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Cortical Representation Underlying the Semantic Processing of Numerical Symbols: Evidence from Adult and Developmental Studies

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

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CORTICAL REPRESENTATION UNDERLYING THE SEMANTIC PROCESSING OF NUMERICAL SYMBOLS: EVIDENCE FROM ADULT AND DEVELOPMENTAL STUDIES

(Thesis format: Integrated-Article)

by

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Graduate Program in Psychology

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

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Abstract

Humans possess the remarkable ability to process numerical information using numerical symbols such as Arabic digits. A growing body of neuroimaging work has provided new insights into the neural correlates associated with symbolic numerical magnitude processing. However, little is known about the cortical specialization underlying the representation of symbolic numerical magnitude in adults and children. To constrain our current knowledge, I conducted a series of functional Magnetic Resonance Imaging (fMRI) studies that aimed to better understand the functional specialization of symbolic numerical magnitudes representation in the human brain.

Using a number line estimation task, the first study contrasted the brain activation associated with processing symbolic numerical magnitude against the brain activation associated with non-numerical magnitude (brightness) processing. Results demonstrated a right lateralized parietal network that was commonly engaged when magnitude dimensions were processed. However, the left intraparietal sulcus (IPS) was additionally activated when symbolic numerical magnitudes were estimated, suggesting that number is a special category amongst magnitude dimensions and that the left hemisphere plays a critical role in representing number.

The second study tested a child friendly version of an fMRI-adaptation paradigm in adults. For this participant's brain response was habituated to a numerical value (i.e., 6) and signal recovery in response to the presentation of numerical deviants was investigated. Across two different brain normalization procedures results showed a replication of previous findings demonstrating that the brain response of the IPS is modulated by the semantic meaning of numbers in the absence of overt response selection.

The last study aimed to unravel developmental changes in the cortical representation of symbolic numerical magnitudes in children. Using the paradigm tested in chapter 2, results demonstrated an increase in the signal recovery with age in the left IPS as well as an age-independent signal recovery in the right IPS. This finding indicates that the left IPS becomes increasingly specialized for the representation of symbolic numerical magnitudes over developmental time, while the right IPS may play a different and earlier role in symbolic numerical magnitude representation.

Findings of these studies are discussed in relation to our current knowledge about symbolic numerical magnitude representation.

Keywords: Symbolic numerical magnitude, Arabic numerals, fMRI, numerical and non-numerical magnitude representation, intraparietal sulcus (IPS), development of symbolic number representation, cortical specialization, hemispheric lateralization

Statement of Co-Authorship

The research for this doctoral thesis was conducted in collaboration with and under the guidance of my advisor Dr. Daniel Ansari. Dr. Ansari contributed to all theoretical and methodological aspects of the studies and to the preparation of the final manuscript. The first study was conducted in cooperation with Dr. Michael Schneider, Dr. Roland Grabner and Dr. Robert Siegler. These authors added significantly to all theoretical, analytical and experimental aspects of the first experiment. The development of study design and data collection was done in close collaboration with Dr. Schneider and Dr. Grabner of ETH Zürich, Switzerland. Studies two and three of the present work were entirely conducted at the University of Western Ontario. Dr. Ian Holloway contributed to the creation of the experimental paradigm of these studies. Finally, Celia Goffin spent countless hours assisting in many aspects of study two and three. This involved data collection, data analysis as well as scheduling participants. Hereby I acknowledge that the present manuscript is my own work, however, it should be noted that Dr. Daniel Ansari contributed significantly to the final manuscript.

Dedication

To my family! To my spouse! To my friends!

To all who supported me in pursuing this challenge!

Acknowledgement

It would not have been possible to write this doctoral thesis without the help and support of all the people around me. Thanks to all of you!!

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I am most grateful to my parents and my grandparents who encouraged and supported me throughout my life. Thanks for supporting my determination to find my potential and to contribute to this world.

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Chapter 1: General Introduction

1.1. The importance of number

Since the dawn of civilization humans have been intrigued and fascinated by the concept of number. The idea to use arbitrary symbols (e.g., Hindu-Arabic numerals) to represent numerical magnitudes is doubtlessly one of the greatest cultural achievements in the history of mankind. Early philosophers such as Aristotle were occupied by the beauty of numbers and spent countless hours dwelling in the realm of mathematics. And even famous artists such as the German Renaissance painter and mathematician Albrecht Dürer expressed their fascination for numbers in their paintings (e.g., “The Magic Square” in Dürer’s famous work *Melancholia I)*. However, beyond the mathematical aesthetic that numbers radiate, it is especially their practical use that has significantly transformed the existence of the human species on this planet.

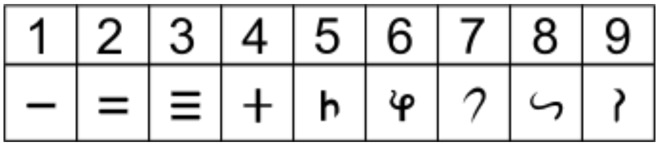
Without them, citizens in the western world would not be living in comfortable and well-tempered apartments. Without them, we would not be able to use computers to write down our ideas. Even fundamental concepts such as time and space would be immeasurable. From these examples it is readily apparent that numbers have significantly contributed to the development of our modern societies.

At the beginning of the 21st century we are all deeply influenced by a world that is full of symbolic numerical meaning (i.e., the understanding that numerical symbols such as the Arabic digits represent numerical magnitudes - the total amount of items within a given set). In order to navigate through this world and to contribute to our modern societies, the acquisition of symbolic numerical knowledge has become vital for every individual. In modern societies all individuals learn the meaning of numerical symbols via formal and informal education. The importance of becoming a numerate individual in modern societies has been demonstrated in research that has shown that the ability to process numerical information significantly influences the professional, social and private live of individuals (Butterworth, Varma, & Laurillard, 2011; Dowker, 2005; Parsons & Bynner, 2005; Ritchie & Bates, 2013). For example, it has been estimated that young adults (between 16 and 29 years of age) with poor literacy and poor numeracy skills spend only 86 percent of their employment time in full-time employment, while adults with competent literacy and numeracy skills spend 95 percent of this time in full-time employment (Parsons & Bynner, 2005). Moreover, a recently published paper has demonstrated that early skills in mathematics measured at the age of 7 predict the socioeconomic status of adults at age 42, over and above socioeconomic status effects present at birth (Ritchie & Bates, 2013). Some evidence even suggests that proficiency in the domain of mathematics is a better predictor for life success compared to literacy (Butterworth et al., 2011; Dowker, 2005; Romano, Babchishin, Pagani, & Kohen, 2010), and it has been demonstrated that the annual costs of low numeracy in the UK reaches up to £2.4 billion (Gross, Hudson, & Price, 2009). Beyond these socio-economic factors, individuals suffering from developmental dyscalculia, a severe learning difficulty in the domain of mathematics, are seriously hampered in their day-to-day activities and even simple tasks such as setting the time or calculating the tip in a restaurant become an enormous struggle (Landerl & Kaufmann, 2008; Vogel & Ansari, 2012).

