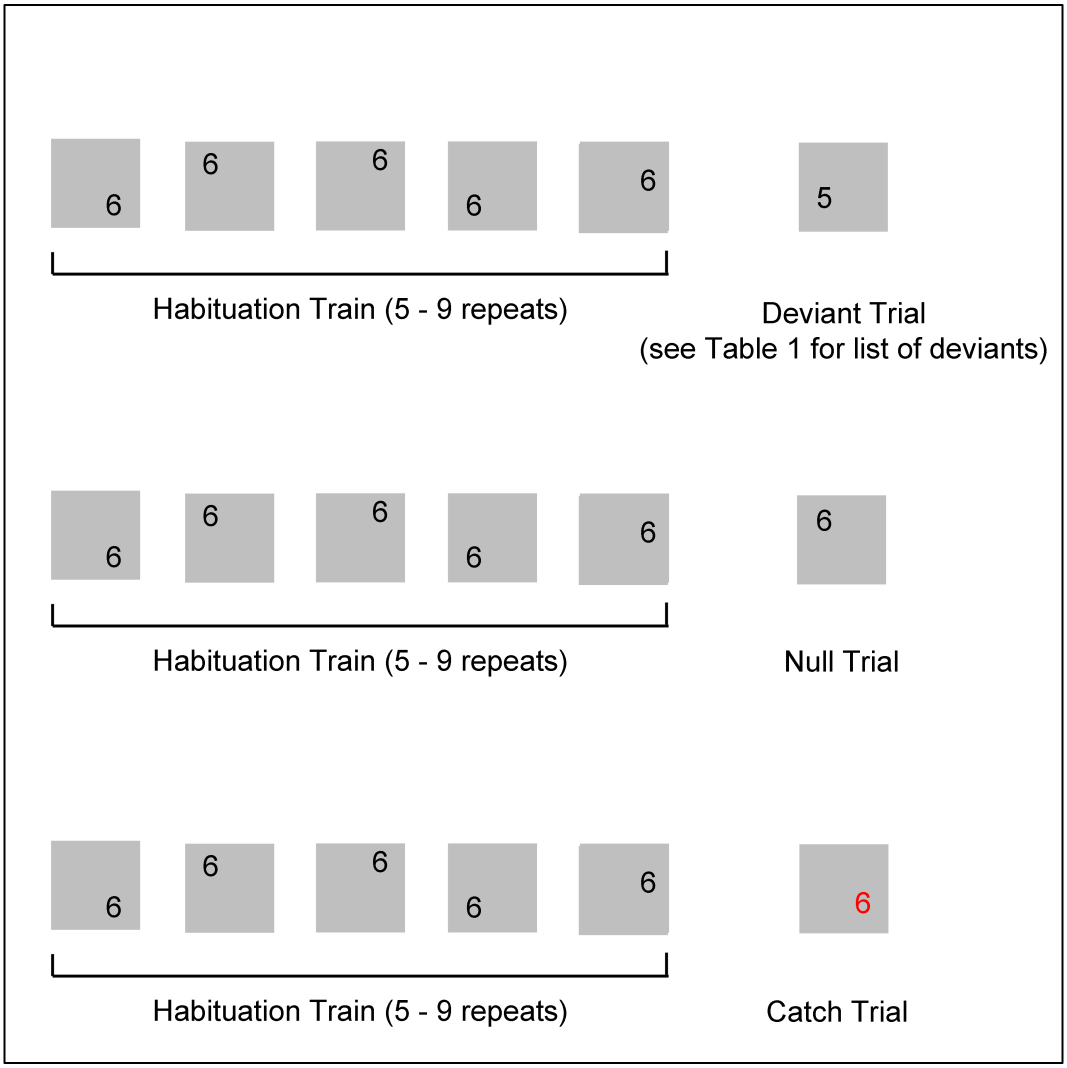

Figure 3.1 Illustration of the habituation, deviant, null, and catch trial types. See Table 1 for a complete list of the deviants used.

Table 3.1 Numerals and ideographs for each ratio

	Ratio 2.0	Ratio 1.5	Ratio 1.2	Ratio 1.0	Ratio 1.3	Ratio 1.5	Ratio 2.0
Numerals	3	4	5	6	8	9	12
Ideographs	三	四	五	六	八	九	十二

3.2.3.2 Non-symbolic comparison task

After the adaptation runs were completed, participants performed a non-symbolic numerical comparison task in which two dot arrays were presented. Participants were instructed to select the larger magnitude with a button press. The dot arrays were paired such that they represented one of three numerical ratios: 0.5, 0.66, or 0.75. Contour length, density, and individual dot size were controlled such that the larger number of dots could not be reliably predicted from any of the non-numerical variables continuous with it. Specifically, in half of the trials, the total area of each array in a given pair was equal, while the perimeters of each area were set such that the ratio between them was the inverse of the ratio of the number of dots. In the other half of the trials, the areas of each array in a given pair were defined such that the ratio between them was the inverse of the ratio between the number of dots, while the overall perimeter of each array in a pair was the same for both arrays. Sixteen trials for each ratio were presented in an event-related fashion with a jittered inter-trial interval of 5-9 seconds (average 7500ms).

3.2.4 fMRI Data Acquisition

Functional and structural images were acquired in a 3-Tesla Siemens Tim Trio whole-body MRI scanner, using a Siemens 32-channel head coil. A gradient echo-planar imaging $T2^*$ sequence sensitive to the blood oxygenation level dependent (BOLD) contrast was used to acquire 38 functional images per volume, which were collected in an interleaved order (3mm thickness, 80 x 80 matrix, repetition time (TR): 2000 ms, echo time (TE): 52ms, flip angle: 78°) and covered the whole brain. 355 volumes were acquired for each functional run. High-resolution anatomical images were acquired with a T1-weighted MPRAGE sequence (1 x 1 x 1 mm, T1 = 2300 ms, TE = 4.25 ms, TR = 2300 ms, flip angle: 9°).

3.2.5 fMRI Data Preprocessing

All functional images were preprocessed using BrainVoyager QX 2.4.1 (Brain Innovation, The Netherlands). The steps included slice scan time correction (cubic spline interpolation), correction for 3D head motion (trilinear motion detection and sinc motion correction) and temporal high-pass filtering (GLM-Fourier 2 cycles). All runs had less than 3mm overall head motion and were thus included in the analysis. Each functional image was then coregistered to the subject's anatomical image, transformed into Talairach space, and smoothed with a 6 mm full width at half maximum Gaussian smoothing kernel (Talairach & Tournoux, 1988).

3.2.6 Data Analysis

3.2.6.1 Statistical Threshold

Each of the statistical maps reported in my study was first thresholded with an uncorrected *p*-value of .001. Subsequently, the maps were corrected for multiple comparisons to a statistical level of $p < .05$ using the cluster level correction plugin built into BrainVoyager. This procedure was identical to the one described above in Experiment 1. A review of this approach to multiple comparison corrections can be found here (Forman, Cohen, & Fitzgerald, 1995).

3.2.6.2 Ratio-dependent Adaptation/Rebound

The analysis of these data was adapted from one recently published by Notebaert and colleagues (2011). For each participant, a design matrix was created with three predictors: a parametrically weighted predictor for all ratio trials (parametric effect of ratio); a predictor in which all ratio trials were weighted equally (main effect of ratio); and a predictor for catch trials. The adaptation and null trials were modeled as baseline. In the ratio predictor, all of the deviant trials were included and each was given a weight value equal to that of its ratio to the adaptation number (see Table 1). Deviants 5 and 8 were given a weight of 1.25; deviants 4 and 9 were given a weight of 1.5; deviants 3 and 12 were given a weight of 2.0. To allow the general linear model (GLM) to mathematically distinguish the ratio effect from the main effect, the BrainVoyager analysis package automatically centered the weights on zero by subtracting the mean of the weights from each weight before convolving the predictors with the hemodynamic response function. A whole-brain multi-subject general linear model (GLM) was calculated to test for regions exhibiting a significant ratio-dependent parametric increase of activation with increasing ratio. The resulting GLM consisted of three predictors, including one for catch trials (when the number turned red and participants had to press a button), one for the main effect of ratio, and a final one for the parametric effect of ratio. To maximize the sensitivity of the parametric test of ratio, I used a conjunction analysis to isolate regions whose activation profile exhibited both a significant main effect of ratio and a significant parametric effect of ratio. This approach was used because a region could theoretically show a significant effect of ratio, but not show any evidence of numerical processing greater than baseline. I avoided this problem by testing for regions that were sensitive to a conjunction of the main effect (all deviants > baseline) and the parametric effect (increased activation with decreasing ratio). To plot the ratio effect in each region, I extracted and plotted a parameter estimate of the mean activation across runs for the null trials and each deviant number(see Figures 2-4).

I designed my analyses to test the two *a priori* hypotheses outlined above. To review: commensurate with previous literature evincing its role in the semantic processing of numerals, I hypothesized that the IPS would show ratio-dependent processing in response to the Hindu-Arabic numerals. I expected that this activity would be highly similar across both groups. I tested this with Analysis 1, which canvassed the brain for regions showing ratio-dependent modulation (Main ∩ Parametric) in the Hindu-Arabic Numeral condition. I first tested for regions showing ratio-dependent modulation across both groups (Analysis 1a). I followed this by examining whether any regions showed significant group differences in ratio-dependent modulation by Hindu-Arabic numerals (Main Chinese ∩ Parametric Chinese) > (Main Control ∩ Parametric Control) (Analysis 1b). Following the same line of reasoning, I also hypothesized that the IPS would show ratio-dependent modulation in response to ideographs, but only in the Chinese readers. Mirroring my first analysis, Analysis 2 identified the ratio-dependent neural correlates of ideograph processing (Main ∩ Parametric). Initially, I looked within the Chinese and control groups separately to test for regions showing ratio-dependent modulation in response to the ideographs (Analysis 2a and 2b, respectively). I then tested whether any regions reflected significant group differences in the semantic processing of ideographs (Main Chinese ∩ Parametric Chinese) > (Main Control ∩ Parametric Control) (Analysis 2c).

Because of the relative nature of fMRI analysis, any voxelwise group difference I detect could reflect three different patterns that would have distinct functional implications. On the one hand, it is possible that both groups could show a significant effect, but that this effect is significantly greater in one group relative to the other. Alternately, it is possible that neither group exhibits an effect that is significantly different than baseline, but that the groups differ enough that I detect a significant difference. Finally, it is possible that one group shows an effect that is significantly greater than baseline, but the other group does not. To test between these hypotheses, any significant group difference were further analyzed using simple contrasts of the means with baseline (one way *t*-test) to further determine the nature of the group difference.

3.2.6.3 Distinguishing shape from semantic processing

As noted in the introduction, a recent behavioral study demonstrated that, in some contexts, the shape of Hindu-Arabic numerals can be processed independently of the semantic meaning of the numerals (Cohen, 2009). To address whether any of the ratio dependent effects I observe could be accounted for by differences in the visual features of the numerals, I performed an analysis looking for an effect of numeral shape similarity on the hemodynamic response function. I created a physical similarity predictor using an adapted version of the physical similarity function outlined by Cohen (2009). Using this approach, each numeral is first converted into the type of numeral that is used in old-fashioned digital alarm clocks or other appliances. In this way, each numeral can be created out of a pattern of seven lines, some of which are shared between two numerals and some which are not shared. I then calculated the ratio of shared features to the number of shared features plus the number of non-shared features (Shared/(Shared + Not Shared)). As the number of not shared features increases (i.e., as the numerals become visually dissimilar) the denominator of the equation increases and the calculated similarity value decreases. Using this Physical Similarity Function, I calculated the following similarity values and used them as weights in a parametric predictor. Numeral 3 = 1.75, Numeral 4 = 2.33, Numeral 5 = 1.2, Numeral 8 = 1.17, Numeral 9 = 1.75, Numeral 12 = 2.25. These weights correlated with the ratio weights (*r* = .63). In harmony with the ratio-dependent analysis, I examined which brain regions exhibited a significant conjunction of the Main and Parametric effects of the shape predictor.

In addition to my analysis using a physical similarity predictor, the cross-linguistic nature of my study afforded my an additional and unique way to investigate differences between shape and semantic response to numerical symbols. Because the control group did not know the meaning of the Chinese symbols, any response to numerical ideographs could therefore only be caused by differences in the visual features of the symbols rather than their meaning. Therefore, Analysis 2b, described above, provided data to examine the asemantic (shape-dependent) response to numerical ideographs (Main Control ∩ Parametric Control).

3.2.6.4 Non-symbolic Task

To analyze the non-symbolic comparison task, I modeled the numerical ratio of each trial resulting in a parametric predictor with three ratios (.25, .50, & .75). This predictor was then regressed across the whole brain and resulted in a GLM that tested for a main effect (all deviant trials equally weighted) and a parametric effect (each deviant trial weighted by ratio). Using an analysis comparable to the two described above, I isolated regions of the cortex that showed a conjunction of the main and parametric effects of non-symbolic numerical ratio. I then directly compared the neural correlates of the non-symbolic ratio effect between groups across the whole brain. This analysis was included to verify that the two groups showed comparable numerical representation in response to non-symbolic numerical stimuli.

Although it was only indirectly relevant to my central question, my data provided a unique opportunity to examine the relationship between individual differences in non-symbolic representations of magnitude and mathematical achievement scores in adults. As reported above, the Chinese group demonstrated better mathematical achievement relative to the control group. I was therefore curious whether behavioral performance on the non-symbolic comparison task administered in the scanner was systematically related to mathematical achievement scores. This question is driven by the mixture of results reported by previous studies testing the association between non-symbolic magnitude representation and arithmetic performance. Evidence from some studies has supported a link between these two variables (Halberda, Mazzocco, & Feigenson, 2008), whereas other studies have found that math skills are correlated with symbolic but not non-symbolic representations of numerical magnitude (Holloway & Ansari, 2009). I examined whether the group difference in mathematical achievement was related to better behavioral performance on the non-symbolic comparison task. In accordance with previous literature (Bugden, Price, McLean, & Ansari, in press; Bugden & Ansari, 2010) I used a regression analysis to create standardized regression coefficients reflecting the parametric effect of ratio (.25, .50, .75) on reaction time for each individual. I then examined group differences in these values to establish whether the non-symbolic ratio effect is related to mathematical achievement. In addition to reaction time, I also examined whether individual differences in overall accuracy accounted for differences in math achievement.

3.3 Results

3.3.1 Whole-brain analyses

3.3.1.1 Analysis 1: Adaptation to Hindu-Arabic numerals

Analysis 1a revealed that both the left IPS and the left fusiform gyrus (FG) showed a significant response to the conjunction of main and parametric effects in Hindu-Arabic numerals across both groups (Figure 3.2). These were the only regions revealed in this analysis. No other regions were significantly activated when the threshold was lowered to $p < .05$ uncorrected. To determine whether both groups activated the left IPS equally, I conducted a whole-brain between groups *t*-test (Main Chinese ∩ Parametric Chinese) > (Main Control ∩ Parametric Control) (Analysis 1b, not pictured). The results of this analysis statistically demonstrated that the activation in the left IPS and left FG was comparable across groups, as no region showed greater activation for one group relative to the other even at $p < .05$ uncorrected.

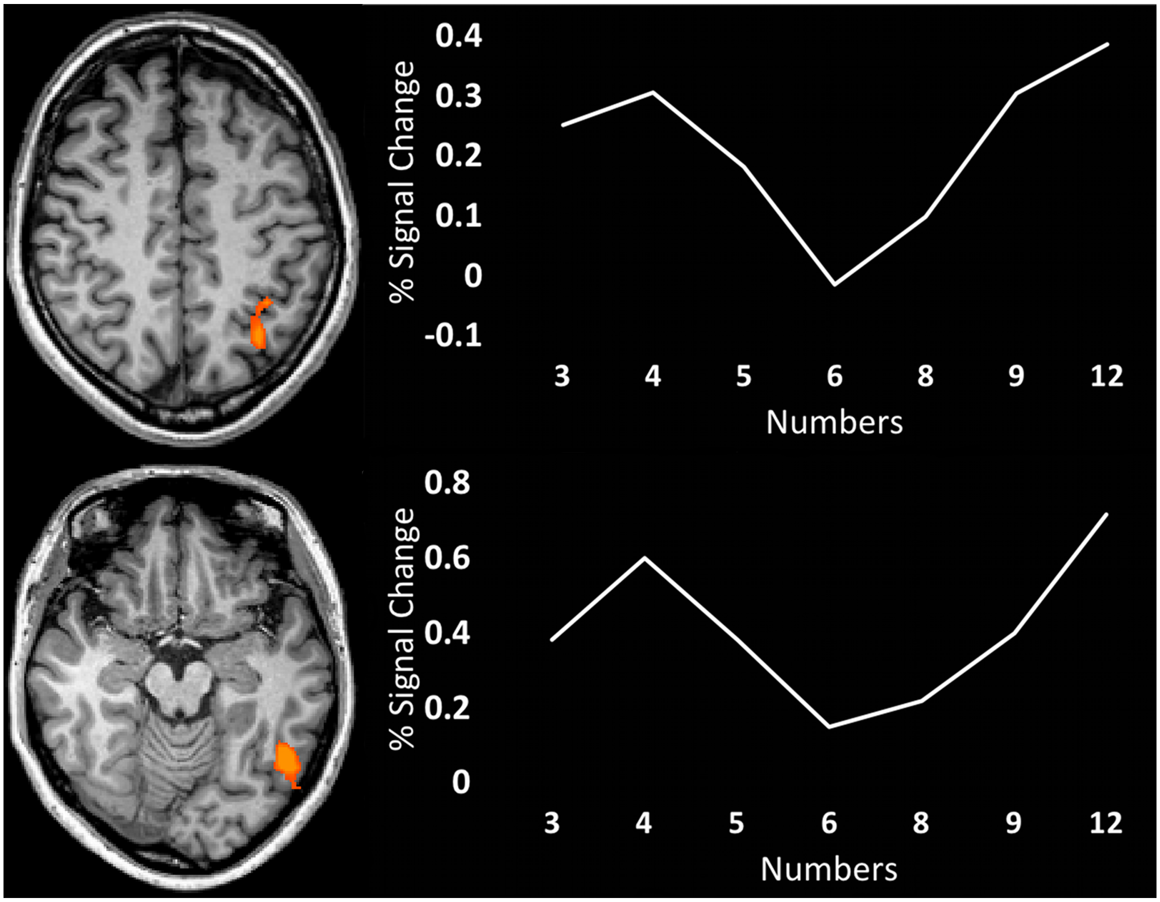

Figure 3.2 Activation of the left IPS and left FG showed ratio-dependent modulation in response to Hindu-Arabic Numerals across both groups. The IPS activation consisted of 670 anatomical voxels with an average *t*-statistic of 2.5. The peak voxel is located at Talairach coordinates -31, -65, 36. The FG activation consisted of 853 anatomical voxels with an average *t*-statistic of 2.0. The peak voxel is located at Talairach coordinates -46, -47, -12. The functional map ($p < .001$) was corrected at the cluster level to be significant at $p < .05$, $k = 10$ functional voxels. Line graphs represent parameter estimates reported as percent signal change for the adaptation number and deviants.