From the examples above, the tremendous importance of numerical abilities is readily apparent and, therefore, semantic knowledge (i.e., the representation of numerical magnitude) that is conveyed by numerical symbols is crucial for every individual. Given the tremendous impact numerical knowledge exerts on our societies and individuals, there is an urgent need to better understand the cognitive and neurocognitive mechanisms that underlie the development of symbolic numerical understanding. Having discussed the impact and the importance of research, the following sections will introduce the reader to the field of numerical cognition. As such, the first part will provide a brief developmental history of the Hindu-Arabic numeral system, which is currently the most commonly used numerical notation system around the globe. After this historic overview, the next section will provide a review about our current understanding on how the human mind and brain process numerical magnitude.

1.2. History of Hindu-Arabic numerals

Today, Arabic numerals are the most prevalent and widespread symbolic numerical notation system on the planet (Ifrah, 1985; Menninger, 1992). Like no other notation system, the Arabic numerals have influenced the life on our planet. Even in countries such as China and Japan, which developed their own symbolic numerical systems over centuries, Arabic numerals have become the predominant notation system for expressing numerical information. The following section will describe the historic development of the Arabic numerals, focusing on its first appearance in India and its main transformations up to its present form.



1	2	3	4	5	6	7	8	9
𑁒	𑁓	𑁔	𑁕	𑁖	𑁗	𑁘	𑁙	𑁚

Figure 1.1: The Brahmi numerals in the first century A.D. Reprinted from Brahmi numerlas, In *Wikipedia*,n.d., Retrieved August 26, 2013, from http://en.wikipedia.org/wiki/Brahmi_numerals. Reprint with permission.

The graphic ancestors of the modern Arabic numerals can be traced back to the early days of the Maurya Dynasty in India in the 3rd century BC (for an extenisve overview on the history of numbers see Ifrah, 1985 and Menninger, 1992). During the days of the Indian emperor Ashoka, the Indian Brahmi numerals (see Figure 1.1) were commonly used for arithmetic. Similar to the modern form, each numerical magnitude (i.e., the total amount of items within a given set) was presented by a single and unique number symbol, the digit. However, the Brahmi numerals of these days lacked the numerical symbol 0. As such, the “nothing” was not yet invented and separate numerical symbols were used for each of the tens (10, 20, 30, etc.) and for each of the hundreds (100, 200, 300, etc). Although the Brahmi system lacked the numeral “0”, it was one of the first number systems that assigned individual arbitrary symbols (i.e., symbols that do not express an iconic resemblance to the numerical magnitudes they represent) to express numerical magnitudes. As such, the Brahmi system was among the first to overcome the “*iconic*” (i.e., concrete) numerical notation system in which fingers, body parts, notches on a stick or scratches on stone were used to express and convey numerical meaning (Dehaene, 1992; Ifrah, 1985; Menninger, 1992). These ancient notation forms were commonly used to establish one-to-one correspondence with the number of items to be enumerated. For instance, in ancient times the quantity “four” would have been carved as IIII marks on a stone. However, the *concrete* system is a very tedious way to express numerical magnitudes, especially once the amount of items to be enumerated reaches a certain magnitude at which discrimination of consecutive items becomes difficult (e.g., IIIII vs. IIIIII). To overcome this problem some cultures invented new systems (e.g., grouping) in which the marks were organized in more recognizable patterns (e.g., 5 is represented with a space between the marks III II). Others, like the early Brahmi numeral system in India, introduced arbitrary shapes (see Figure 1.1) in order to represent numerical magnitudes more efficiently. However, this early Indian number system was not yet based on the modern *place-value* system and numerical expressions were instead additively composed. For instance, using the appropriate symbols the number 32 would have been written as “10 10 10 1 1”. In this *additive* form of numerical expression the power of ten served frequently as the numerical base, however, other cultures such as the Sumarians used different numbers as numerical base (e.g., 60).

At around A.D. 600 a new writing system based on the Brahmi digits appeared (Ifrah, 1985; Menninger, 1992). In this new system numerals were not used additively to express complex numbers, but each digit was instead used in a *positional* order to construct larger multi-digit number. For example, the number 232 was expressed by multiples of 10’s and 100’s in such a way that 2 x 100 + 3 x 10 + 2 relates to the positional coding of 2 3 2. However, the still unknown “0” left this notation system ambiguous. Take for instance the numbers 32 and 302. The number 302 would have been expressed as 3 2, and the number 32 would have been expressed as 3 2. As can be readily seen the ambiguity of this expression was not satisfying, which ultimately gave rise to the next transformational step, the introduction of the number “0”. The invention of “nothing”, as a placeholder, enabled the writer to express the multi-digit number 302 with the well-known *place-value* system as 302. The origin of this important advancement appears to be lost in history and only speculations remain how it occurred. However, one can assume that the Indian culture was simply ripe for this tremendous change and in the 9th century the success of this new writing system quickly spread to neighbouring countries such as Persia and Arabia.

With the Arabic conquer of Africa the Arabic numerals travelled west along the northern shores of the African continent. During this period the system was divided into a Western and into an Eastern (which is still used in Turkey) form. The Western form was first introduced to Europe at around A.D. 1000 in Spain, during the Arabic conquest of the Iberian Peninsula (Ifrah, 1985; Menninger, 1992). The European medieval culture was, however, resistant to this new unknown way of using numbers and many saw Arabic numerals as an expression of the devil. It took another 500 years before the Arabic numerals were used as the main enumeration system in Europe. This development was mainly driven by the popularity of the Arabic numerals by merchants and tradesman in Italy. After the successful conquer of Europe the Arabic numerals quickly spread around the entire globe and it became the common notation form we are all familiar with.

The cultural development and transformation of the Arabic numeral system is remarkable. It is also notable that different numerical notation systems were introduced independently across different cultures on different continents. This independent appearance of different notation systems is frequently taken as evidence to suggest that the human species is endowed to perceive numerical magnitudes and that the invention of numerical notation systems was a natural step to occur (Butterworth, 1999). So, is there a foundational ability in humans to process numerical magnitudes? The next section will discuss accumulating research evidence that suggests that a variety of animal species as well as human infants are able to perceive and to discriminate between non-symbolic numerical magnitudes. Furthermore, I will discuss empirical evidence that indicates that the way non-symbolic numerical magnitudes are processed may be universal.

1.3. A sense for non-symbolic numerical magnitudes

The following section discusses empirical evidence that suggests that animals, non-human primates and human infants are able to perceive and to discriminate non-symbolic numerical magnitudes. In doing so, this section will provide arguments that humans might be endowed with an early ability to approximate non-symbolic numerical magnitude (e.g. dot arrays). In addition, this section will provide a general scaffold upon which to situate the main body of experimental work discussed in the present thesis.

What is meant by non-symbolic numerical magnitude? The term non-symbolic numerical magnitude can be defined as the number of items displayed in a given set (Ansari, 2008; Butterworth, 1999; Dehaene, 1999). In this sense, non-symbolic numerical magnitudes refer to a quality that defines the number of items in a set independently of their visual appearances or categorical classification. In other words, whether you have 2 apples and 3 peas in a basket or 4 cherries and 1 grape the overall number of items in the basket is 5. Therefore, non-symbolic numerical magnitudes describe an abstract quality that refers to the number of items displayed in a set. Non-symbolic numerical magnitudes can be either represented as exact or approximate magnitudes. Approximation refers to an imprecise estimation of the number of items in a set. In contrast, the exact assessment of numerical magnitudes refers to a precise representation of number (for example by counting the individual items in a set).

An increasing number of empirical studies have provided scientific evidence to suggest that a variety of animal taxa, including humans, are able to discriminate and approximate non-symbolic numerical magnitudes. For instance, non-symbolic numerical abilities have been consistently demonstrated in non-human primates such as chimpanzees (Boysen, Bernston, Hannan, & Cacioppo, 1996) and macaques (Brannon & Terrace, 1998; Cantlon & Brannon, 2006; Roitman, Brannon, & Platt, 2007), in birds, such as pigeons (Honig & Stewart, 1989; Roberts & Mitchell, 1994) and parrots (Pepperberg & Carey, 2012; Pepperberg, 2006, 2012), in amphibians (Krusche, Uller, & Dicke, 2010), fish (Agrillo, Dadda, Serena, & Bisazza, 2009; Gabay, Leibovich, Ben-Simon, Henik, & Segev, 2013) and rats (Meck & Church, 1983; Platt & Johnson, 1971). The sheer amount of non-symbolic numerical abilities in the animal kingdom provides compelling evidence to suggest that numerical information is a salient property in the environment, which provides crucial information to guide behaviour. For instance, approximating and comparing the number of fruits on different branches of a tree might guide one's behaviour to choose the branch that will provide more food. In an environment that is guided by natural selection the ability to perform numerical approximation and discrimination might be the difference between surviving or not (Butterworth, 1999; Dehaene, 1997).

Besides the scientific evidence demonstrating the presence of non-symbolic numerical abilities among different animal taxa, experimental work has provided crucial information about the mechanisms underlying the discrimination of non-symbolic numerical magnitudes. Specifically, several studies with non-human primates have demonstrated that the speed (also the error rate) with which monkeys discriminate (i.e., the process of distinguishing which set of items contains more items) non-symbolic numerical magnitudes is inversely related to the numerical ratio between numerical magnitudes being compared (for a review see Brannon, 2006; Cantlon, 2012). In other words, the discrimination performance of animals decreases as a function of an increase in numerical ratio (see also Figure 1.3). For instance, monkeys trained to perform a number comparison task with dot arrays have been shown to be faster and less error prone when the numerical arrays being compared elicit a small ratio (e.g., the numerical ratio between an array of 4 dots and an array of 8 dots is 4/8 = 0.5) compared to an array of dots that elicit a large ratio (e.g., the numerical ratio between an array of 8 dots and an array of 9 dots is 8/9 = 0.89; Cantlon & Brannon, 2006). This numerical ratio effect (NRE) has been taken as evidence to suggest that animals represent non-symbolic numerical magnitudes as approximate entities and the discrimination of non-symbolic numerical magnitudes follows Weber's law, which states that the threshold with which two magnitudes are compared increases linearly with the overall size of the magnitudes being discriminated. Therefore, the discrimination between 54 apples and 55 apples will be considerable more difficult than the discrimination of 4 apples and 5 apples. Although the numerical difference between the sets in both examples is exactly 1, however, the numerical ratio differs. Based on this evidence, the data suggests that the representation of non-symbolic numerical magnitudes might be based on an approximate system – the approximate number system (ANS) - in which numbers are internally represented as noisy quantities (see also Figure 1.2) that follow a Gaussian distribution (either on a logarithmic scale with a fixed variability of internal noise, or on a linear scale in which the internal noise increases linearly; Dehaene, 2003; Gallistel & Gelman, 2000).

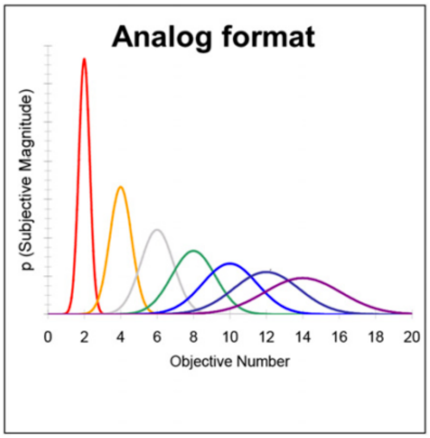


Figure 1.2: Representation of numerical magnitudes as Gaussian distributions on a linear scale with a linear increase in the noise (variability) of the distribution. Reprinted from "Math, monkeys, and the developing brain," by J. F. Canton, 2012, Proceedings of the National Academy of Science of the United States of America, 109, p. 10726. Copyright National Academy of Sciences, USA. Reprinted with Permission.

The scientific evidence reviewed above suggests that the discrimination of non-symbolic numerical magnitudes is based on an approximate number system that does not rely on language capabilities. In addition to the evidence derived from animal studies, a growing number of studies have demonstrated that even preverbal human infants are able to discriminate non-symbolic numerical magnitudes (Libertus & Brannon, 2009; Xu & Spelke, 2000; Xu, Spelke, & Goddard, 2005). Results of several infant habituation (habituation is a decreased response to a stimuli after its repeated presentation) studies have demonstrated that infants ability to discriminate non-symbolic numerical magnitudes is subject to a similar numerical ratio effect as was observed in animals (Hyde, Boas, Blair, & Carey, 2010; Libertus & Brannon, 2009; Xu & Spelke, 2000; Xu et al., 2005). Thus, the current evidence from infant's studies suggests that numerical abilities are present early in life and that the underlying mechanisms of non-symbolic numerical magnitude discrimination is similar across species. This similarity in discrimination performance across different species including humans has led authors to suggest that humans are equipped with an inborn preverbal ability to approximate numerical magnitudes, which has been called "*Approximate Number System*" or the "*Sense for Numbers"* (Dehaene, 1997).