3.3.3.2 Analysis 2: Adaptation to Ideographs

Analysis 2a demonstrated that activation in the right IPS showed ratio-dependent modulation in response to numerical ideographs in the Chinese readers (Figure 3.3). No other regions were found to show significant ratio-dependent modulation in Chinese readers at my predetermined threshold. However, if a more liberal threshold ($p < .005$, cluster corrected to $p < .05$) is used, Analysis 2a reveals bilateral IPS and left fusiform gyrus activation. The control group also showed a neural response to numerical ideographs. Analysis 2b, which examined the control group separately from the Chinese readers, revealed that the left fusiform gyrus, but no regions in the IPS, showed a significant conjunction of main and parametric effects (see Figure 3.5) in the control group. No other regions showed such an effect at the lower threshold of $p < .05$, uncorrected.

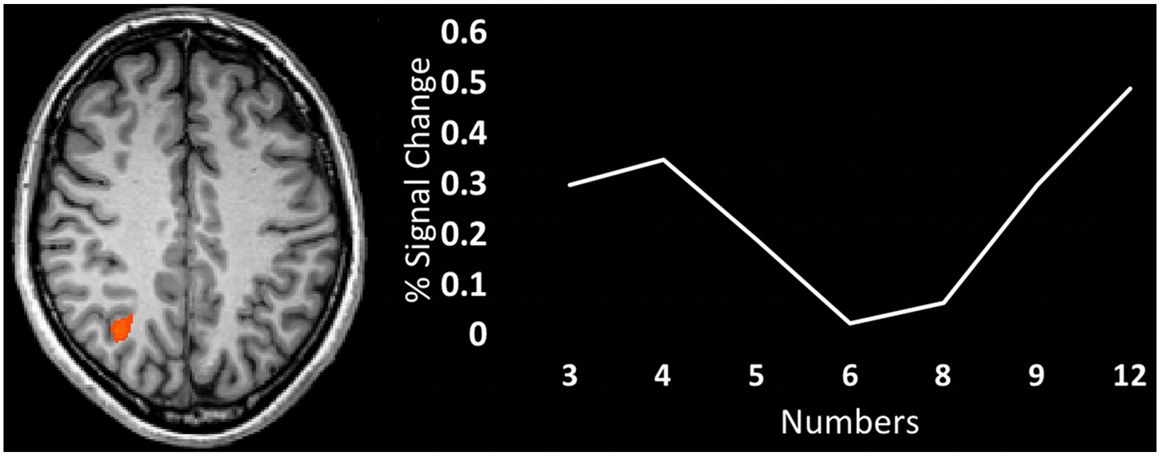

Figure 3.3 Activation of the right IPS showed ratio-dependent modulation in response to numerical ideographs in Chinese readers. The right IPS activation comprised 585 anatomical voxels and showed an average *t*-statistic of 2.2. The peak voxel is located at Talairach coordinates 26, -56, 39. The functional map ($p < .001$) was corrected at the cluster level to be significant at $p < .05$, $k = 10$ functional voxels. Line graphs represent parameter estimates reported as percent signal change for the adaptation number and deviants.

Analysis 2c revealed only one region whose activation pattern reflected group differences in ratio-dependent modulation in response to numerical ideographs: the right IPS (Figure 3.4). In this region, the effect of numerical ratio (parametric effect) was greater in the Chinese readers compared to the control group participants. Tested against zero, the Chinese group showed significant ratio-dependent activity in the IPS ($M = 0.406$, $SE = 0.101$, $t\ (12) = 4.0$, $p = .001$). This was not the case for the control group who did not exhibit ratio-dependent activation in response to Chinese ideographs that was statistically different than zero ($M = 0.153$, $SE = 0.089$, $t\ (12) = 1.7$, $p = .11$) (Figure 3.4, bar chart). No group difference was found in the left FG even when the statistical threshold was reduced to $p < .05$.

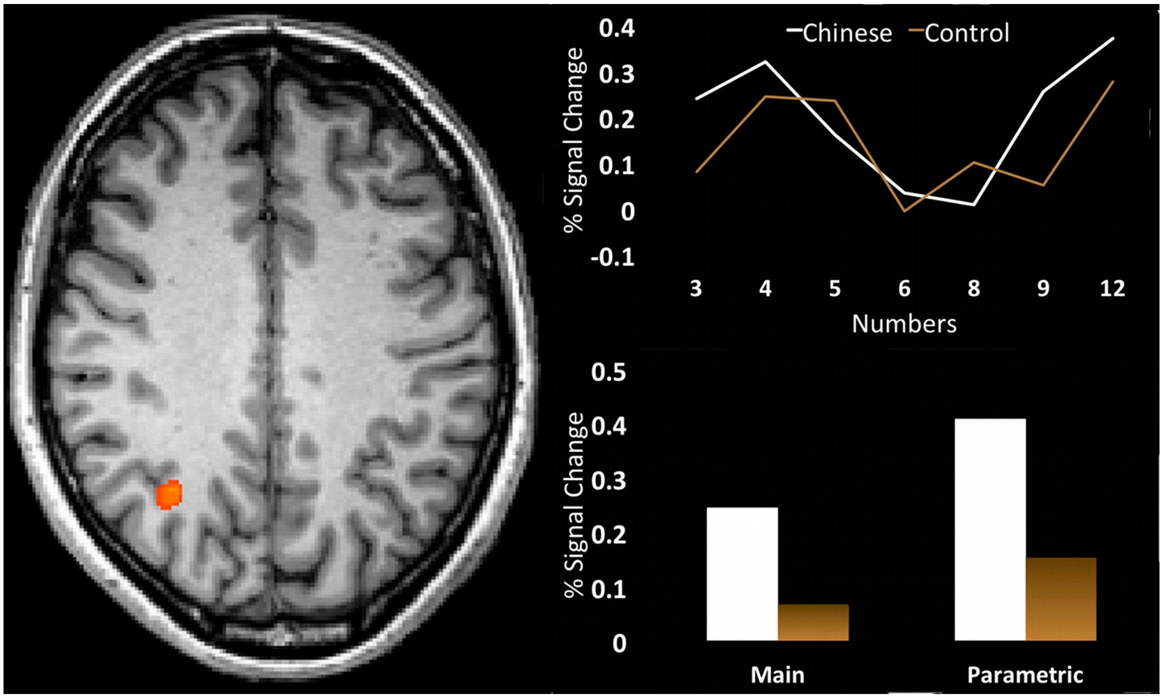

Figure 3.4 Activation of the right IPS showed a significant group difference in the conjunction of main and parametric effects in response to Chinese ideographs. The activated region in the IPS consisted of 300 antomical voxels with an average *t*-statistic of 3.8. The peak voxel is located at Talairach coordinates 29, -56, 36. Functional maps ($p < .001$) were corrected at the cluster level to be significant at $p < .05$, $k = 10$ functional voxels. Line graphs represent parameter estimates reported as percent signal change for the adaptation number and deviants for the Chinese (white line) and control (orange line) groups. Bar charts represent the parameter estimates for the average main effect and parametric effect response for the Chinese (white) and control (orange) groups.

3.3.3.3 Physical similarity analysis

I examined the effect of physical similarity in two ways. My first approach tested the parametric effect of physical similarity using parametric values calculated using the adapted verions of Cohen’s formula, described above (Cohen, 2009). This analysis revealed that the left fusiform gyrus, but not the IPS, demonstrated an activation pattern that was parametrically modulated by the shape predictor. My second approach to investigating shape-dependent processing of numerical symbols was to examine the ratio-dependent response to numerical ideographs in the control group (Analysis 2b). This analysis also revealed a significant activation in the left fusiform gyrus (see Figure 3.5).

Figure 3.5 Overlayed activations in the left FG from three of my analyses: Hindu-Arabic numerals across groups (orange), Chinese ideographs in the control group (dark red), and the similarity function (brown).

3.3.3.4 Non-symbolic comparison analysis

The behavioral data from the non-symbolic comparison task across the groups showed higher reaction time for increasing ratio, but no group by ratio interaction F_{ratio} (2,

44) = 133, $p < .001$; $F_{\mathrm{ratioXgroup}}$ (2, 44) = 1.4, $p = .25$. Similarly, error rate increased with increasing ratio across the groups, but this pattern did not differ between groups F_{ratio} (2, 44) = 29, $p < .001$; $F_{\mathrm{ratioXgroup}}$ (2, 44) = 1.4, $p = .27$.

On the neural level, across the groups, a network of frontal and parietal regions showed a significant conjunction between the main and parametric effect. These included the right anterior IPS(35, -41, 36), the right posterior IPS (20, -62, 39), the left IPS (-22, -50, 39), the anterior cingulate gyrus (5, 10, 45) the right anterior insula (32, 19, 9), and the right inferior frontal gyrus (41, 4, 27). However, none of these regions, nor any others, showed significant group differences, even at the reduced threshold of $p < .05$, uncorrected.

3.4 Discussion

Human knowledge develops over a life-long interaction of biology and culture. One of the key questions facing modern cognitive neuroscience is how the human brain adapts its intrinsic, evolutionarily preserved knowledge and skills to process culturally transmitted information, such as numerical symbols (Dehaene & Cohen, 2007). Investigations characterizing the neural circuitry underlying the processing of numerical symbols in the brain typically fall into one of three categories: developmental studies, training studies and those that contrast symbolic and non-symbolic processing. All three of these have yielded important clues about the symbolic representation of numerical magnitude in the brain. However, as discussed above, all three also suffer their particular limitations. While developmental studies reveal the effect of chronological age on functional brain organization, such studies cannot be used to establish whether brain changes are caused by maturation of brain circuits, experience and learning, or a complex interaction between these factors (Poldrack 2010). Training studies, while free of brain maturation confounds, conflate a relatively brief period of training with the breadth and depth of learning that results from prolonged processes of enculturation. Comparisons of symbolic and non-symbolic processing can provide broad insights about the neural correlates of number symbol processing, but are limited in their specificity. Indeed, none of these approaches has yielded insight into the differences in neural substrates of the semantic relative to the asemantic processing of numerical symbols.

The present experiment was designed to further constrain our understanding of the brain regions that underlie semantic and asemantic processing of number symbols. I hypothesized that parietal regions would be implicated in the semantic processing of symbolic quantities and, furthermore, that the left parietal lobe, in particular, would respond to numerical symbols. While previous adaptation experiments have characterized the neural correlates of symbolic number processing using similar adaptation designs (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Notebaert, Nelis, & Reynvoet, 2011; Piazza et al., 2007), my study diverged from this previous research in its ability to distinguish semantic from asemantic processing of numerical symbols. Moreover, my investigation of the semantic processing of numerical ideographs is the first of its kind.

To test my hypotheses, I investigated the neural correlates specific to the semantic processing of numerical symbols by comparing the neural correlates underlying Chinese ideographs, which were known only to one group, and Hindu-Arabic numerals, which were known to both groups. Using an fMRI adaptation paradigm, I isolated brain regions whose activation patterns reflected sensitivity to the semantic information embedded in numerical symbols—both numerals (Analysis 1) and ideographs (Analysis 2). I then tested whether these results could be accounted for by differences in numerical shape or by group differences in how basic non-symbolic quantities are represented. I found partial support for my hypotheses. Commensurate with previous studies, I discovered that the left IPS shows sensitivity to the numerical ratio of Hindu-Arabic numerals. In contrast, the right IPS was implicated in the semantic representation of numerical ideographs only in those participants who knew their numerical meaning. The left fusiform gyrus, on the other hand, exhibited activation related to the physical similarity of the numerical symbols rather than ratio-dependent processing. Below, I discuss the results I obtained against the background of my hypotheses and put forth a theoretical explanation for the symbol-dependent laterality differences observed across my analyses.

My first hypothesis stated that across both groups the meanings of Hindu-Arabic numerals should be represented in the parietal lobe in and around the intraparietal sulcus. Consistent with this hypothesis, the results from Analysis 1a showed that activity in the left IPS was found to be correlated with numerical ratio. The activation in this region was not found to differ between groups (Analysis 1b), suggesting that the role of this brain area in Hindu-Arabic numeral processing was equivalent in both groups. I also showed parietal activation in response to the Chinese numerical ideographs, but commensurate with my hypothesis, only in the Chinese readers who were the only participants who knew what the symbols meant. This group difference was statistically confirmed with Analysis 2c, which revealed that the effect of numerical ratio was found to be significantly stronger in the right IPS in the group of Chinese readers relative to the control group. A series of planned *t*-tests demonstrated that the group difference in the right IPS was characterized by significant parametric modulation to the semantics of the ideographs in the Chinese readers that was absent in the control group.

In addition to demonstrating the role of the IPS in the semantic processing of numerical ideographs, my data also demonstrate a high degree of similarity in the neural correlates underlying the representation of Hindu-Arabic numerals across both groups. The null result of Analysis 1b, even at a low threshold, suggests that the cultural and linguistic differences between the groups do not influence the basic representation of symbolic numerical magnitude. This fact stands in direct contrast to other research suggesting that cultural differences influence the neural correlates of basic arithmetic (Tang et al., 2006). Taken together, my data and those of Tang et al. (2006) suggest that the role of culture and language on the neuroanatomical substrates of numerical processing depends on the nature of the process being observed. While the basic representation of symbolic numerical magnitude may be highly comparable across culture, arithmetic processing with its deeper reliance on linguistic processing and the mental manipulation of numerical magnitudes appears to be more susceptible to cultural influences. Future research is necessary to truly clarify the role of culture in numerical neurocognition.

Taken together, the findings from Analyses 1 (adaptation to Hindu-Arabic numerals across groups), 2a (adaptation to Chinese ideographs in Chinese readers) and 2c (adaptation to Chinese ideographs between groups) provide strong evidence for the role of the parietal lobe in the semantic representation of numerical symbols. My results validate previous data linking the IPS to the semantic representation and processing of symbolic numerical magnitude by providing an exact replication of the data reported by Notebaert et al. (2011). I provide an important extension to these previous findings with my demonstration that the parietal response to numerical symbols is general across cultures.

In addition to the high similarity in the processing of Arabic numerals in the two groups, they also exhibited absolutely no difference in the neural response to numerical ratio when the numerical information was presented as non-symbolic arrays. Of the three perceptual formats (Hindu-Arabic numerals, numerical ideographs, and non-symbolic arrays) that were tested in this study, the only one that showed significant differences between the groups was the culture-specific Chinese ideographs.

In accordance with previous research, which has hinted at left hemisphere dominance for numerical symbol processing, I anticipated finding left hemisphere dominance for both numerals and ideographs. I found partial support for this hypothesis.

The analyses reported suggest a strong left lateralization in the parietal activation underlying the processing of Hindu-Arabic numerals, which is consistent with data reported by Notebaert et al. (2011). The left-lateralization of numerals, however, stands in contrast to the right parietal response to numerical ideographs. However, the neural response to numerical ideographs shows much weaker evidence of lateralization as a slightly reduced statistical threshold revealed bilateral IPS response to ideographs. What can account for these notation dependent differences in laterality? I propose that the neural differences could reflect differences in how numerals and ideographs are used in Chinese culture. For this proposal to be considered plausible, two conditions must be met. It must be the case that, in Chinese culture, ideographs and numerals are used in divergent ways. Secondly, it must be demonstrated that specialization of the left hemisphere is possible, such as through changes in laterality over developmental time.

Speaking to the first condition, numerical ideographs, while clearly recognized and understood by readers of the Chinese languages, are used less frequently than the Hindu-Arabic numerals, which officially replaced them in 1955 (for more information see the chapter entitled “Spoken Numbers and Number Symbols in China and Japan” in Menninger, 1992). Ifrah sums up this point nicely: “The [Hindu-Arabic numerals] are a kind of visual Esperanto: Europeans, Asiatics, Africans, Americans or Oceanics, incapable of communicating by the spoken word, understand each other perfectly when they write numbers using the figures 0, 1, 2, 3, 4…, and this is one of the most notable features of our present number-system. In short, numbers are today the one true universal language” (Ifrah, 1981, p. 594) Both cultures use Hindu-Arabic numerals, rather than ideographs or number words, to teach and perform formal mathematical operations. Indeed, as Menninger states, “There is another difference between the [Hindu-Arabic] and the Chinese numerals: with the former it is possible to make written computations, but not with the latter...Thus the Chinese have always made their computations on the abacus...” (Menninger 1992, p.458). The use of numerals for mathematical training implies that educated individuals from both cultures have had a great deal more practice (and therefore have more fluency in) accessing the quantitative meaning of Hindu-Arabic numerals relative to number words or ideographs.

Does the left hemisphere show developmental and functional specialization in other domains? Evidence for this second condition can be found in neuroimaging studies of the development of reading. Such research has demonstrated a right-to-left shift in the neural correlates related to syntactic processing (Nuñez et al. 2011) as well as phonological, semantic, and orthographic tasks (Spironelli & Angrilli 2009). In similar fashion, my data suggest that activity in the IPS shifts from bilateral recruitment for non-symbolic and relatively unrefined symbolic representation of quantity (such as can be found in contemporary use of Chinese numerical ideographs) to a left-lateralized recruitment as symbolic representations become highly refined (such as can be found in contemporary use of Hindu-Arabic numerals). This assertion presupposes that the representation of numerical magnitude is present in the parietal lobe before formal schooling and is focused in the right intraparietal sulcus, as has been shown in recent studies (Cantlon et al. 2006; Hyde & Spelke 2011; Izard et al. 2008). I suggest that, as is the case in reading, the left IPS becomes increasingly active in the representation of numerical magnitude over developmental time through an interaction of brain maturation and training in the use of numerical symbols. My data add important nuance to previous findings, which have suggested a specialization of the left IPS for symbolic number processing. In particular, rather than suggesting that the left IPS is specialized for the representation of numerical symbols in general, I show that the left IPS is specialized for the highly fluent semantic processing that underlies the use of Hindu-Arabic numerals in Chinese and Western culture *and* which differentiates the use of numerals from numerical ideographs in Chinese culture.

In addition to constraining our understanding of the semantic processing of number symbols in the brain, the present results also shed light on a recent issue that has been raised in the study of numerical cognition. Cohen (2009) demonstrated that a parametric response to numerical ratio is correlated with physical similarity between numerals when participants have to decide whether a target number is the same or different compared a reference number (in his study participants had to decide whether a target Arabic numeral was a 5 or not). More specifically, Cohen’s results showed that the physical similarity between the target and reference was a better predictor of reaction time variability than the numerical ratio, suggesting that subjects were relying on perceptual similarity between the symbols to a greater extent than their semantic referents. Against the background of these findings, Cohen pointed out that we should be cautious how we interpret some behavioral effects that have often been linked to the semantic processing of numerical symbols, as the data may be equally well accounted for by metrics of the physical similarity between numerical symbols. This observation also has implications for brain imaging studies, such as the one reported here. In view of these, I investigated whether any brain regions were modulated by the physical similarity between the adaptation number and the deviants in the Hindu-Arabic numeral condition. The only region to show an effect of physical similarity was the left fusiform gyrus. Thus, the present findings suggest that physical similarity and the numerical magnitude of number symbols are being processed in parallel in the brain, with the IPS sensitive to the numerical magnitude and the fusiform to the physical similarity between the adaptation stimulus (6) and the deviants.

Another way in which my experiment allows my to look at the difference between semantic and perceptual processing of numerical symbols is through the comparison of the activation in response to the ideographs between the two groups. Specifically, in Analysis 2b; Chinese numerical ideographs elicited ratio-dependent responses in the left fusiform gyrus in the control group in a region overlapping with the area that exhibited response to the physical similarity of the Hindu-Arabic numerals. Because this group of participants had no knowledge of the meaning of the ideographs, it is impossible that the response in this group was related to the semantic processing of the ideographs. Instead, the response must have been related to the visual processing of the shape of the ideographs. The fusiform gyrus (see Figure 3.5) has been implicated in shape processing in other studies (e.g.,, Starrfelt & Gerlach, 2007), making this interpretation likely. Taken together, my findings suggest dissociation between the perceptual and semantic processing of numerical symbols in the brain and lend further support that activation of the parietal cortex during symbolic number tasks is reflective of the processing of the semantic referents of numerical symbols.

As a final note, the two groups exhibited substantially different mathematical achievement abilities. Despite these differences, the two groups showed remarkably similar neural and behavioral correlates of non-symbolic number processing. I demonstrated that while the Chinese group showed higher mathematical skills, their mean non-symbolic ratio effect was no different from the control group. The current body of literature on the potential relationship between non-symbolic processing and math is characterized currently by a very mixed pattern of findings. Some studies report a significant relationship (Halberda & Feigenson, 2008; Halberda et al., 2008), while other researchers have failed to find similar results (Holloway & Ansari, 2009; Mundy & Gilmore, 2009). The data from the present study provide another piece of the puzzle, which can help future researchers clarify the relationship between basic, non-symbolic numerical representation and mathematical performance.

3.5 Conclusion

In summary, the findings reported in the present paper make two principal contributions. First, I showed that the left parietal cortex is specialized for the representation of Hindu-Arabic numerals. Against the background of previous demonstrations that the left IPS houses a neural representation that is more finely-tuned than that of the right IPS (Piazza et al., 2007), this brain region may represent an optimal site for the precise numerical representations communicated by the Hindu-Arabic numerals in cultures that use these numerals for mathematical computations. Secondly, the cross-linguistic nature of my study showed clear evidence that the IPS activity is related to semantic rather than asemantic processing – only participants who have a semantic representation of numerical symbols show responses to these in the IPS. Furthermore, the present study reveals that the fusiform gyrus is likely involved in asemantic visual processing of numerical symbols. Future studies should address the development of connectivity between these regions to clarify further how their interplay constructs the symbolic representation of number.

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Interim summary

Chapter 3 was designed to compare the semantic relative to the asemantic processing of numerical symbols. Both the intraparietal sulcus (IPS) and the fusiform gyrus (FG) were associated with the processing of numerical symbols. The data analysis suggested that the IPS was involved in the semantic processing of the symbols, while the FG was involved in the visual processing of the symbols.

One of the goals of Chapter 3 was to clarify and extend the findings of Chapter 2 by identifying regions that are specific to the semantic processing of numerical symbols. While Chapter 2 isolated regions involved in symbolic relative to non-symbolic numerical processing, the data reported in Chapter 3 identified the regions involved in the semantic relative to the asemantic processing of numerical symbols. Although both studies implicated the IPS in the semantic processing of Hindu-Arabic numerals, the laterality of the effect was reversed (right IPS for Chapter 2 and left IPS for Chapter 3). This laterality difference is likely due to differences in the analysis conducted. Chapter 2 focused on identifying regions commonly involved in symbolic and non-symbolic representation, while Chapter 3 looked for regions specifically involved in the semantic processing of numerals. This difference likely reflects a specialization of the left IPS for the representation of symbolic numerical magnitude. However, it must also be acknowledged that the left IPS showed much weaker involvement in the semantic processing of numerical ideographs. The specialization of the IPS will be discussed in more detail in Chapter 5.

In Chapter 2, the semantic comparison of numerals elicited activation in the left superior temporal gyrus (STG) to a significantly greater extent than did the comparison of non-symbolic numerical stimuli. In view of these findings, I hypothesized this region is involved in either the deliberate or automatic activation of the auditory referents of numerals. Although null results should always be interpreted with caution, Chapter 3 showed no involvement of the STG, even when comparing numerical ideographs in Chinese readers versus the control group. This could potentially suggest that the involvement of the STG in Chapter 2 reflects the deliberate recruitment of auditory information by participants when performing a numerical comparison task. However, this interpretation hinges on the involvement of the STG in the auditory or audiovisual processing of numerals, which will be empirically determined in the next Chapter.

Chapter 4: Audiovisual processing of numerals

4.1 Introduction

4.1.1 Background

The numerical abilities of humans have been widely studied and a growing body of literature describes both the behavioral and the neural correlates of numerical magnitude processing (e.g., Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999). One important insight that has emerged from this research is that the processing of numerical magnitude is built upon an evolutionarily ancient system of magnitude representation that is present across animal species (Brannon, 2006; Nieder & Dehaene, 2009). Thus, humans share the ability with non-human animals to approximately represent numerical magnitude from non-symbolic sources such as clusters of berries or piles of rocks.

In addition to this approximate, non-symbolic representation of numerical magnitude, humans have also developed a symbolic notation for expressing numerical magnitude. These symbols allow us to represent and manipulate quantity in a more precise and abstract manner. Indeed, a numeral such as “11” does not refer to any particular set of eleven items, but instead to the abstract concept of eleven: the set of all possible groups of eleven things. In this way, the symbolic representation of number could be considered a representational hybrid, combining the precision of language with the phylogenetically continuous, yet imprecise, representations of numerical magnitude.

This mapping between language and numerical magnitude representation occurs in early childhood through a process that remains poorly understood. The principal mechanism through which children learn to symbolize number is thought to be counting, which teaches a child to associate a number word with a quantitative representation (Gallistel & Gelman, 1992; Sarnecka & Carey, 2008). Interestingly, learning the meaning of counting is a protracted process. Until around age 3.5, children will often demonstrate perfect fluency in reciting the counting sequence, but not understand what the words mean (Wynn, 1990). Eventually, the linguistic representations of the counting sequence become associated with their abstracted semantic referents. Subsequent to this process, near the onset of formal education, children learn to read numerals. In other words, the verbal-semantic representations of early childhood become associated with a visual form, most often the Hindu-Arabic numerals. It is thought that this ability to read numerals becomes a foundation for higher-level mathematical abilities (Holloway & Ansari, 2009; Mundy & Gilmore, 2009; Rousselle & Noël, 2007).

4.1.2 Open questions

Against the background of the above discussion, it is clear that numerals also convey auditory information in the form of number names, visual information in the form of canonical shapes, and audiovisual information in which the auditory and visual information is combined into a unified percept. Yet despite the richness of numerals, little is known about the visual, auditory, and audiovisual representation of numerals. Indeed, because the principal referent of numerals is the quantity they represent, it is understandable that the vast majority of research into the processing of numerical symbols has focused on semantic representation. This emphasis on understanding the semantic processing of numerals has left questions about auditory, visual, and audiovisual representations largely unexplored.

One of the most obvious questions that could be asked about the auditory processing of numerals is whether, and to what extent, the reading of numerals is comparable to the reading of letters. This comparison is compelling, especially when considering that before the dominance of Hindu-Arabic numerals, many cultures, such as the Ancient Greeks, used their alphabet to express numerical information. Thus, to the Hellenic world, numerals and letters were not simply similar, but absolutely identical (Menninger, 1992). Yet despite their similarities, it remains an open question whether the linguistic levels of representation of numerals are comparable to those of letters.

Another open question regards the extent to which the semantic processing of numerals would influence other levels of numeral representation, such as the processing of their auditory referents. In a previous study, Eger and colleagues presented participants with a series of intermixed unimodal visual letters, visual numerals, auditory letter names, auditory number names, visual bars of color, or auditory color names. Participants were instructed to monitor the series of stimuli and press a button whenever they saw or heard a particular letter, number, and color. Relative to letters and colors, when numerical stimuli (visual or auditory) were presented in the series, the intraparietal sulcus (IPS) was significantly activated. This was interpreted as evidence that numerical stimuli could automatically elicit a semantic response even when the task is simply target detection. Moreover, in Chapter 3 of this thesis, the passive viewing of numerals in the adaptation paradigm modulated activity in the left IPS. It is, therefore, possible that passive exposure to visual numerals, auditory number words, or audiovisual numeral-number name pairs could also automatically activate the semantic representation of numerical magnitude found in the IPS.

4.1.3 Audiovisual paradigm and the importance of the congruency effect

To address the questions discussed above, I used an fMRI paradigm that allowed my to compare and contrast the auditory, visual, and audiovisual processing of numerals and letters. Specifically, I adapted a paradigm frequently used in previous research to measure the neural response to letters (van Atteveldt, Formisano, Goebel, & Blomert, 2004). In the original paradigm, participants were presented, in separate runs, with letters (unimodal visual), letter sounds (unimodal auditory), and simultaneous letters and letter sounds (bimodal audiovisual). The audiovisual runs were further separated into runs where the audiovisual information was congruent (letter and sound matched) and runs where the audiovisual information was incongruent (letter and sound did not match). The principal analysis that was employed in this study is a comparison of the neural correlates of congruent to incongruent audiovisual pairs, as this allows the distinction between general multisensory processing and the processing of pairs that are highly overlearned. In other words, the presence of simultaneous auditory and visual information would be expected to elicit a hemodynamic response in multisensory regions, such as the superior temporal cortex (Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004; Calvert, Spence, & Stein, 2004; G. a. Calvert, 1997; Stein & Stanford, 2008). Therefore, to detect learned audiovisual integration (as opposed to general multisensory processing), it is not sufficient to simply examine regions that respond to both auditory and visual stimuli. One must, instead, look for a multisensory response that is modulated by whether the auditory and visual information "belong together." An effect of congruency indicates that a brain region is sensitive to the distinction between a learned or "correct" audiovisual pair and an unlearned or "incorrect" pair (Goebel & van Atteveldt, 2009). In reading, the congruency effect is not only theoretically important, but its presence seems to reflect fluent reading (Blau et al., 2010; Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009; Blomert, 2011). In previous studies, the congruency effect has been associated with activity in primary auditory cortex as well as posterior portions of the superior temporal gyrus.

I adapted the audiovisual paradigm to examine visual, auditory, and audiovisual processing in numerals. I used the basic four conditions (unimodal visual, unimodal auditory, bimodal congruent, bimodal incongruent) with three different audiovisual pairs (numeral-number name, letter-letter name, letter-letter sound). The letter conditions were used as control tasks with which to compare the audiovisual processing of numerals. I included these two different control tasks for the following reasons. The audiovisual processing of letter-letter sound pairs has been repeatedly investigated in previous studies and, therefore, is important to include in this study (for review see Blomert & Froyen, 2010). However, the auditory referents of numerals are number names and not speech sounds. Therefore, I included the letter-letter name pairs in order to contrast the numeral condition with a different type of symbol that is also associated with a verbal name.

I planned my analysis to look for similarities and differences in the three audiovisual pair types across the four conditions. I hypothesized that both the unimodal and bimodal conditions would be highly similar across pair types. Furthermore, commensurate with previous research, I expected to see superior temporal sulcus/gyrus (STS/STG) activity in response to congruent relative to incongruent audiovisual pairs in numerals as well as letters.

4.2 Methods

4.2.1 Participants

Eighteen individuals (nine females, nine males; age range: 19 – 35; mean age: 24) were paid to participate in this study. Participants were recruited from undergraduate and graduate faculties at the University of Western Ontario as well as from the surrounding community in London, Ontario. All participants reported normal or corrected-to-normal vision, no hearing problems, right-handedness, and Canadian English as their first and primary language. Participants gave informed consent as monitored by the Research Ethics Board at the University of Western Ontario.

4.2.2 Stimuli and Experimental Design

Stimuli consisted of eight single digit numbers (1, 2, 3, 4, 5, 6, 8, 9) and eight lowercase letters (b, h, j, k, l, p, r, v) presented in both the visual and the auditory modality. The Numeral 7 was not used because its auditory referent “seven” is two syllables while all other auditory referents used were one syllable. Those particular eight letters were chosen because they have the highest percentage of sound regularity in English. Of all English letters, these are most often associated with only one letter sound. Visual stimuli were presented in white 40 point Arial font and centred on a black background. Auditory stimuli consisted of number names (“one” “three”), letter names (e.g., “bee” “kay”), and phonemes (e.g., /b/ /k/) spoken by a female Canadian English speaker. Auditory stimuli were digitally recorded with a sampling rate of 44.1 kHz with 16-bit quantization. Each sound used in the fMRI experiment was recognized correctly 100% of the time by ten additional participants in a pilot experiment.

Stimuli for each of the three audiovisual pair types: numeral-number name (NN), letter-letter name (LN), and letter-letter sound (LS) were presented in four different conditions. In the unimodal visual (UV) condition, participants were asked to watch a series of either visual letters or numerals presented in silence. The unimodal auditory (UA) condition presented auditory content (letter sounds, letter names, or number names) to the participants without corresponding visual information. In the bimodal conditions, visual and auditory information was presented simultaneously. The bimodal congruent (BC) condition provided visual information that matched the corresponding auditory information, whilst the bimodal incongruent (BI) condition did not. Each condition (UV, UA, BC, BI) was presented separately for each audiovisual pair (LS, LN, NN) resulting in a total of twelve conditions overall.