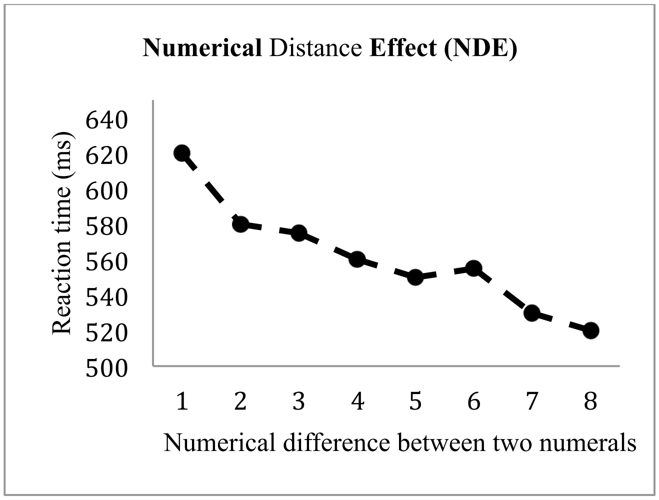
1.4. Symbolic numerical magnitude processing

The previous section discussed the capability of animals and human infants to discriminate non-symbolic numerical magnitudes. However, the ability to use numerical symbols in order to convey numerical magnitude information is a unique human quality.

The central aim of the present dissertation is to discuss and to explore how the human mind and brain represents symbolic numerical magnitude. The following section will discuss two central behavioural effects that have provided important insights into the ways symbolic numerical magnitudes are processed and represented in humans. In addition, a prominent cognitive model of number processing will be described.

In a seminal study, conducted by Moyer and Landauer (1967), adult participants were asked to decide which of two presented single digits is numerically larger. When participants were asked to perform this task as quickly and as accurately as possible, reaction times and error rates systematically decreased with an increase in numerical distance. In other words, participants were less error prone and systematically faster when the distance between the numerals was relatively large (e.g., 2 vs 9, a numerical distance of 7) compered to when the numerical distance between the numerals was relatively small (e.g., 2 vs 3, a numerical distance of 1). The finding demonstrated that the comparison of Arabic digits is subject to a NDE, indicating that the comparison of numerical symbols may not be based on the discrimination of digital units (i.e., if numerals are represented as not-noisy digital units, the absence of a numerical distance effect may be assumed). Instead, the authors took this finding as evidence to suggest that numerals are represented as approximate magnitudes, similar to the representation of non-symbolic numerical magnitude (i.e., the ANS, see also the section “A sense for non-symbolic numerical magnitudes” of this chapter). Since its discovery the symbolic NDE has been taken as an index for the semantic processing of numerical symbols and its analogue representation.

Another effect that was observed is the numerical ratio effect. As described above the NRE takes into account the size of the numerical magnitudes being compared and is therefore consistent with Weber's law. For instance, although the numerical distance is equal the comparison of the number pair 7 - 8 will be slower and more error prone compared to the comparison of the number pair 1 – 2. The NRE accounts for this difference and includes the relative size of the two numbers as an explanatory factor. Both, the numerical distance effect and the numerical ratio effect can be found in non-symbolic as well as in symbolic numerical magnitude discriminations and are taken as an index for numerical magnitude representation. The presence and similarity of the NDE (NRE) in non-symbolic and symbolic numerical processing has been taken as evidence to suggest that that the processing of non-symbolic numerical and symbolic numerical magnitudes refers to a common approximate numerical magnitude system – the ANS. In this sense, symbolic numerical magnitude knowledge is argued to be mapped onto this shared numerical magnitude representation. It should be noted that the numerical distance effect is highly correlated with the numerical ratio effect (see Figure 1.3.). However, the ratio between numerical magnitudes (i.e., numerical ratio effect) explains more variance in numerical comparison data compared to the distance between numerical magnitudes (i.e., the numerical distance effect; Moyer & Landauer, 1967).



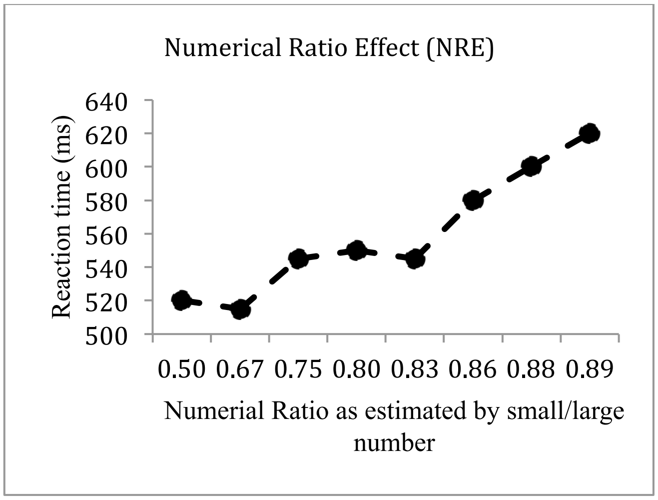


Figure 1.3: The figures illustrate typical reaction time data observed for the numerical distance effect (upper figure) and for the numerical ratio effect (lower figure; figures represent fictional data for the purpose of illustration).

Given the presence of the NDE and the NRE in symbolic numerical magnitude comparisons, it is not surprising that behavioural studies as well as neuroimaging studies, investigating the representation of symbolic numerical magnitudes, frequently use these effects as an index for semantic number processing (Bugden & Ansari, 2010; Holloway

& Ansari, 2008, 2009; Moyer & Landauer, 1967; Sekuler & Mierkiewicz, 1977; Van Opstal, Gevers, De Moor, & Verguts, 2008). For instance, Holloway & Ansari, (2009) investigated whether the size (i.e., the steepness of the slope) of the symbolic numerical distance effect changes with age and whether individual differences in the numerical distance effect are associated with individual differences in mathematical achievement. Participants between 6-years and 8-years of age were asked to indicate per button press, which of two Arabic numerals presented on a computer screen is numerically larger. Consistent with previous work (Sekuler & Mierkiewicz, 1977), the authors showed that the size (i.e., the slope) of the symbolic numerical distance effect decreases with age. Moreover, the authors demonstrated that individual differences in the size of the numerical distance effect significantly correlates with individual differences in mathematical achievement scores. As such the results of the study provide compelling evidence that the size of the symbolic NDE is a good measurement for the preciseness of the internal representation of numerical magnitudes. In other words, the developmental change in the size of the numerical distance effect may be explained by an increase in the precision with which numerals are represented internally. In addition, the correlation between the individual size of the numerical distance effect and the individual scores of the mathematical achievement test provides evidence that the precision of the internal representation may be related to math proficiency. As such the symbolic numerical distance effect has proven to be a relevant measure of symbolic numerical magnitude processing that can be related to mathematical achievement (Holloway & Ansari, 2008, 2009; Moyer & Landauer, 1967; Sekuler & Mierkiewicz, 1977; Verguts & Van Opstal, 2005).

A popular model that integrates the findings of an internal approximate representation of numerical magnitudes into a model of symbolic numerical processing is the "*Triple Code Model"* (TCM) proposed by Dehaene (1992). Specifically, the TCM predicts the existence of three different numerical codes in which basic numerical information can be processed (see Figure 1.4). The auditory verbal code is argued to represent number words (e.g., /*thirteen*/) and is based on a domain-general language system sub-serving the manipulation of number words and the verbal storage of arithmetic facts. Numerals such as the Arabic digits (e.g., 13) are represented in the visual number code, which is strongly connected to the reading and writing of Arabic numerals. Finally, an analogue numerical magnitude code is postulated, which obeys Weber's law and reflects the approximate nature of numerical magnitude representation. The analogue number code is argued to be involved in cognitive operations such as number magnitude estimation and the comparison of non-symbolic and symbolic numerical magnitudes.

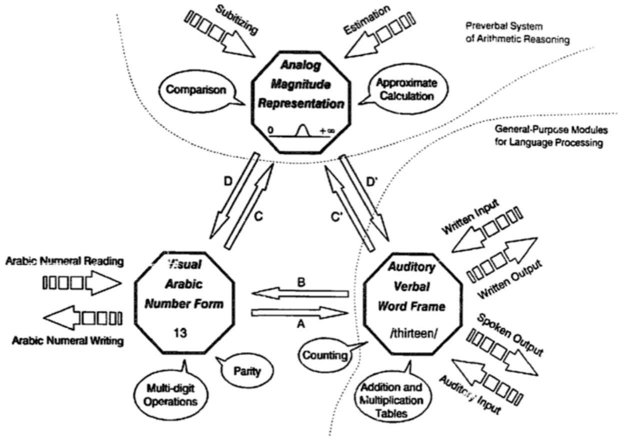


Figure 1.4: The figure displays the Triple Code Model (TCM) proposed by Dehaene (1992). The Arabic Number Form, the Auditory Verbal Word Frame and the Analoge (approximate) Magnitude Representation are the building blocks of the model. Interconnections (shown in the letters A,B,C,C' and D') enable the transformation of information from one code to another code. Reprinted from "Varieties of numerical abilities," by S. Dehaene, 1992, Cognition, 44, p. 31. Copyright Elsevier. Reprinted with permission.

Besides the different number codes the TCM assumes strong interconnectivity between the number codes, which allows for a rapid information transformation from one numerical code to another code. For instance, the presentation of the Arabic numeral "*4"* on a computer screen may be transformed, depending on the task, to the auditory verbal word code */four/*. Within a different context, however, the numeral "*4*" may be transformed to the approximate numerical code, which allows for magnitude comparisons. In addition, the number codes are assumed to be connected to specific input-output procedures, such as to the reading and writing of numerals in the visual Arabic code. In contrast to other models (e.g., the model by McCloskey, 1992), the TCM allows for numerical transformation between the three different numerical codes without assuming one central abstract number representation through which every transformation has to pass through (i.e., a processing bottleneck).

Taken together, the evidence discussed in this section indicates that the discrimination of symbolic numerical magnitudes is subject to a numerical distance effect and a numerical ratio effect similar to the comparison of non-symbolic numerical magnitudes. Thus, it is assumed that numerical distance and numerical ratio are an index of numerical magnitude representation that is governed by Weber's law. Furthermore, I reviewed evidence that the size of the numerical ratio effect in children may be a good indicator for the precision with which symbolic numerical magnitudes are represented in the human mind. Despite these advances in our understanding, still little is know about the ways the human brain represents symbolic numerical magnitude and how symbolic numerical representation develops over time. In the next section I will provide an introduction to the neuronal architecture related to the processing of symbolic numerical magnitudes in the human brain.

1.5. Neuronal architecture of symbolic number processing

This next section will describe the basic neuronal architecture underlying the processing of symbolic numerical magnitude. For this, neuropsychological evidence will be discussed that indicates that the parietal lobe of the human cortex plays a central role in numerical magnitude processing. Then evidence from neuroimaging studies will be presented that has further constrained our understanding of the neural correlates associated with the representation of symbolic numerical magnitudes in the human brain.

Our current understanding of the brain mechanisms underlying the processing of numerical magnitude depends on two main sources of evidence. Accumulating evidence from neuropsychological case studies with brain-damaged patients has provided great insights into the anatomical and functional principles underlying the neuronal processing of numerical information. Of particular importance are data that converge to suggest that the processing of numerical magnitude information is independent from domain-general mechanisms such as language (Cipolotti, Butterworth, & Denes, 1991; Dehaene & Cohen, 1997; Delazer & Butterworth, 1997). These findings imply that the processing of numerical magnitude is a domain-specific property and forms a cognitive domain in its own right. Furthermore, evidence from neuropsychological studies has indicated that the functioning of the parietal lobe of the human cortex is central to numerical operations and that damage to this region can severely impair the processing of numerical information on different levels (for a review see Dehaene, Piazza, Pinel, & Cohen, 2003). For instance, Cipolotti, Butterworth and Denes (1991) reported the case of a 59-year-old right-handed patient C.G, who suffered from a cerebral vascular accident resulting in the damage of the fronto-parietal cortex. The patient showed classical symptoms of Gerstmann’s syndrome (i.e., finger agnosia, right-left disorientation, agraphia and acalculia; for a review on Gerstmann's syndrom see Lebrun, 2005). However, in addition to these well-known symptoms, C.G. expressed a very selective deficit in the processing of numerical magnitudes above the number 4. At the same time, however, the processing of other semantic categories remained intact, providing strong evidence to suggest that the processing of numerical magnitude may be domain specific and independent of domain general mechanisms. In line with other neuropsychological case (Dehaene & Cohen, 1997; Delazer & Butterworth, 1997) studies, the work by Cipolotti and colleagues (1991) was able to demonstrate the importance of the parietal lobe for the processing of symbolic numerical magnitude. Together, there is substantial evidence to suggest that the parietal lobe is involved in domain specific processing of numerical information.