The twelve conditions were each presented to the participants in separate blocks of 21400ms. Each unimodal block was presented once over the course of a run and each bimodal block was presented twice over the course of a run. Each participant completed two runs and thus four blocks of each of the bimodal conditions and two blocks of each of the unimodal conditions. The blocks were pseudo-randomized over the course of a run such that the same block was never presented twice in a row. At the beginning and end of each run as well as between each block a fixation period of 16000ms was presented.

Because most of my stimuli included an auditory signal, I employed a sparse sampling paradigm to eliminate the confound of scanner background noise (Hall et al., 1999). Sparse sampling takes advantage of the temporal delay in the hemodynamic response function. Typically, and in this experiment, a stimulus or series of stimuli are presented in silence followed by the recording of a single functional volume, which samples the hemodynamic response as it peaks from the preceding stimulation. My use of this type of paradigm required my to divide my blocks of trials into separate mini-blocks. Thus, for each block of trials, participants would be presented with five stimuli (350ms) in the absence of scanner noise followed by short fixation in which a single functional volume (1500ms) was collected. The inter-stimulus interval, which might be described instead as a stimulus buffer, was 350ms. Six stimulus buffers were included: one between each stimulus trial, one before the first stimulus, and one following the last stimulus. In total, the five stimuli (350ms x 5 = 1750ms), the six buffers (350ms x 6 = 2100ms) and the single volume acquisition (1500ms) resulted in a mini-block (TR) that was 5350ms long. Four mini-blocks were collected in each larger block, resulting in a total of twenty stimuli per block (5350ms x 4 = 21400ms). Please see Figure 4.1 for details. In total, then, I collected two runs, each consisting of thirty-seven blocks (nineteen blocks of fixation: 16000 x 19 = 304000ms; eighteen blocks of trials: 21400 x 18 = 385200ms) totalling roughly 11.5 minutes.

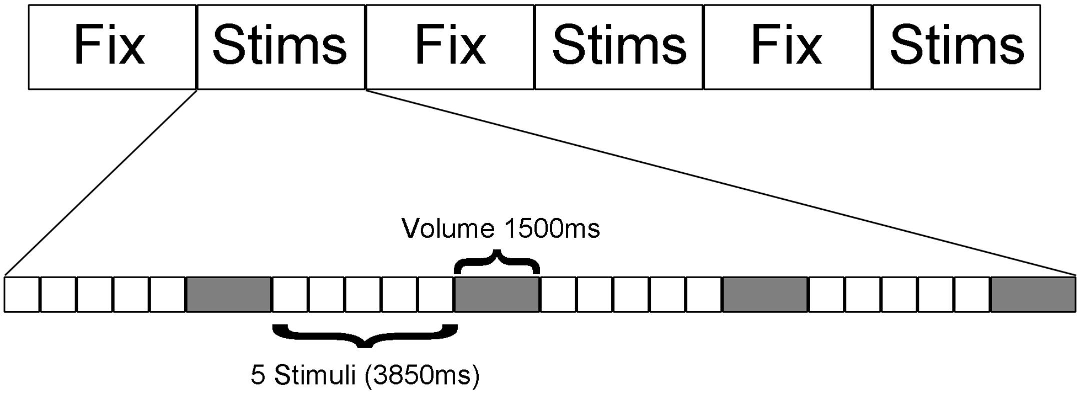

Figure 4.1 Cartoon depiction of sparse sampling paradigm. Each block of stimuli was made up of four mini-blocks in which five stimuli were presented followed by a volume acquisition. White squares represent stimuli presented without the collection of functional neuroimaging data. Gray rectangles represent the acquisition of a single functional volume. Punctuating blocks of stimulation were blocks of fixation.

4.2.3 MRI Data Acquisition

Functional and structural images were acquired in a 3-Tesla Siemens Tim Trio whole-body MRI scanner, using a Siemens 12-channel head coil. A gradient echo-planar imaging T2* sequence sensitive to the blood oxygenation level dependent (BOLD) contrast was used to acquire 28 functional images per volume, which were collected in an interleaved order (3mm thickness, 64 x 64 matrix, repetition time (TR): 5350 ms, echo time (TE): 30ms, flip angle: 78°) and covered the whole brain with the exception of the most anterior and inferior section of the temporal poles. 256 volumes were acquired for each functional run. High-resolution anatomical images were acquired with a T1 weighted MPRAGE sequence (1 x 1 x 1 mm, T1 = 2300 ms, TE = 4.25 ms, TR = 2300 ms, flip angle: 9°).

4.2.4 fMRI Data Preprocessing

All functional images were preprocessed using BrainVoyager QX 2.2.0. The steps included slice scan time correction (cubic spline interpolation), correction for 3D head motion (trilinear motion detection and sinc motion correction) and temporal high-pass filtering (GLM-Fourier 2 cycles). All runs had less than 3mm overall head motion and were thus included in the analysis. Each functional image was then coregistered to the subject's anatomical image, transformed into Talairach space, and smoothed with a 6 mm full width at half maximum Gaussian smoothing kernel (Talairach & Tournoux, 1988).

4.2.5 fMRI Analysis Strategy

The analysis for this study was adapted from (van Atteveldt et al., 2004). For each participant, a design matrix was created with twelve predictors: each of the four conditions (UV, UA, BC, BI) for each of the three audiovisual pair types (LS, LN, NN). The resulting random-effect whole-brain general linear model included these twelve predictors.

4.2.5.1 Analysis of unimodal effects

The central goal of this study was to compare the neural correlates of visual processing, auditory processing, and audiovisual integration in numbers with the corresponding correlates elicited by letters. My analysis was thus two-fold. To test for similarities and differences in the unimodal processing of numerals and letters, I conducted five analyses. To identify regions commonly involved in visual processing, I performed a conjunction of visual letters and visual numerals. To identify regions commonly involved in auditory processing, I performed a conjunction of number names, letter names, and letter sounds. To test for differences between the visual processing of letters and the visual processing of numerals, I conducted a whole brain *t*-test (letters > numerals) balanced for the uneven number of conditions. To test for differences in the auditory processing across the three notations, I conducted a whole brain single factor analysis of variance (three levels: number names, letter names, letter sounds). Finally, to test for amodal number specific activation I ran a conjunction analysis of (numerals > letters) ∩ (number names > letter names).

4.2.5.2 Analysis of bimodal effects

The second series of analyses were designed to test for similarities and differences in audiovisual integration in the three pair types. To do this, I conducted a whole brain two factor analysis of variance. Factor 1 was notation and had three levels (NN, LN, LS). Factor 2 was congruency and had two levels (C, I). The interaction of notation X congruency reveals regions where the congruency effect is significantly different between symbol types. The main effect of notation reveals regions differentially involved in audiovisual processing regardless of congruency. The main effect of congruency shows commonalities in the congruency effect across all three pair types. The most important of these analyses to my purposes is the interaction of notation by congruency, as it statistically demonstrates differences in audiovisual *integration* between different types of audiovisual pairs. As detailed in the introduction, the congruency effect is designed to measure audiovisual integration rather than a more general multisensory processing.

Against the background of this reasoning, I structured my specific analysis as follows. I initially conducted a 3 x 2 analysis of variance using pair type (LS, LN, NN) and congruency (congruent, incongruent) as within-subjects factors. Within this analysis, I focused upon the interaction of pair type and congruency as a means to reveal any statistical differences in the congruency effect between pair types. Any significant interaction was further analyzed by performing post-hoc contrasts within each significant region using BrainVoyager's ROI analysis module. Of secondary interest was the detection of any main effects (condition or congruency). Because this analysis of variance is unable to statistically test for the presence of congruency-related modulation within each condition independently, I employed a subsequent series of three whole-brain *t*-tests to verify and supplement the results of the initial analysis.

4.2.6 Statistical thresholding

All statistical maps presented and interpreted below were given an uncorrected statistical threshold of $p < .005$. A cluster-correction algorithm was then used to mathematically determine the number of functional voxels that a given cluster must be in order to be 95% certain that the cluster did not occur simply due to chance. This so-called cluster correction is a common way to account for the inflation of type I error due to comparisons across multiple voxels (Forman, Cohen, & Fitzgerald, 1995). For any significant F-statistics, post hoc contrasts were conducted to clarify the directionality of the significant effect. Each contrast was corrected for multiple comparisons using the Bonferroni method.

All figures are presented in radiological convention, i.e., seen from below, resulting in the right side of the image representing the left side of the body and vice versa. Any supplemental bar charts are meant only as rediscriptions of the significant effects. The bars within the bar charts represent z-standardized parameter estimates. Error bars represent standard error of the mean of the parameter estimates.

4.3 Results

4.3.1 Unimodal Effects

4.3.1.1 Conjunction of visual response

The conjunction of visual response revealed a wide network of regions including much of the occipital cortex, the bilateral superior parietal lobe, left pre- and postcentral sulcus, and the superior frontal gyrus spanning the midline of the brain.

4.3.1.2 Conjunction of auditory response

The conjunction of auditory response revealed a similarly large collection of regions including bilateral superior temporal regions and an activation spanning the left precentral and postcentral sulcus. The conjunction of these conditions was also found in anterior medial regions of primary visual cortex. This analysis also yielded a reverse conjunction. Bilateral posterior regions of primary visual cortex showed a response in which both conditions were significantly less active than baseline.

4.3.1.3 Contrast of visual response to letters and numerals

No regions were found that showed significantly differential response to visually presented letters and visually presented numerals.

4.3.1.4 Contrast of auditory response

The left angular gyrus (see Figure 4.2) showed significant main effect of notation. This effect was characterized by significant activation in response to letter names *t* (19) = 3.18, *p* < .05 as well as letter sounds *t* (19) = 5.51, *p* < .05, but not to number names *t* (19) = .385, *p* = .7.

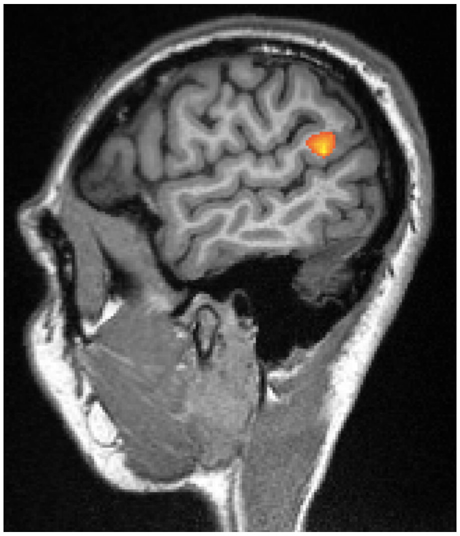

Figure 4.2 Significant main effect of notation in left angular gyrus.

4.3.1.5 Number specific activations

To identify regions that showed more unimodal activation in response to numerical stimuli relative to letter stimuli, I conducted a conjunction analysis of (numerals > letters) ∩ (number names > letter names). No regions showed a significant response to this analysis.

4.3.2 Bimodal Effects

4.3.2.2 Main effect of notation

A main effect of notation (LS, LN, NN collapsed across congruent and incongruent trials) was found in three regions of the cortex. The right supramarginal gyrus (SMG) showed a greater response during the NN condition relative to the conditions utilizing letters. Conversely, two regions in and around the left fusiform gyrus showed more activity in response to letters than numerals. One region spanning parts of the left lingual gyrus and left fusiform gyrus showed significant activation in the LN condition relative to the other two conditions, as revealed by post-hoc contrasts. The second region, located ventrolateral to the former and encompassing portions of the inferior occipital gyrus and the fusiform gyrus, showed stronger response to the two letter conditions than the numeral condition. Please see Figure 4.3 for details.

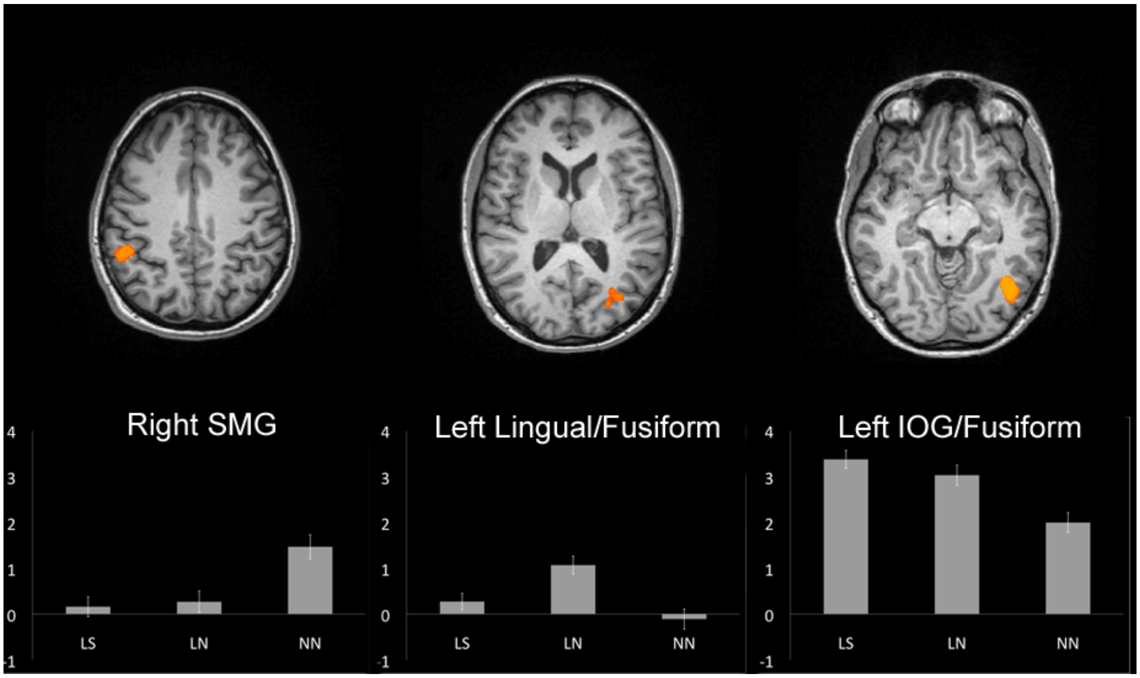

Figure 4.3 Regions showing a significant main effect of condition across both levels of congruency including the right SMG (47, -38, 42), the left lingual/fusiform gyrus (-31, -68, 9), and the left IOG/fusiform gyrus (-40, -59, -6). Bar charts are included to illustrate the nature of the interaction. The bars within the bar charts represent *z*-standardized parameter estimates of the (from left to right) letter-letter sound pairs (LS), letter-letter name pairs (LN), and numeral-number name pairs (NN). Error bars represent standard error of the mean of the parameter estimates.

4.3.2.3 Main effect of congruency

A main effect of congruency was found across an extensive bilateral fronto-parietal network of brain regions, reported in full in Table 4.1. The pattern of activity in each of these regions is characterized by an incongruency effect, or greater activation during the incongruent relative to the congruent pairs, across all three conditions. No region showed a significant congruent > incongruent effect across all three conditions.

Table 4.1 Regions showing a main effect of congruency (incongruent > congruent).

	X	Y	Z
Right inferior temporal gyrus	60	-53	-3
Right middle frontal gyrus	39	28	39
Right inferior frontal gyrus	47	-2	18
Right intraparietal sulcus and surrounding parietal lobules	32	-44	39

Cerebellum	2	-71	-33
Left middle and inferior frontal gyri	-43	16	33
Posterior cingulate	-4	-56	18
Left intraparietal sulcus and surrounding parietal lobules	-40	-56	42
Left middle and inferior temporal gyri	-46	-38	3

Descriptions and Talairach coordinates are presented for each region.

4.3.2.1 Interaction between congruency and notation

A significant interaction between audio-visual congruency and notation was found in three regions of the superior temporal cortex. One region in the right posterior STG (Figure 4.3) and two regions in the left STG (Figure 4.4), one anterior and one posterior showed a significant interaction. The bar charts in the bottom sections of Figures 4.3 and 4.4 illustrate the pattern of the interaction. A congruency effect, characterized by greater activation in response to congruent relative to incongruent audiovisual pairs (see the two rightmost bars in each chart) is present in the numeral-number name and letter-letter name conditions. A comparable congruency effect is absent in the letter-letter sound condition. To help clarify this effect further, I looked for an effect of congruency in each notation individually. Figures 4.5 and 4.6 illustrate a significant congruency effect in the left STG in response to both the letter-letter name pairs and the numeral-number name pairs. I then performed an additional analysis of variance to test for an interaction of congruency and condition across the whole brain, but only within the NN and LN pairs. No interaction was detected, suggesting commonality in the audiovisual integration of LN and NN pairs. No effect of congruency was found for the letter-letter sound pairs when the congruency effect was analyzed for this condition alone, even when I reduced the threshold to $p < .05$ uncorrected.

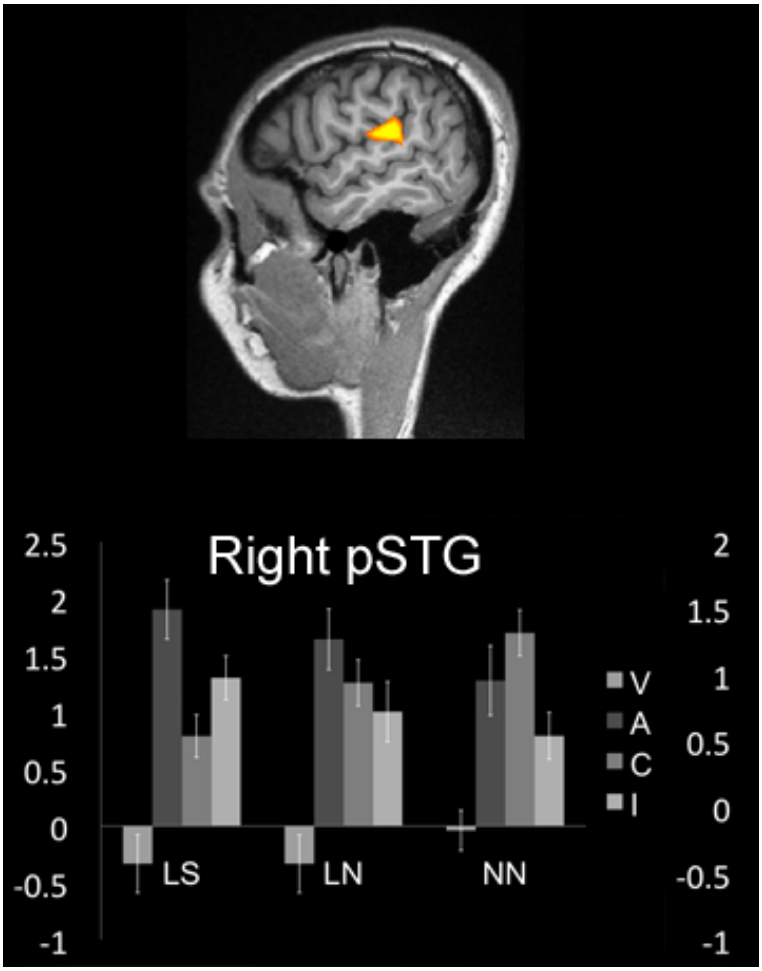

Figure 4.4 Significant congruency by notation interaction in the right pSTG (44, -32, 21).

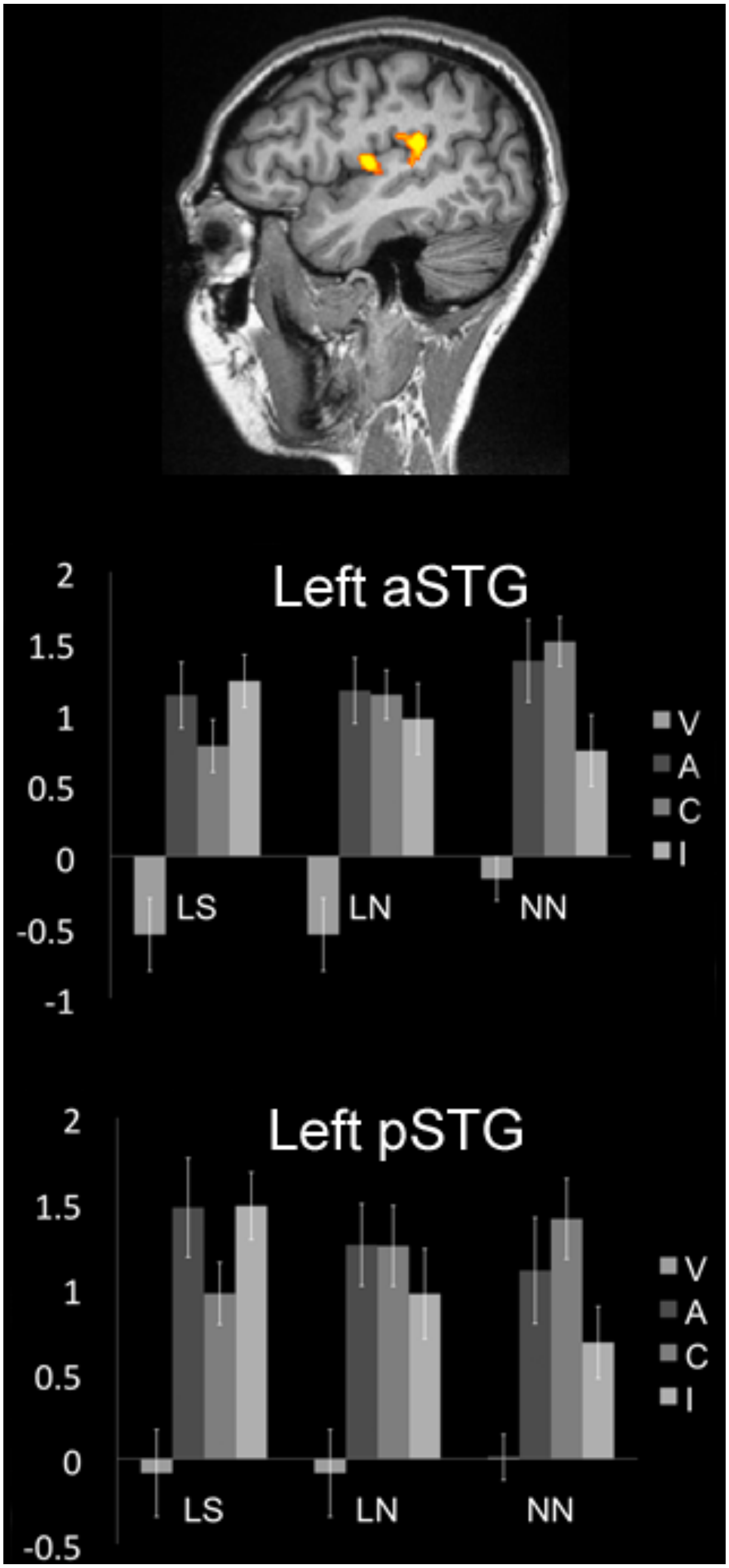
Left aSTG
2
1.5
1
0.5
0
-0.5
-1
LS
LN
NN
V
A
C
I
Left pSTG
2
1.5
1
0.5
0
-0.5
LS
LN
NN
V
A
C
I

Figure 4.5 Significant congruency by notation interaction in the left anterior STG (aSTG) (-46, -8, 8), and the left posterior STG (pSTG) (-43, -28, 9). Bar charts are included to illustrate the nature of the interaction. The bars within the bar charts represent *z*-standardized parameter estimates of the (from left to right) visual, auditory, congruent, and incongruent conditions. Error bars represent standard error of the mean of the parameter estimates.

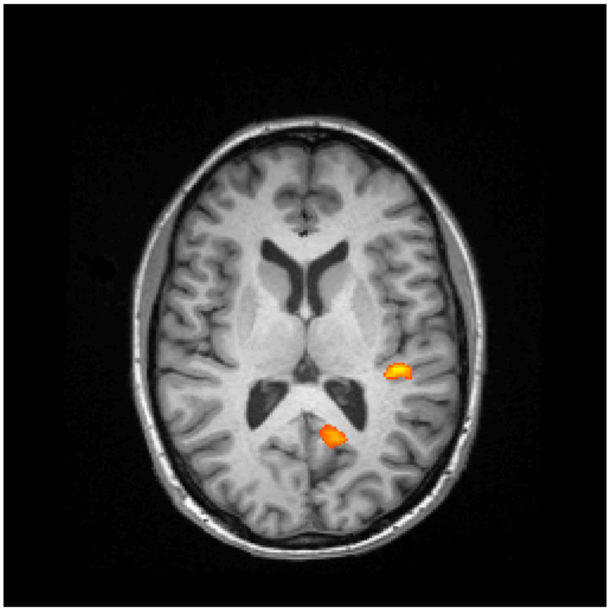

Figure 4.6 A region in the left STG (-40, -26, 12) showing a significant congruency effect in response to letter-letter name pairs.

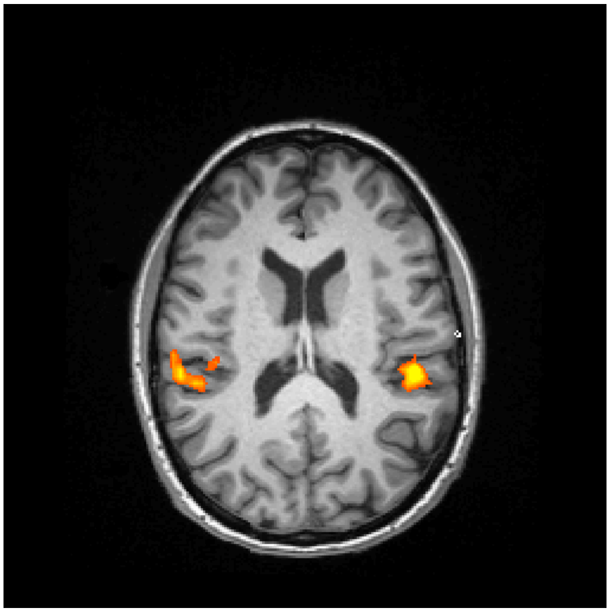

Figure 4.7 Regions showing a significant effect of congruency in response to the numeral-number name pairs, including the bilateral STG (38, -29, 9) and (-55, -8, 9). Other regions not pictured include two additional portions of the bilateral STG (56, -20, 21) and (-46, -26, 18) and, as well as the left SMG (-55, -26, 24).

4.4 Discussion

Numerical symbols, such as Hindu-Arabic numerals, are perhaps the most widely used symbolic system in the world. Across languages and cultures, Hindu-Arabic numerals convey quantitative meaning to those who know them. Since the transmission of numerical information is their primary use, it is not surprising that the vast majority of research interrogating the processing of numerals has focused on the semantic level of processing. However, numerals are more than simply semantic entities. The visual form of each numeral is associated with an auditory referent. In this way, numerals are, on the surface, very similar to letters. It is plausible, therefore, that processing the connections between auditory and visual information embedded in numerals relies on neural circuits highly similar to those used for the audiovisual processing of letters. On the other hand, numerals differ from letters in that their principal referent is semantic, not auditory. It is, therefore, also plausible that reading numerals would rely on neural circuits unique from those used in letter reading. In this experiment, I employed fMRI to examine the veracity of these two opposing possibilities. I measured the neural response to unimodal visual, unimodal auditory, congruent audiovisual, and incongruent audiovisual stimulation in the form of numerals and letters. I then compared and contrasted the neural responses to these four conditions in the three types of audiovisual pairs. Below, I discuss the results of these analyses and their implications for my understanding of the processing of Hindu-Arabic numerals.

4.4.1 Similarities and differences in unimodal response

As expected, the conjunction between the visual and auditory processing of letters and numerals revealed primary visual and auditory regions, respectively. While no differences were found in the visual processing of letters and numerals, the auditory processing across the three symbols types revealed one salient difference. The left angular gyrus (Figure 4.2) responded significantly to letter sounds and letter names, but showed no comparable response to number names. The left angular gyrus has often been implicated in phonological processing, and in particular, categorical phoneme detection (for reviews see Seghier, 2012; Turkeltaub & Coslett, 2010). My data are commensurate with that role of the left angular gyrus.

My results that show no differential activation for visual letters and numerals contrast with a recently reported study in which two regions in the left angular gyrus were shown to be active in response to the passive viewing of Hindu-Arabic numerals (Price & Ansari, 2011). In that study, participants viewed four conditions: numerals, scrambled numerals, letters, and scrambled letters. A region in the left ventral angular gyrus showed more activation for numerals relative to all other conditions. In addition, a region in the left dorsal angular gyrus showed more activation for letters and numerals relative to scrambled letters and numerals. My study, in contrast, showed no difference in response to visually presented numerals and letters. This difference could reflect that the activations reported by Price & Ansari (2011) resulted from the contrast of whole symbols with scrambled versions, whilst my contrast did not involve scrambled versions of the stimuli.

My results also conflict with previously reported findings by Eger and colleagues (2003). In this study, participants monitored a stream of unimodal auditory and visual letters, numbers, and colors and pressed a button whenever a target was presented, in either the visual or the auditory modality. When the neural response during the presentation of numerical stimuli was contrasted with the presentation of letters and colors, the authors found significant bilateral IPS activity. They suggested that because the IPS showed a response even when the task did not require them to specifically attend to the numerical meaning of the numerals and number names, that the simple presentation of numerical stimuli automatically activates the associated numerical magnitude representation. In my results, I found no evidence that the IPS showed activation in unimodal numerals and number names relative to unimodal letters, letter names, and letter sounds. One reason for this discrepancy could be the difference in attentional components across the two studies. In the results reported by Eger et al., participants were monitoring streams of stimuli for a particular target and, therefore, were required to directly compare each visual or auditory numerical stimulus to this target. My study, in contrast, was truly passive as no attentional demands were placed on participants as they viewed or listened to the stimuli.

4.4.2 Similarities and differences in bimodal response

4.4.2.1 The congruency effect

In the congruency effect analysis, I contrasted the neural response to congruent audiovisual pairs with the response to incongruent audiovisual pairs. The results of this suggest that the audiovisual processing of numbers and letters relies on highly comparable brain regions. As seen in Figures 4.4, 4.5, and 4.6, both the NN condition and the LN condition recruited the left posterior superior temporal gyrus to a significantly greater extent when the audiovisual pairs were congruent relative to when they were incongruent. This congruency effect is considered the litmus test of audiovisual integration in the brain (Goebel & van Atteveldt, 2009). In other words, because the superior temporal cortex is associated a wide variety of multisensory tasks, it is expected to respond robustly when simultaneous auditory and visual information is presented (Beauchamp et al., 2004; Driver & Noesselt, 2008; Ghazanfar & Schroeder, 2006; Stein & Stanford, 2008) Thus, it is crucial to test not only for audiovisual processing, but for an effect of audiovisual congruency. This ensures that the isolated regions are sensitive to the link between a specific visual stimulus and its specific auditory referent. The activation in the bilateral STG also converges with previous literature, conducted with Dutch participants, that implicates the STG in the audiovisual integration (congruent > incongruent) of letters and letter sound pairs (see Blomert, 2011; Blomert & Froyen, 2010 for reviews). Taken together, the results of this analysis support the notion that the reading of both letters and Arabic numerals relies on highly comparable audiovisual processes in the brain.

Due to the paucity of research into the topic, it is challenging to situate my findings in the context of a broader literature on audiovisual processing of numerals. It has been previously theorized that the left angular gyrus would be involved in the audiovisual processing of numerical symbols due to its repeated implication in arithmetic fact retrieval (Dehaene & Cohen, 1995; Dehaene, Piazza, Pinel, & Cohen, 2003). This theory posits that when facts such as 8 X 4 = 32 are learned, they are learned in a purely verbal way, i.e., the problem 8 X 4 is associated directly with the solution 32 without any intervening semantic processing of the numbers. The angular gyrus, it was suggested, mediates this asemantic, verbal processing of numerals. More recent theory has suggested that the left angular gyrus is involved in accessing the stored solution of the problem from long term memory (Zamarian, Ischebeck, & Delazer, 2009). While retrieving verbal mathematical facts from memory clearly involves an amount of audiovisual processing, the complexity of tasks that elicit angular gyrus activation disallows simple explanations of the left angular gyrus' role in numerical processing. In contrast, the audiovisual processing involved in my experiment was relatively straightforward and more "process pure" in that the congruency effect simply identifies regions that are tuned to the learned association between a visual symbol and its auditory referent.

Eger and colleagues (2003) (discussed above) suggested that the semantic representations housed in the intraparietal sulcus can be automatically activated by passive tasks. However, the task they used was not entirely passive and required that participants compare numbers to a target. In the completely passive environment of my study, no evidence of IPS activation was found. This suggests that the presence of numerical stimuli does not necessarily evoke representations of numerical magnitude. Moreover, it suggests that the audiovisual processing of NN pairs occurs independently from the semantic processing of numerals. Future research will be needed to clarify how the audiovisual processing of the superior temporal lobe integrates with the semantic representations of the parietal lobe in the service of tasks, such as arithmetic, that utilize the both audiovisual and semantic representations.

4.4.2.2 The potential role of orthographic transparency

Surprisingly, I found no evidence of a congruency effect in the superior temporal gyrus in one of my control conditions: letter and letter sound pairs. This appears to contradict both previous data published on this relationship and my own claims of a common substrate of audiovisual processing in numerals and letters. However, it might instead provide greater nuance into the role the STG plays in audiovisual integration. A large number of studies have showed audiovisual integration in bilateral STG in Dutch readers (Blau et al., 2010; Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009; Froyen, Bonte, van Atteveldt, & Blomert, 2009; van Atteveldt, Blau, Blomert, & Goebel, 2010; van Atteveldt, Formisano, Blomert, & Goebel, 2007; van Atteveldt, Formisano, Goebel, & Blomert, 2004, 2007; van Atteveldt, Roebroeck, & Goebel, 2009). This has lead some theorists to argue that the STG becomes tuned to pairings between letter and letter sounds only because such pairings are highly regular in a transparent orthography, such as that found in Dutch (Blomert, 2011). In the Dutch alphabet, each letter corresponds to one and only one letter sound. Hence the correspondence between letter and sound is considered 100% transparent. In contrast, LS pairs in English are opaque. The letter “t” can sound like /t/ when in the word “meter,” /sh/ when in the word “motion,” and /th/ when in the word methane. The correspondence between the visual letter and its auditory referent depends on context. Blomert (2011) hypothesized that the congruency effect in the STG reflects the transparency of the Dutch orthography and, therefore, might not be found in English.