While there is ample evidence from patients with parietal damage to suggest that that the intraparietal sulcus (IPS) is critically involved in the processing of numerical magnitude information, the exact anatomical architecture and the functional principles underlying the processing of numerical operations remained elusive. With the advent of functional neuroimaging technologies new evidence was generated to further constrain the neuronal architecture related to the processing of symbolic numerical magnitudes. Important information about the neuronal mechanisms underlying the representation of symbolic numerical magnitudes has been derived from symbolic numerical comparison studies. As discussed in the previous sections, the NDE has been related to the representation of symbolic and non-symbolic numerical magnitudes. As such it is not surprising that the majority of neuroimaging studies exploring the neural correlates of numerical magnitude processing used the number comparison task as a way to further investigate the neuronal architecture of symbolic numerical magnitude presentation in the human brain.

Early neuroimaging studies of number comparison used event-related brain potentials (ERPs) to measure how the neuronal time course of number processing is affected by numerical distance. In one of the earliest investigations, Grune, Mecklinger and Ullsperger (1993) asked participants to perform a number comparison task while ERPs were recorded from their scalp. The findings from this study demonstrated that numerical distance affects ERPs 300 milliseconds following the presentation of digits pairs. The positive going ERP (the P300) differed significantly between pairs of digits that were separated by a relatively small numerical distance compared to pairs that expressed a comparatively large numerical distance. Specifically, the amplitude of the P300 was thereby larger for number pairs that were separated by a large numerical distance compared to digit pairs that were small in numerical distances. This finding is important as it suggests that numerical distance influences brain activation before participants make an overt response and hence, seems to affect processes related to stimulus encoding and activation of representations that will allow for discrimination to occur.

In another ERP study Dehaene, (1996) presented participants with both Arabic digits and number words and asked them to judge whether the presented digit or number word was smaller or larger than 5 while ERPs were acquired. In this study, Dehaene (1996) identified several, temporally separate, stages that occurred during numerical magnitude comparison. Specifically, he found an initial difference between words and digits in early components that could be localized (using source localization) to visual areas of the brain. These components were not sensitive to the numerical distance and hence, likely to be reflective of visual identification rather than semantic processing. This was followed by a distance effect on components occurring at electrodes over bilateral parietal sites between 170-200 milliseconds following stimulus onset. The effect of numerical distance on this component was not found to differ between number words and digits. A later effect was also reported related to differences in the electrophysiology as a function of the response side for a given trial.

These ERP findings are interesting for a number of reasons. First of all, they reveal a temporal independence in the brain of semantic processing of numerical magnitude (as indexed by the NDE) from the visual identification of the numerical stimuli as well as the response execution. Second, these findings extend those by Grune and colleagues (1993), discussed above, by demonstrating that numerical distance affects brain activation at very early processing stages (within the first 200 milliseconds). Finally, the source localization data presented by Dehaene (1996) suggest that the areas of the parietal cortex may play a critical role in numerical magnitude processing.

While providing exquisite information about the temporal structure in the brain, event-related brain potentials (even when source localization algorithms are used) cannot precisely elucidate the brain regions that are involved in numerical magnitude processing. Using functional Magnetic Resonance Imaging (fMRI), Pinel and colleagues (1999) were the first to investigate the neural basis of the numerical distance effect. Their findings showed that bilateral regions of the intraparietal sulcus (IPS) within the parietal lobe are parametrically modulated by numerical distance during numerical magnitude comparison tasks. In other words, the amount of brain activation in these brain regions is inversely related (greater activation for close numerical distances compared to large numerical distances) to the numerical distance of the numbers being compared (see Figure 1.5).

This finding indicates that the IPS is a crucial structure in the processing of numerical magnitudes in a symbolic format and that the neural activity within this region is modulated by numerical distance, indicating that the neural representation of symbolic numerical magnitude may be governed by Weber's law.

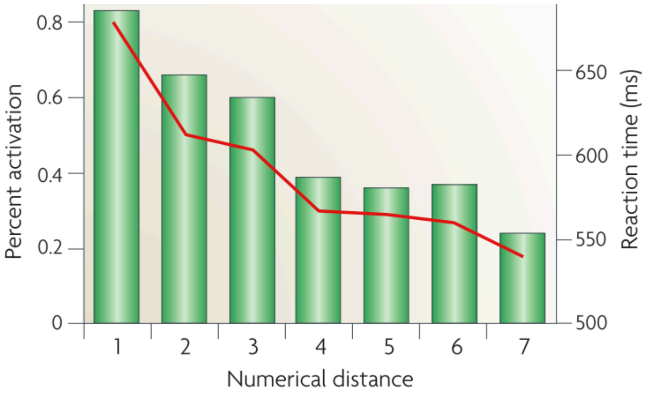


Figure 1.5: The figure illustrates the typical parametric modulation (i.e., the numerical distance effect) oft the IPS observed in number comparison tasks. Note that the brain activation decreases with an increase in numerical distance. This effect is argued to reflect a decrease in neural representational conflict (representational overlap of numbers) when numerals are compared that are farther away. Reprinted from "Effects of development and enculturation on number representation in the brain," by D. Ansari, 2008, Nature Reviews Neuroscience, 9, p. 280. Copyright Nature Publishing Group. Reprinted with permission.

The finding of a parametric modulation of the parietal cortex with numerical distance has since been replicated multiple times by other authors and laboratories (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Bugden & Ansari, 2010; Holloway & Ansari, 2010; Kaufmann et al., 2006; Pinel, Dehaene, Rivière, & LeBihan, 2001). However, it is important to note that investigations of the neural basis of the numerical distance effect do not merely reveal distance effects on activation of parietal regions. Many of the above-cited published studies reported distance effects across a distributed network of regions, including areas of the frontal cortex whose activity is also modulated by numerical distance. These findings, however, converge with findings from neuropsychological case studies to suggest that the parietal lobe and more specifically the IPS is critical for the processing of numerical magnitude information (for a review see Dehaene et al., 2003). Furthermore, the neuroimaging data suggest that numerical distance (numerical ratio) is a powerful predictor for brain activation that can be used to further constrain our understanding of how the human brain represents numerical magnitudes.

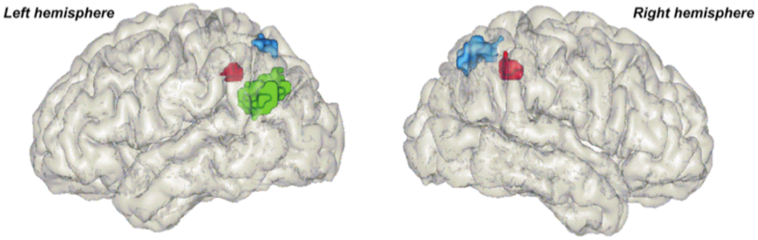


Figure 1.6: This view illustrates three parietal regions that are commonly activated in numerical tasks (Dehaene et al., 2003). In blue the bilateral posterior superior parietal lobe (PSPL), in green the left Angular gyrus and in red the bilateral horizontal segment of the intraparietal sulcus (IPS). The IPS is commonly engaged in processes that involve representations of numerical magnitude such as the comparison of two numerals. Reprinted from "Three Parietal Circuits for Number Processing," by S. Dehaene, 2003, Cognitive Neuropsychology, 20(3), p. 494. Copyright Taylor & Francis. Reprinted with permission.

Together, accumulating evidence from neuropsychological case studies as well as from neuroimaging studies has constrained our understanding about the neuronal architecture of symbolic numerical magnitude representations. Converging evidence suggests that the processing of numerical magnitudes is domain-specific and relates to regions of the parietal lobe, in particular the IPS (see also Figure 1.6). The neural activity of the IPS has been demonstrated to be modulated by numerical distance (numerical ratio), suggesting that this region is involved in processing the semantics of numerical magnitudes. Furthermore, the numerical ratio dependency of brain activation suggests that the IPS represents numerical magnitudes as approximate magnitudes in which close numerical distances elicit a larger representational overlap compared to numerical distances that are farther apart. While these studies have unravelled the principles of numerical magnitude representations in the human brain many important questions remain to be answered. Some of them are addressed in the present thesis. The next sections will provide a compact literature overview of current issues that motivated the questions addressed in the present work.

1.6. Neural correlates of numerical and non-numerical magnitude processing

The preceding section discussed evidence that suggests that the IPS of the parietal cortex is involved in representing symbolic numerical magnitudes. Another question that has recently received much attention is to which extent the human parietal cortex distinguishes between the representation of numerical and non-numerical magnitudes such as brightness, time and space. The current evidence from neuropsychological and neuroimaging studies converge to suggest that the parietal cortex sub-serves both common as well as distinct neural representations underlying the processing of numerical and non-numerical magnitudes (Cappelletti, Freeman, & Cipolotti, 2009, 2011; Cohen Kadosh et al., 2005; Dormal, Andres, & Pesenti, 2008; Dormal, Dormal, Joassin, & Pesenti, 2012; Dormal & Pesenti, 2009; Pinel, Piazza, Le Bihan, & Dehaene, 2004). Some of the evidence points towards hemispheric differences. Especially the involvement of the left IPS is commonly demonstrated for symbolic numerical magnitudes in contrast to non-numerical magnitudes, which are more strongly associated with activation of the right parietal cortex.

One of the first fMRI studies to investigate the neural correlates of symbolic numerical and non-numerical magnitude processing was conducted by Pinel and colleagues (2004). The authors measured the brain activity of participants who performed a number comparison task, a brightness comparison task and a physical size comparison task in the scanner. In the number comparison task, participants had to decide which of two simultaneously presented numerals is numerically larger. In the brightness condition, participants were asked to indicate which of two presented numerals is brighter and in the size comparison task the participants had to judge which of the two numbers was printed in the larger font. In all conditions the distances between stimuli (i.e., number distance, brightness distance, size distance) were systematically manipulated in order to elicit distance related effects in all conditions. Results of this study showed that the brain activity of bilateral regions was modulated by the manipulation of distance. Specifically, the IPS was commonly activated when participants performed the number and the physical size comparison task (a significant distance effect for both conditions). In addition, significant brain activity was found in regions of posterior parietal cortex in response to brightness and size comparisons. Together, this evidence demonstrates the parietal cortex is involved in the processing of numerical and non-numerical magnitudes. Moreover, the data of this study suggest that the processing of numerical and non-numerical magnitudes draws upon common as well as distinct regions of the parietal cortex.

While the study above provided evidence for a common activation of the IPS for the processing of number and physical size, another fMRI study found number specific as well as common activations in relation to the processing of non-numerical magnitudes. Using similar comparison tasks (i.e., number, brightness and size comparisons) as in the study by Pinel (2004), Cohen Kadosh et al. (2005) investigated the brain response of symbolic numerical magnitude processing and non-numerical magnitude processing in healthy adults. The results demonstrated considerable overlap of all three conditions in regions of the parietal cortex. However, when analyzing distance effects the authors were able to demonstrate that especially the left IPS was uniquely engaged in the processing of symbolic numerical magnitudes. Thus, besides demonstrating overlapping brain activations between different magnitude dimensions, this study indicated that the regions of the left IPS might play a dedicated role in representing symbolic numerical magnitudes. This finding provides evidence to suggest that number may be a special domain amongst other magnitudes and that the left IPS is crucial for representing symbolic numerical magnitudes.

The evidence reviewed above provides converging evidence to suggest that symbolic numerical magnitudes and non-numerical magnitudes rely neither on a fully independent magnitude system, nor on a single common magnitude representation (Cohen Kadosh et al., 2005; Dormal, Andres, & Pesenti, 2008; Dormal, Dormal, Joassin, & Pesenti, 2012; Dormal & Pesenti, 2009; Pinel et al., 2004). Moreover, there is growing evidence that points towards number as a special case amongst different magnitude dimensions and that left IPS may play a special role in the representation of symbolic numerical magnitudes. The question of laterality, however, remains elusive and more research is needed in order to better understand the contribution of different brain regions to the processing of symbolic numerical and non-numerical magnitudes

1.7. Developmental changes in the cortical representation of symbolic numerical magnitudes

Much of the research on the representation of symbolic numerical magnitudes focused on work with adult participants and little attention had been paid to the ways in which learning and development may modulate the brain circuits underlying the representation of symbolic numerical magnitudes. Recently, a growing body of experimental work has accumulated which investigates the neural mechanisms underlying the processing of symbolic numerical magnitudes over developmental time. These studies have provided evidence for dynamic changes in the neural correlates of symbolic numerical magnitude processing as well as similarities in the brain areas engaged during symbolic numerical magnitude processing between children and adults.