My data converge with and extend this hypothesis. When English readers are presented with NN or LN pairs, the congruency effect is highly comparable to the congruency effect seen in Dutch readers. In contrast, when English readers are presented with LS pairs, the congruency effect is absent. The similarity between NN and LN pairs on the one hand and Dutch LS pairs on the other hand could be due to the transparency of the audiovisual pairs. However, one might argue that the English LS pairs I selected for my study are, in themselves, highly transparent. It is here that my data expand on the previous theory. Rather than reflecting a feature of the transparency of the audiovisual pairs directly, I propose that the congruency effect in the STG emerges only when the audiovisual pairs are learned in a context in which they are always transparent. While the single letter English LS pairs used in my study are transparent on their own, the regularity of their audiovisual relationships becomes much more irregular in the context of reading whole words in English. Thus, the context in which English LS pairs are learned is one in which the audiovisual pairs are regularly changing depending on the word in which the letters appear. In contrast, the other three audiovisual types (LN, NN, and Dutch LS) are learned in a context in which the transparency of the audiovisual pairs is always 100%. In light of this, I suggest that the congruency effect reflects the context in which audiovisual pairs are learned rather than the transparency of the particular audiovisual pair.

4.4.2.3 Audiovisual processing across levels of congruency

As discussed above, the integration of numerals and number names is best measured by the effect of congruency. This congruency effect was clearly localized to the bilateral superior temporal gyrus. However, I was also curious whether differences between symbols types existed across audiovisual processing as a whole. As illustrated in Figure 5, when the three pair types were compared across both congruent and incongruent pairs, the right supramarginal gyrus showed greater modulation to numerals than it did to either letter condition. At this juncture, I can only speculate as to the role this region plays in the audiovisual processing of numerals. The supramarginal gyrus, which is located just anterior and lateral to the angular gyrus, has been implicated in one study whose questions were relevant to the present findings. Roux and colleagues reported results from an electrocortical stimulation study conducted over 6 years in which various areas of the neocortices of 53 patients were stimulated just prior to neurosurgery (Roux, Lubrano, Lauwers-Cances, Giussani, & Démonet, 2008). Of the 257 language areas stimulated in the study, 3 regions resulted in the specific impairment of numeral reading: the dominant supramarginal gyrus, a section of the fusiform gyrus, and a portion of Broca's area. While this study converges with ours to implicate the supramarginal gyrus in the auditory processing of number names, my studies differ in the laterality of the findings.

Relative to audiovisual processing of NN pairs, LN and NN pairs showed significant activation in the left fusiform gyrus. This region has repeatedly been implicated in the visual processes of reading (Cohen et al., 2000; Dehaene & Cohen, 2007; McCandliss, 2003; Schlaggar & McCandliss, 2007). Because my findings relate to the audiovisual and not simply the visual processing of letters, they could suggest that the fusiform gyrus, like superior temporal regions, is involved in audiovisual processing of letters in general, but not specifically involved in audiovisual integration (i.e., not significantly more active for congruent relative to incongruent pairs). The difference between LN/LS pairs and NN pairs could also be seen to contrast with the data reported in Chapter 3 in which the fusiform gyrus was sensitive to the visual form of the numerals. This lack of convergence could be due to differences in the analysis used. In Chapter 3, the analysis was designed to look for parametric response to changes in numeral shape, whereas the present analysis collapsed across all numeral shapes and compared this to baseline.

4.4.2.4 Processing incongruency across symbol type

On a final note, my analysis also revealed a main effect of congruency across all three audiovisual pair types. An examination of the parameter estimates suggests that this effect would be better described as a main effect of incongruency. That is, across all three pair types, a highly similar network of regions responded more robustly to incongruent relative to congruent audiovisual pairs. These regions are commonly found in studies of task-related cognitive conflict (for review, see Roberts & Hall, 2008). Importantly, this main effect of incongruency verifies that participants were able to notice the incongruency across all three types of audiovisual stimuli. Therefore, it cannot be argued that the lack of a congruency effect in LS pairs reflects an inability of participants to distinguish congruent from incongruent letter letter sound pairs.

In summary, this study explored the neural correlates underlying the audiovisual processing of numerals and compared these with those involved in the audiovisual processing of letters. Broad similarities were found in the visual and auditory processing of both letters and numerals. In addition, the audiovisual integration of numerals with their number names was highly similar to the audiovisual integration of letters and letter names. Interestingly, comparable activation in response to the audiovisual integration of letters and speech sounds was absent, potentially suggesting a role of orthographic transparency in audiovisual processing in English. Future research is required to examine the interplay between audiovisual and semantic processing of number. Of particular interest is whether individual differences in the audiovisual processing of number are related to individual differences in semantic or mathematical processing. Equally important is the exploration of neural connections between the inferior parietal semantic regions of number and the superior temporal audiovisual regions identified by this study.

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Chapter 5: Conclusion

5.1 Summary of results

Numerical symbols are one of the most common and important stimuli in modern life. Yet despite their ubiquity, little is known about how the brain processes the visual, auditory, audiovisual, and semantic information that is embedded in such symbols. To fill this gap in our understanding of numerical neurocognition, this thesis presented three empirical studies designed to characterize the neurobiological correlates associated with processing Hindu-Arabic numerals (see Figure 5.1 for summary).

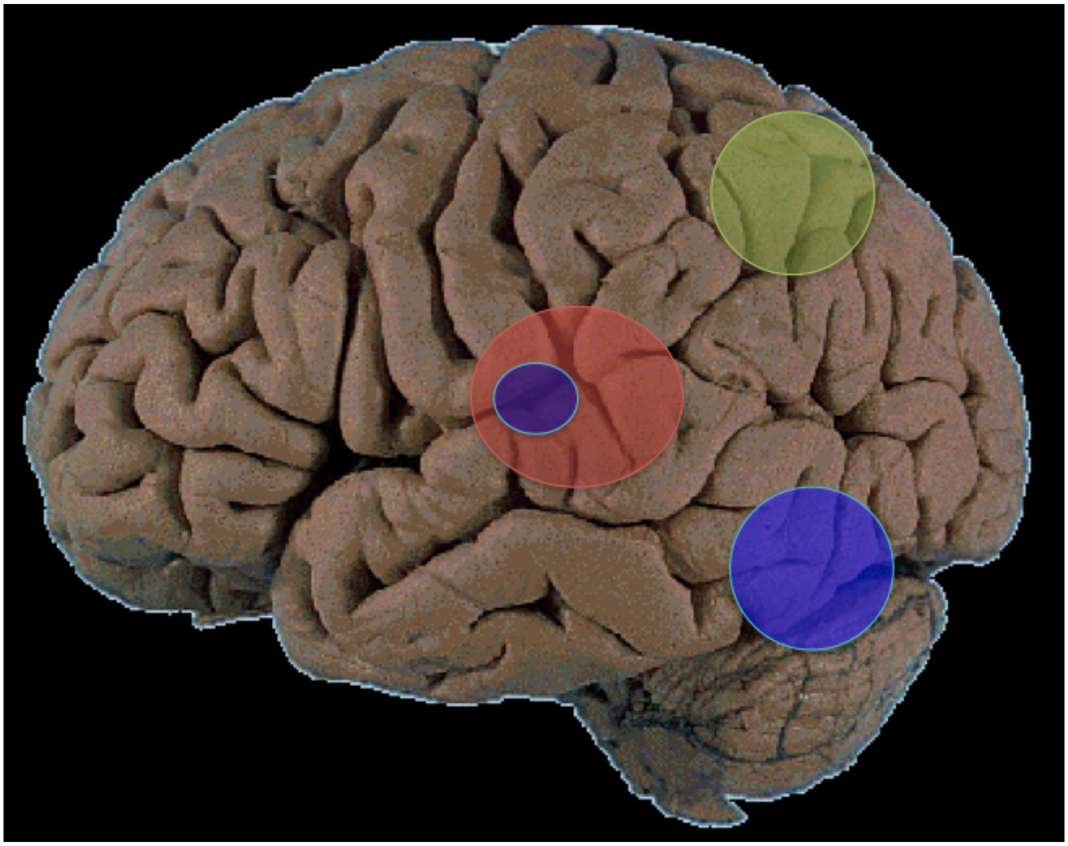

Figure 5.1 Cartoon summary of brain regions described in the three studies above. The semantic processing of numerical magnitude associated with symbols is associated with the intraparietal sulcus (green). The processing of the visual form of numerals is associated with the fusiform gyrus (blue). The auditory processing of numerals is associated with activation in the superior temporal cortex (red). A subsection of this region is implicated in the processing of audiovisual information in numerals (purple).

In Chapter 2, the neural correlates of Hindu-Arabic numerals were compared with those of non-symbolic arrays. The analysis revealed brain regions associated with each stimulus format specifically, as well as correlates shared across symbolic and non-symbolic representations. The comparison of numerals relative to non-symbolic arrays was correlated with activity in the left superior temporal gyrus (STG) and the left angular gyrus (AG). The reverse contrast revealed that the right posterior superior parietal lobe was associated specifically with the comparison of non-symbolic arrays. In addition to areas specifically modulated by numerical symbols or non-symbolic arrays, a common representation was found in the right intraparietal sulcus (IPS), whose activity was correlated with both symbolic and non-symbolic comparison. The data were interpreted as reflecting specific encoding pathways for numerals in the STG and AG that converge upon an abstract numerical magnitude representation housed in the IPS. While these data describe broad differences between symbolic and non-symbolic processing, they were not able to specifically address the brain regions that are involved in the semantic, relative to the asemantic, processing of numerical symbols. That question requires a comparison between numerically meaningful and novel symbols—a reflection that inspired Chapter 3.

In Chapter 3, a cross-linguistic fMRI adaptation paradigm was used to compare the processing of Hindu-Arabic numerals and the numerical ideographs found in written Chinese. The neural responses to these two types of symbols were collected in two groups: a group of individuals who could read both the ideographs and the numerals and a control group of individuals who could read only the numerals. Both groups showed evidence of semantic processing of numerals in the left IPS and visual processing of numerals in the left fusiform gyrus (FG). Relative to the control group, the Chinese readers showed activity in the right IPS in response to ideographs. Within the control group, the only region that responded to ideographs was the left FG. The results were interpreted as reflecting semantic processing of numerical symbols in the IPS and asemantic visual processing of numerical symbols in the FG. This experiment was able to isolate the visual and semantic correlates of numerical symbols, but was silent regarding asemantic auditory processing. This curiosity about the auditory and audiovisual processing of numerals led to Chapter 4.

In Chapter 4, the visual, auditory, and audiovisual correlates of numerals and their associated number names were compared with two control conditions: letter-letter names and letter-letter sounds. The results suggested a high degree of overlap between the visual and auditory processing of numerals and letters, but some differences in regions responding to audiovisual integration were found. The congruency effect, which is the litmus test of audiovisual integration, showed expected activation in bilateral superior temporal regions for congruent numeral-number name pairs (NN) and left lateralized activation in response to congruent letter-letter name pairs (LN). STG activation was absent in letter-letter sound pairs (LS), which potentially reflects a difference in the orthographic transparency of LS pairs relative to NN and LN pairs. Overall, the neural correlates were quite similar across letters and numerals, but three salient differences were found. A number specific activation was found in the right supramarginal gyrus (SMG) for audiovisual numerals relative to audiovisual letters.

Inversely, the left FG showed more activity for audiovisual letters than for audiovisual numerals. Finally, auditory letter sounds and letter names showed significantly more activation in the left AG than auditory number names.

Together, these three studies give the first account of the neural correlates underlying the visual, auditory, audiovisual, and semantic processing of numerical symbols. Below, each of these levels of representation is considered in more detail. The subsequent section will discuss what the results of these experiments can tell us about the automatic versus deliberate activation of these levels of representation. Following this is a review of the limitations of these studies and future directions that this line of research could take.

5.2 Visual processing of numerals

Evidence for the neural correlates of the visual processing of numerals was found in the cross-linguistic study of Chapter 3. In the analysis, the neural response to a parametric ratio-dependent predictor was compared with the neural response to a parametric shape-dependent predictor. This comparison suggested that the left FG is involved in the visual processing of numerals. This conclusion was supported by the control group, in which the only region that responded to the novel numerical symbols (ideographs) was the left FG. Taken together, these data suggest that the left FG is sensitive to differences in symbol shape.

The audiovisual experiment of Chapter 4 adds nuance to the role that the left FG plays in the visual processing of numerals. In that study, the visual presentation of both letters and numerals was related to activation in bilateral visual cortex, including the FG. This activation did not differ between numerals and letters, as a comparison of the neural correlates to unimodal visual letters and unimodal visual numerals showed no differences. This suggests coarse similarities between the visual processing of numerals and letters. However, the left FG also showed an important symbol-related difference in this study. Collapsed across congruent and incongruent audiovisual pairs, the left FG showed significant modulation to audiovisual letters and no comparable modulation to audiovisual numerals. This difference could suggest that the audiovisual processing of letters requires more visual information than that of numerals, potentially due to the differences in orthographic transparency between numerals (which are always transparent) and letters (which are transparent with their names but not with their sounds).

The role of the fusiform gyrus has long been theorized to be involved in the visual processing of numerals (Dehaene & Cohen, 1995). While the present data confirm this hypothesis, a recent report found no evidence of FG activation for the visual processing of numerals (Price & Ansari, 2011). In their experiment, the authors passively presented participants with both whole and scrambled numerals and letters. Their results indicated that only the left angular gyrus was recruited during the passive viewing of whole letters and numerals relative to their scrambled counterparts.

Moreover, another portion of the left AG showed more modulation for numerals relative to letters. The present study, in contrast, showed no evidence of AG activation in response to the visual processing of numerals. One reason for this discrepancy is the difference between the tasks involved in each experiment. Price & Ansari asked participants to monitor a hash mark (#) and to indicate, with a button press, whenever that symbol turned red. The experiment detailed in Chapter 3 asked participants to monitor the numerical symbols directly and indicate whenever a red symbol appeared. While this difference is small, it could be important. In the present experiment (Chapter 3), the salient feature (press a button whenever the symbol turns red) had to be detected within the visual form of the numeral. In the experiment reported by Price & Ansari, the visual form of the numerals and letters were not important. Only the hash mark required attention. This could indicate that the left FG is not automatically activated by the presence of numerical symbols, but instead activated when the shape of the numerals is the feature to which participants are attending. These findings highlight the potential effects of task set on the neural activations observed.

5.3 Auditory and audiovisual processing of numerals

Chapter 4 demonstrated that the auditory processing of number names was localized to regions spanning large portions of the superior temporal cortex. This activity was highly similar to that which responded to letter names and letter sounds as confirmed in the conjunction analysis. The only regions that showed significant notation-related differences in auditory processing was the left angular gyrus, which was more active during the two letter conditions than the number name condition. The involvement of the left angular gyrus is likely related to the discrimination of phonemic information during the audiovisual letter tasks (Turkeltaub & Coslett, 2010).

The audiovisual integration (distinguishing congruent from incongruent pairs) of numerals and number names was localized to bilateral regions of the posterior superior temporal gyrus, which is commensurate with previous research highlighting the importance of this region in audiovisual integration of letters (Blomert & Froyen, 2010; van Atteveldt, Formisano, Goebel, & Blomert, 2004). The role of this region in audiovisual processing can help clarify the results of the experiment presented in Chapter 2. In that experiment, symbolic numerical comparison elicited activation in this the left STG relative to non-symbolic comparison and both control conditions. Against the background of the results from Chapter 4, the involvement of the STG in Chapter 2 may suggests that participants who perform a symbolic numerical comparison task are recruiting auditory referents of numerical symbols to help them complete the task.

5.4 Semantic processing of numerals

The IPS has repeatedly been associated with the representation of numerical magnitude (Brannon, 2006; Dehaene, Piazza, Pinel, & Cohen, 2003; Nieder & Dehaene, 2009). The data reported in Chapters 2 and 3 are consistent with this interpretation of IPS activity. In Chapter 2, the right IPS was commonly activated in both symbolic and non-symbolic comparison relative to the control tasks. The results of Chapter 3 also implicated the IPS, but in the opposite hemisphere of the brain. The left, but not the right IPS showed a significant adaptation/rebound response to numerals, which is thought to reflect this region's sensitivity to the representation of numerical magnitude associated with the symbols. In contrast to Hindu-Arabic numerals, the neural response to numerical ideographs was more bilateral. The right IPS showed the strongest tuning to the semantics of the ideographs, but, at a slightly lower threshold, the left IPS also showed sensitivity to the numerical meaning of the ideographs.

Although the data presented in Chapters 2 and 3 clearly implicate the IPS in the semantic processing of numerals, the laterality of this effect is challenging to interpret. Some theorists have speculated that the left IPS becomes specialized for the symbolic representation of numerical magnitude (Ansari, 2007, 2008). The data presented in this thesis are only partially commensurate with this hypothesis. While only the left IPS showed specificity for the representation of Hindu-Arabic numerals in Chapter 3, the right IPS was implicated in the representation of numerical ideographs. In addition, activity in the right IPS was significantly correlated with the numerical comparison of Hindu-Arabic numerals in Chapter 2. Thus, the data suggest that non-symbolic arrays and Chinese ideographs are represented in the right IPS, while the representation of Hindu-Arabic numerals is sometimes associated with right IPS activity and sometimes associated with left IPS activity.

One reason for the laterality differences reported in these data could be the expertise associated with different levels of representation. Research investigating the neural correlates of numerical representation in infants, who have very little experience with numerical magnitude and none with numerical symbols, has implicated the right IPS (Hyde & Spelke, 2011; Izard, Dehaene-Lambertz, & Dehaene, 2008). In addition, the right IPS seems to be implicated in the common representation of symbolic and non-symbolic numerical magnitude as demonstrated in Chapter 2 and in other data (Holloway & Ansari, 2010). In other words, it is possible that the right IPS houses the basic non-symbolic representation of numerical magnitude, which becomes associated with numerical symbols over development. The left IPS, in contrast, could house a more refined, experience-dependent representation that emerges as individuals become more experienced with using numerical symbols in the precise manner needed to perform arithmetic. The data from Chapter 3 support this notion as the representation of numerical ideographs, which are not used for arithmetic in Chinese culture, was associated with right IPS activity and the representation of Hindu-Arabic numerals, which are used for mathematics in Chinese culture, was associated with the left IPS. However, this interpretation is speculative. It falls to future studies to clarify the differential role of the left and right parietal lobe in the representation of numerical symbols.

5.5 Recruitment of representations: intentional or automatic?

In addition to yielding a description of the neural correlates associated with the auditory and semantic representations of numerals, the results of these three studies provide insight into whether these levels of representation are intentional or automatically evoked during various tasks. Simply put, when one sees a Hindu-Arabic numeral, do either the auditory or semantic representations associated with that symbol become active automatically? The following discussion uses the results of Chapters 2-4 to address this question.

5.5.1 Automatic activation of auditory referents

In Chapter 4, the auditory and audiovisual processing of numerals was associated with activity in bilateral STG. The STG was also implicated in Chapter 2, as the semantic comparison of numerals elicited activation in the left superior temporal gyrus to a significantly greater extent than did the comparison of non-symbolic numerical stimuli. Why would the STG be more active during symbolic comparison relative to non-symbolic comparison? One possibility is that viewing numerals automatically activates the auditory referent associated with them. However, Chapter 3 showed no involvement of the STG during the passive viewing of numerical symbols. While null results should always be interpreted cautiously, this could suggest that the auditory processing of numerals depends on how the numerals are used in a particular task.

5.5.2 Automatic activation of semantic referents

A similar question could be asked of the semantic processing of numerals. Both behavioral (Dehaene & Akhavein, 1995; Girelli, Lucangeli, & Butterworth, 2000; Rubinsten, Henik, Berger, & Shahar-Shalev, 2002) and neuroimaging (Ansari, Dhital, & Siong, 2006; Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003; Piazza, Pinel, Le Bihan, & Dehaene, 2007) studies have argued that numerical magnitude representations are automatically activated even when they are task irrelevant. For example, Eger and colleagues (2003) found that bilateral IPS was activated in response to numerals when participants were simply asked to scan a series of stimuli for a target. Because the task can be completed with only the visual information of the stimuli and not their semantic meaning, Eger et al. argued that the presence of numerals automatically elicits representations of numerical magnitude. The data from the audiovisual integration study of Chapter 4 conflict with this account. In this study, the comparison of numerical vs. non-numerical stimuli did not reveal activity in the IPS, but rather in the right supramarginal gyrus. These data find convergence with those reported by Price & Ansari (2011) who also showed no IPS activation in response to the passive viewing of numerals. One reason for the discrepancy between these data and those reported by reported by Eger and colleagues, is that the latter were collected from an active task that involved comparing a numeral to target. It is possible that participants were making this comparison, not based solely on the visual features of the numerals, but also on their numerical value.

This could account for why the IPS was activated during that task, but not during the passive viewing of numerals in Chapter 4 or in Price & Ansari (2011).

It must also be acknowledged, however, that the passive viewing of numerals was related to IPS activity in Chapter 3, where a clear adaptation/rebound response was seen in the left IPS. In other words, the passive viewing of numerals automatically elicited ratio-dependent IPS activation in Chapter 3, but did not in Chapter 4. This difference could be due to the analyses used in the two studies. The adaptation paradigm uses an analysis that is highly sensitive to ratio-dependent modulation. Therefore, it is possible that this analysis is able to detect IPS activity that is too subtle to be seen in a coarser level of analysis such as numerals > letters.

In summary, the results of these three studies cannot definitively address whether semantic and auditory referents of numerical symbols are automatically activated when Hindu-Arabic numerals are seen. While future research will have to clarify this issue, is seems likely that the various representations of numerals are not automatically activated, considering how numerals are used in modern life. Although numerals such as bank balances and speed limits refer to quantitative referents, other numerals such as those found on sports jerseys or fast food value menus are simply nominal designations rather than quantitative ones. Thus, individuals are often faced with situations where the numeral 5 does not refer to five of anything, but instead to a particular thing that is called “Number 5.” Likewise, numerals are sometimes used as ordinal categories, such as in certain waiting rooms where each person is given a number to designate her place in line. In this situation, the numeral 49 does not imply that she is associated with the cardinal value of 49, but rather that she comes before the person who has numeral 50 and after the person who has numeral 48. In other words, because numerals are fluently used in a variety of contexts, the representation elicited by a given numeral is likely to be highly dependent upon the context in which it is used.

5.6 Limitations and future directions

The most significant limitation of the studies presented in this thesis is the lack of connectivity analyses between the regions that were identified. The studies identified a trifecta of regions, each of which is involved in a different level of processing of numerals. The left FG is employed to decode the visual information of the numeral's shape. The STG integrates this visual information with the auditory number name associated with the numeral. The IPS houses the numerical magnitude representations that numerical symbols convey. However, it is still unknown whether and how these various levels of representation are connected to one another in the brain. Future research that employs methods such as diffusion tensor imaging tractography or effective functional connectivity analyses will be required to identify the structural connections between these regions.

In a similar vein, the functional interaction between these differing levels of representation still remains to be studied. How, for example, do the auditory and numerical magnitude representations interact during arithmetic and does this interaction differ depending upon the type of arithmetic being performed, e.g., subtraction versus multiplication? Similarly, does the integration of numerals and number names relate to the ability to perform arithmetic in much the same way that the integration of letters and speech sounds relates to reading ability (Blau et al., 2010; Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009)?

It remains to be investigated how ordinal representations of numerical symbols interface with the visual, auditory, and semantic (cardinal) representations characterized in the above studies. One intriguing possibility is that, as children learn how to use symbolic representations of number, order processing could provide the initial link between the auditory number names and the representations of numerical magnitude. Ordinality is also another point of overlap between the processing of numerals and the processing of letters. Future studies should examine how the audiovisual representations localized in the STG interact with ordinal representation and how these, in turn, interact with representations of numerical magnitude.

Another limitation of the present body of work is that the definition of "semantic representation of numerals" was restricted only to approximate representations of numerical magnitude housed in the IPS. However, many numerical symbols used in higher mathematics have a very different kind of semantic meaning. On the one hand, constants such as pi or e refer to numerical values that can be approximated but cannot be physically represented. On the other hand, a whole class of imaginary numbers exists such as i (i.e.,) whose semantic referents cannot be represented by the approximate magnitude system. Truly understanding the neural correlates of semantic processing of numerical symbols implies understanding how the brain represents irrational and imaginary numbers as well as cardinal values. Related to both this and an earlier point, the semantic referents of numerical symbols are sometimes not numerical at all. Previously, the example of nominal representations was given, such as the numbers that dental workers assign to teeth. The meaning of the numerical symbol in that context is a particular tooth in a particular location in the mouth. Another example is the numbers given to particular tax forms. In that context, in the United States, 1040 refers to a particular form, not to the numerical value 1,040. Does the semantic processing of these nominal representations of number interface with the representation of numerical magnitude? Or is such processing more akin to the semantic processing of words?

Finally, future research will be required to characterize the developmental trajectory of numerical symbols and their neural instantiation. For example, does the auditory representation of numerals play a greater role in young children's semantic understanding of numerals than it does in adults? Do children who excel at reading numerals also excel at reading letters and words? Are children who are taught more than one form of numerical symbol (such as Hindu-Arabic numerals and Roman numerals) better able to understand numerical information in general? These and many other questions remain to be addressed as researchers clarify the development of numerical symbol processing.

5.7 General conclusion

In conclusion, the body of research presented above has identified and described the neural correlates of visual, auditory, and semantic processing of numerical symbols. Many of the brain regions implicated in these levels of processing are highly similar to those related to reading. Indeed, the ability to use numerical symbols is predicated on the ability to use language and the ability to read. However, numerals are also a special class of symbol as their principal referent is numerical magnitude, which is a system of representation that is not dependent upon language abilities. Thus, studying the neurobiology of numeral processing can help us understand how culturally-mediated information interacts with and shapes biologically-mediated systems in the brain.

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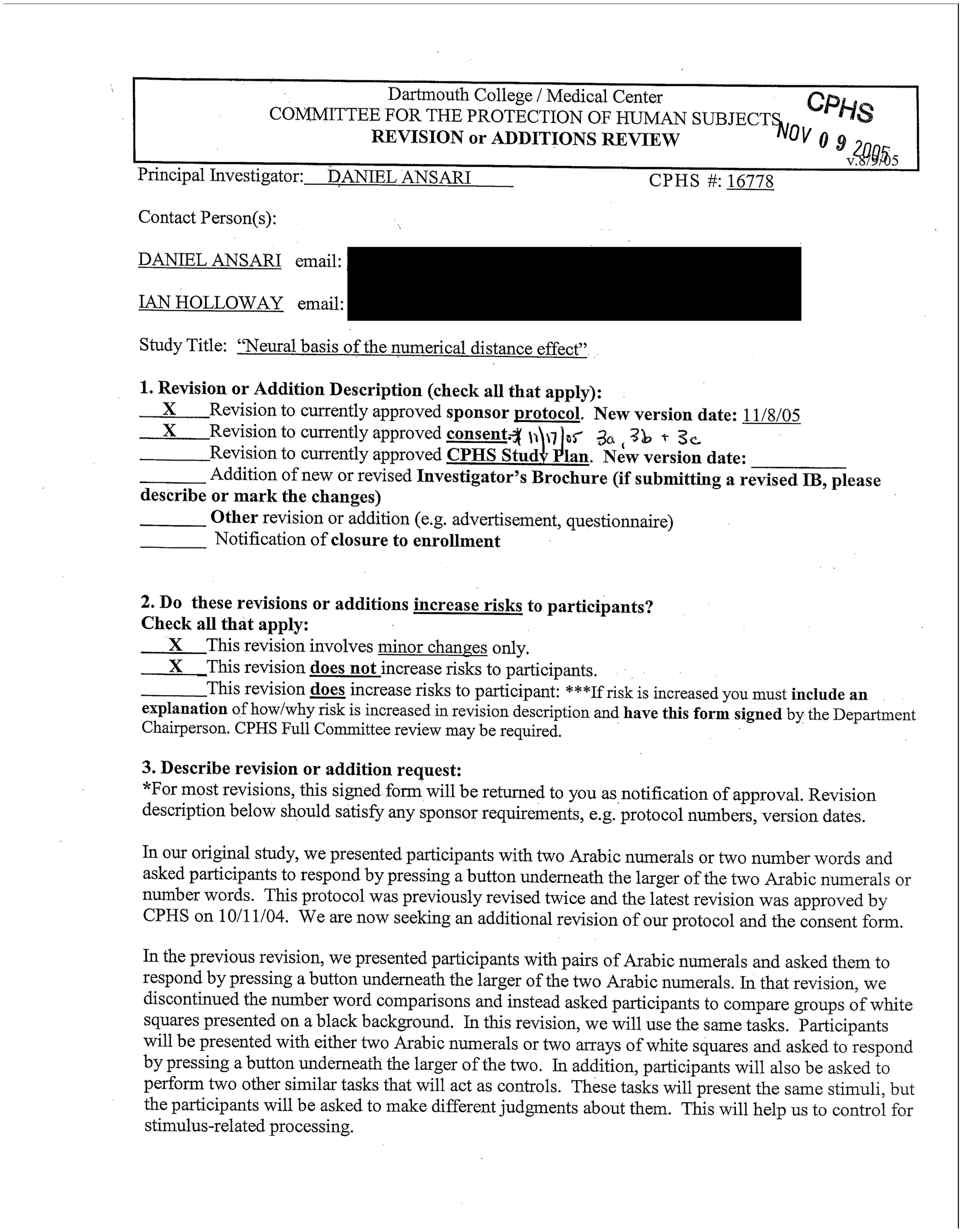
Appendix A: Documentation of ethics approval



Dartmouth College / Medical Center
COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS
REVISION or ADDITIONS REVIEW

CPHS
NOV 09 2005

v.8/9/05

Principal Investigator: DANIEL ANSARI   CPHS #: 16778

Contact Person(s):

DANIEL ANSARI email: [redacted]

IAN HOLLOWAY email:

Study Title: "Neural basis of the numerical distance effect"

1. Revision or Addition Description (check all that apply):

__X__ Revision to currently approved **sponsor protocol**. **New version date:** 11/8/05
__X__ Revision to currently approved **consent**. * 11/17/05 3a, 3b + 3c
_____ Revision to currently approved **CPHS Study Plan**. **New version date:** ______
_____ Addition of new or revised **Investigator's Brochure (if submitting a revised IB, please describe or mark the changes)**
_____ **Other** revision or addition (e.g. advertisement, questionnaire)
_____ Notification of **closure to enrollment**

2. Do these revisions or additions increase risks to participants?
Check all that apply:

__X__ This revision involves minor changes only.
__X__ This revision **does not** increase risks to participants.
_____ This revision **does** increase risks to participant: ***If risk is increased you must **include an explanation** of how/why risk is increased in revision description and **have this form signed** by the Department Chairperson. CPHS Full Committee review may be required.

3. Describe revision or addition request:

*For most revisions, this signed form will be returned to you as notification of approval. Revision description below should satisfy any sponsor requirements, e.g. protocol numbers, version dates.

In our original study, we presented participants with two Arabic numerals or two number words and asked participants to respond by pressing a button underneath the larger of the two Arabic numerals or number words. This protocol was previously revised twice and the latest revision was approved by CPHS on 10/11/04. We are now seeking an additional revision of our protocol and the consent form.

In the previous revision, we presented participants with pairs of Arabic numerals and asked them to respond by pressing a button underneath the larger of the two Arabic numerals. In that revision, we discontinued the number word comparisons and instead asked participants to compare groups of white squares presented on a black background. In this revision, we will use the same tasks. Participants will be presented with either two Arabic numerals or two arrays of white squares and asked to respond by pressing a button underneath the larger of the two. In addition, participants will also be asked to perform two other similar tasks that will act as controls. These tasks will present the same stimuli, but the participants will be asked to make different judgments about them. This will help us to control for stimulus-related processing.

The revision of 10/11 investigated the commonalities and differences in neural activation during comparisons of symbolic (Arabic numerals) and non-symbolic (Arrays of Squares) stimuli. This newest revision will be use the same protocol to replicate and extend upon the previous study. In this study we will continue focus the developmental changes of neural activation during symbolic number processing.

In addition to adding two control tasks, we are planning to use a slightly larger age range of children. Rather than using children aged 8-11 as was done in the 10/11 revision, this study will recruit children from age 6-12. By extending the age range of the children participants, we hope to find out more specifically how the functional neuroanatomy that underlies numerical processing changes over developmental time.

Recent studies have characterized the functional neuroanatomy of numeric representations in adults (Piazza *et al.*, 2004; Shuman, 2004; Kadosh *et al.*, 2005) and children (Ansari *et al.* 2005). These studies have found that children utilize different brain areas than adults for numerical representation, implying that a change in the functional neuroanatomy involved in numerical representation must occur as children develop. Hence, by studying the processing of symbolic and non-symbolic numerical magnitude over developmental time, we expect to map out this change.

New References

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Shuman, M., & Kanwisher, N. (2004). Numerical magnitude in the human parietal lobe; tests of representational generality and domain specificity. *Neuron, 44*(3), 557-569.

4. Attach revised protocol and/or consent (HIGHLIGHT all revisions) or other materials for review.

Signature of PI: electronic submission Date: ____________

Signature of Section Chief or Department Chairperson: ____________________
(Required if risks to patients are increased.)

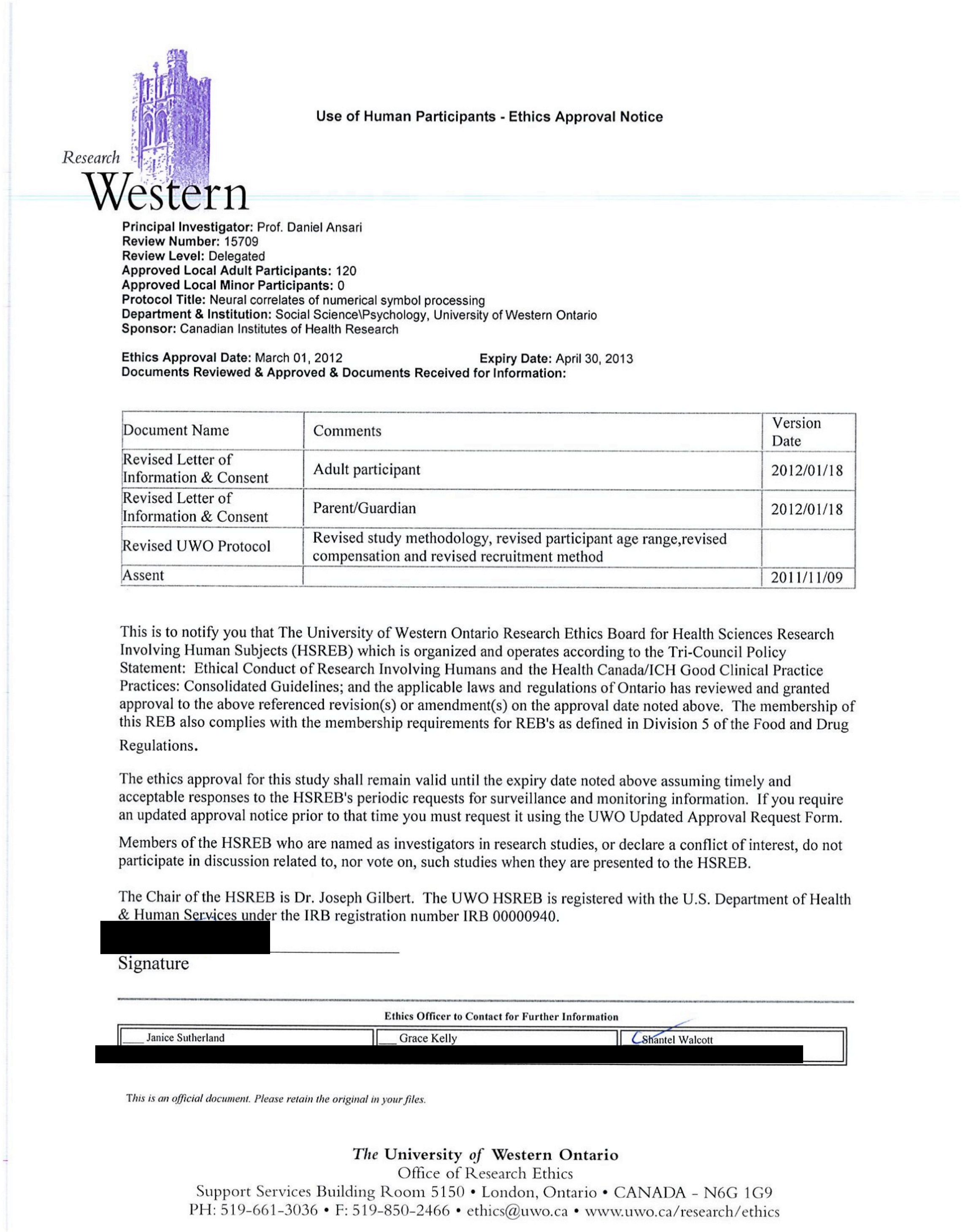
TO: Lori Wettemann

[✓] Approved: **This signifies notification of CPHS APPROVAL of the revision or addition described above.**
Note to CPHS reviewer(s): Please contact the CPHS office with comments for follow up or other options:
[ ] Not Approved [ ] Abstain [ ] Conditionally Approved

[ ] CPHS Acknowledged

CPHS REVIEWER'S SIGNATURE: [redacted] DATE: 11/29/2005

*11/28/05 consult w/ pediatric specialist



Research Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Prof. Daniel Ansari
Review Number: 15709
Review Level: Delegated
Approved Local Adult Participants: 120
Approved Local Minor Participants: 0
Protocol Title: Neural correlates of numerical symbol processing
Department & Institution: Social Science\Psychology, University of Western Ontario
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: March 01, 2012 **Expiry Date:** April 30, 2013
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Letter of Information & Consent	Adult participant	2012/01/18
Revised Letter of Information & Consent	Parent/Guardian	2012/01/18
Revised UWO Protocol	Revised study methodology, revised participant age range,revised compensation and revised recruitment method	
Assent		2011/11/09

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Signature

Ethics Officer to Contact for Further Information

___ Janice Sutherland	___ Grace Kelly	[✓ Shantel Walcott]
[redacted]		

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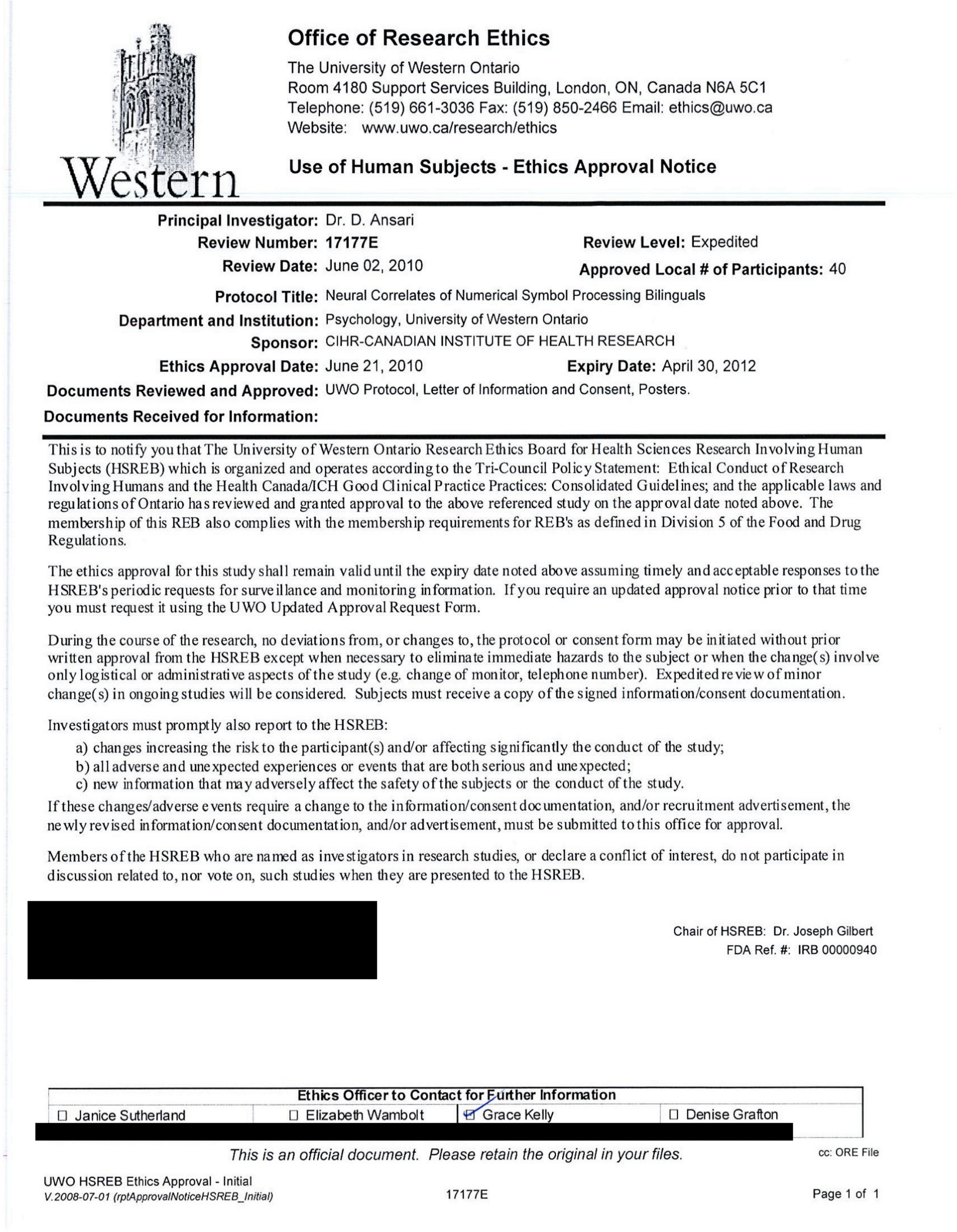

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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. D. Ansari
Review Number: 17177E **Review Level:** Expedited
Review Date: June 02, 2010 **Approved Local # of Participants:** 40
Protocol Title: Neural Correlates of Numerical Symbol Processing Bilinguals
Department and Institution: Psychology, University of Western Ontario
Sponsor: CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH
Ethics Approval Date: June 21, 2010 **Expiry Date:** April 30, 2012
Documents Reviewed and Approved: UWO Protocol, Letter of Information and Consent, Posters.
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:
- a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
- b) all adverse and unexpected experiences or events that are both serious and unexpected;
- c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

[redacted]

Chair of HSREB: Dr. Joseph Gilbert
FDA Ref. #: IRB 00000940

Ethics Officer to Contact for Further Information			
☐ Janice Sutherland	☐ Elizabeth Wambolt	☑ Grace Kelly	☐ Denise Grafton

[redacted]

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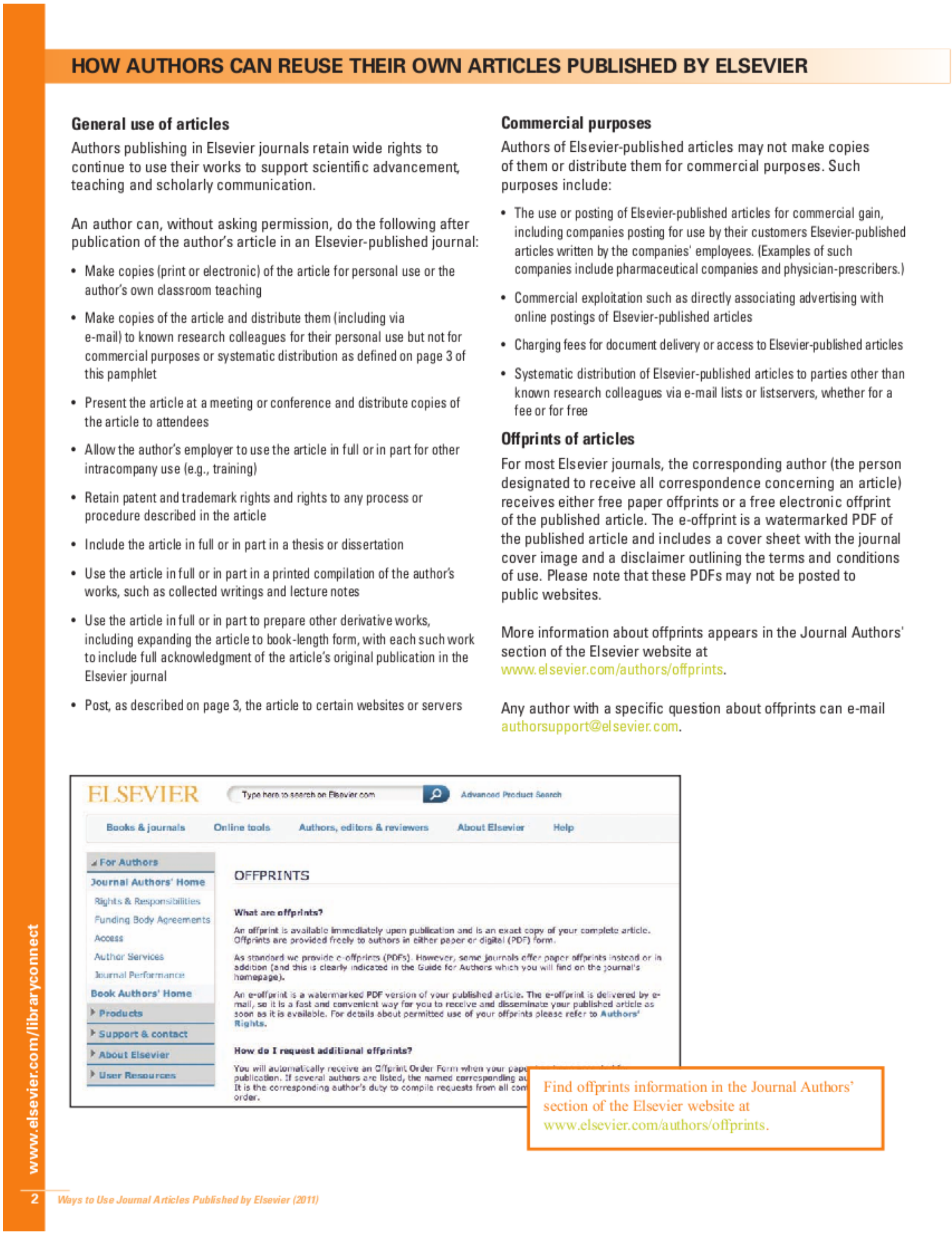

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- *2005-2006 (transferred)*
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- *2006-2007*
  M.Sc. Psychology
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  London, ON Canada

- *2007-Present*
  Ph.D. candidate in Psychology
  The University of Western Ontario
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ADVANCED COURSES

- *June 2006*
  NUMBRA Summer School (*Abstract selected for oral presentation)*
  "Summer School on numeracy, reading,
  dyslexia and dyscalculia: brain development,
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  Jyvaskyla, Finland

- *November 2005*
  BrainVoyager QX Workshop
  Washington, D.C. USA
  October 2005
  The Visiting Fellowship Program in Functional MRI
  Martinos Center for Biomedical Imaging,
  Massachusetts General Hospital
  Charlestown, MA USA

HONORS AND AWARDS

- *April 2009*
  Vanier Canada Graduate Scholarship

- *January 2008*
  U.S. Alumni Entrance Award at the University of Western Ontario

- *July 2007*
  Fellow
  John Merck Summer Institute on the Biology of Developmental Disabilities

- *March 2006*
  Honorable Mention
  National Science Foundation Graduate Research Fellowship

REFEREED PUBLICATIONS

Holloway, I.D. & Ansari, D. (2010). Developmental specialization in the right intraparietal sulcus for the abstract representation of numerical magnitude. *Journal of Cognitive Neuroscience.*

- **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.*
- Raizada, R.D., Tsao, F.M., Liu, H.M., **Holloway, I.D.**, Ansari, D., Kuhl, P.K. (2010). Linking brain-wide multivoxel activation patterns to behaviour: Examples from langague and math. *Neuroimage, 51(1): 462-471.*
- **Holloway, I.D.** & Ansari, D. (2009). Mapping numerical magnitudes onto symbols: the distance effect and children's mathematical competence. *Journal of Experimental Child Psychology, 103(1): 17-29.*
- **Holloway, I.D.** & Ansari, D. (2008). Domain-specific and domain-general changes in children's development of number comparison. *Developmental Science, 11(5): 644-9.*
- Van Eimeren, L., Niogi, S.N., McCandliss, B.D., **Holloway, I.D.**, Ansari, D. (2008) White matter microstructures underlying mathematical abilities in children. *Neuroreport, 19(11): 1117-21.*
- Price, G., **Holloway, I.D.,** Räsänen, P., Vesterinen, M., & Ansari, D. (2007). Impaired parietal magnitude processing in Developmental Dyscalculia. *Current Biology, 17(24): R1042-3*

BOOK CHAPTERS

Ansari, D., **Holloway, I.D.**, Price, G. R, & Van Eimeren, L. (2008) Towards a developmental cognitive neuroscience approach to the study of typical and atypical number development. Dowker, A. (Ed.) *Mathematical Difficulties: Psychology, Neuroscience, and Intervention.* Oxford, UK: Elsevier.

Ansari, D., Price, G.R., & **Holloway, I.D.** (in press) Typical and atypical development of basic magnitude representations: perspectives from behavioral and neuroimaging studies. Ferrari, M. & Vuletic, L. (Eds.) *The Developmental Interplay between Mind, Brain, and Education: Essays in honor of Robbie Case.* Amsterdam, NL: Springer.

NON-REFEREED PUBLICATIONS

Holloway, I.D. (2002). Hemispheric Differences in Word Recognition as Measured by the Stroop Task. *Proceeding of The National Conference on Undergraduate Research (NCUR)*.

CONFERENCE ABSTRACTS

Holloway, I.D. & Ansari, D. (2008). Age-related specialization of the right inferior parietal cortex for the abstract representation of numerical magnitude.. *Presented at 15th Annual Meeting of the Organization for Human Brain Mapping, San Francisco, CA. USA.*

Ansari, D. & **Holloway I.D.** (2008) Common and segregated neural pathways for the processing of symbolic and nonsymbolic numerical magnitude: evidence from children and adults. *Presented at MGH-Foundation IPSEN-Cell Exciting Biologies 2008: Biology of Cognition Workshop, Paris, France.*

Holloway, I.D. & Ansari, D. (2008). Format-specific neural correlates for symbolic and nonsymbolic numerical processing. *Presented at 18th Annual Meeting of the Canadian Society for Brain, Behavior, and Cognitive Science., London, ON, Canada.*

Holloway, I.D., Price, G.R., & Ansari, D. (2008). Developmental specialization for symbolic number processing in the left supramarginal gyrus – an fMRI study. *Presented at Annual Meeting of the Cognitive Neuroscience Society, San Francisco, CA, USA.*

Holloway, I.D. & Ansari, D. (2007). Developmental Changes in Numerical and Non-Numerical Comparison Reveal Domain-General and Domain-Specific Factors in the Emergence of Number Semantics and Mathematical Skills. *Presented at Association for Psychological Science (APS) 19th Annual Convention, Washington, D.C.*

Holloway, I.D. & Ansari, D. (2006). How domain-specific are developmental changes in the distance effect? *Presented at NUMBRA Summer School "Summer School on numeracy, reading, dyslexia and dyscalculia: brain development, culture and remediation."*

TEACHING

The University of Western Ontario, Department of Psychology
PSYCH 380: Psychological Statistics Using Computers, Lab Section,

- Fall 2006
- Winter 2007
- Fall 2007
- Winter 2008