One of the first studies to investigate the neural basis of the symbolic numerical distance effect in children and adults, Ansari et al. (2005) found differences in the brain regions modulated by numerical distance between a group of 9-12 year old children and a group of adults. Specifically, children were found to exhibit a symbolic numerical distance effect on right frontal brain regions (right inferior and middle frontal gyri), while adults exhibited a symbolic numerical distance effect on parietal brain regions such as the right IPS and bilateral regions of the precuneus. This finding suggested a shift from the initial reliance on frontal brain regions to an increasing age-related specialization of the parietal cortex for the processing of symbolic numerical magnitude. These findings were supported by a similar observation by Kaufmann et al. (2006) using a number stroop paradigm, in which an age-related fronto-parietal shift in brain activation was observed between children and adults. The engagement of frontal brain regions in children (distance related modulations of frontal brain areas) has been posited to reflect the engagement of frontal brain resources such as cognitive control and conflict resolution. More specifically, it has been argued that the parietal brain representations of symbolic numerical magnitude in children may be more overlapping and hence, less precise compared to the representation of adults. Consistent with behavioural evidence (Holloway & Ansari, 2008; Sekuler & Mierkiewicz, 1977) this indicates that children engage more cognitive resources of the frontal lobe (i.e., executive functions) in order to resolve the representational overlap of numerical magnitudes in the context of number comparison.

It should be noted that the strongest evidence to date points towards an age-related specialization of the parietal cortex for the processing of symbolic numerical magnitude. However, functional neuroimaging studies with children are inherently noisy and heavily confounded by performance differences across different ages. In addition, non-numerical processes such as response selection are well known to activate regions of the IPS. Hence, it is currently unclear whether developmental changes observed in parietal areas are directly related to changes in the underlying representation of symbolic numerical magnitude or to changes in non-numerical processing such as response selection. Moreover, there is a great need for studies that move beyond the relatively coarse comparison of children and adults towards a characterization of the full developmental trajectory underlying the neural correlates of symbolic numerical magnitude processing. Clearly, more evidence is needed in this area in order to further constrain our knowledge about the development of symbolic numerical magnitude representation.

1.8. Overview of the thesis

The previous sections provided a general introduction about how the human brain represents symbolic numerical magnitudes. The evidence discussed showed that the discrimination of symbolic numerical magnitudes is dependent on the numerical distance (numerical ratio) between the numbers being compared. Furthermore, evidence has shown that the size of the numerical distance effect decreases with age and that individual differences in the size of the numerical ratio effect correlate with mathematical achievement. Neuropsychological studies as well as work with neuroimaging technology has indicated that the parietal lobe is involved in the processing of symbolic numerical magnitudes and the brain activation of the IPS is modulated by numerical distance (numerical ratio) when numbers are being compared.

As already discussed, there is a growing body of evidence that indicates that the left IPS is particularly important for the processing of symbolic numerical magnitudes compared to the processing of non-numerical magnitudes. The first fMRI study with adults in chapter 2 further explored this question and contrasted the neural correlates associated with the processing of symbolic numerical to the brain activation associated with non-numerical magnitudes (i.e., brightness). A task that has been used to investigate the spatial properties (the mapping of numerical symbols onto an internal mental number line) of symbolic numerical magnitude representations is the number line estimation task. In this task participants are asked to place a numerical probe onto the correct position along a spatially extended number line (e.g., place the number 35 on the correct position of a number line that ranges from 0 – 100). By contrasting the brain activation associated with the mapping of numerical symbols into space (i.e., the placing of the probe on a spatially extended number line) with the brain activation associated with mapping non-numerical magnitudes (i.e., brightness) into space, the first study was able to investigate commonalities and differences in cortical specialization for the processing of symbolic numerical magnitudes in contrast to the processing of non-numerical magnitudes.

While the results of the first study are useful to contrast the brain activation of symbolic numerical magnitude against the brain activation of non-numerical magnitude processing, the number line estimation task as well as the number comparison task are heavily confounded by non-numerical cognitive mechanisms such as response selection and performance differences. As such it is unresolved whether activation differences found in the IPS are directly related to the processing of symbolic numerical magnitudes per se, or, whether brain activations are related to non-numerical operations such as response selection. Since the ultimate goal of the present work was to investigate developmental changes in cortical specialization of symbolic numerical magnitude representation, we piloted an adjusted child friendly fMRI adaptation paradigm in adults. This design minimizes confounding variables such as performance differences and response selection. Hence, this paradigm allows for a stringent investigation into the developmental changes in the cortical representation of symbolic numerical magnitudes. As such the second study aimed to replicate findings of numerical ratio dependent signal recovery effects observed in the brain of human adults.

As already pointed out in the paragraph above, the last study of the thesis, discussed in chapter 5, investigates developmental changes in the cortical representation of symbolic numerical magnitudes in a group of children ranging from 6 to 14 years of age. Using the paradigm tested in study 2 of the present thesis, this study minimized the impact of confounding variables and, hence, aimed to further constrain our current knowledge about how the human brain represents symbolic numerical magnitudes over developmental time.

Overall, the three studies conducted in the present work investigated how the human brain represents symbolic numerical magnitudes and how the neural correlates of symbolic numerical magnitude change over developmental time. As such the present work further constrains our existing knowledge by providing new insights about developmental changes in the cortical representation of symbolic numerical magnitudes.

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Chapter 2: Neural correlates underlying the processing of numerical and non-numerical magnitude

2.1. Introduction

Research into the neural correlates of numerical cognition has implicated the parietal lobe, and more specifically the intraparietal sulcus (IPS), as a critical brain region for processing the abstract meaning of numerical magnitude (the total number of items in a set). Brain activity in this region is consistently activated whenever participants are presented with symbolic (e.g., Arabic digit) or non-symbolic (e.g., dot arrays) numerical magnitudes (for a review see Nieder & Dehaene, 2009).

Most tasks that have investigated the neural correlates of symbolic numerical magnitude processing have focused on the comparison of symbolic numerical magnitudes. In such comparison tasks, numerical symbols are presented on a screen and participants are either asked to decide which of two simultaneously presented digits is numerically larger/smaller, or whether a presented numeral is numerically larger/smaller than a non-presented reference number (e.g., 5).

The rationale for using comparison tasks to tap into the neural correlates of symbolic number processing is based on behavioral data. Such tasks yield a very robust behavioral effect, the numerical distance effect (NDE) – an inverse relationship between the numerical distance of two numerals and the corresponding reaction times. More specifically, the larger the numerical distance between two numerals, the faster and more accurate the behavioral response (Moyer & Landauer, 1967). This effect appears to reflect an approximate representation of symbolic numerical magnitudes. Specifically, numerical magnitudes that are close in distance (e.g., 4 and 5) exhibit a greater representational overlap than do numerical magnitudes that are further apart (e.g., 4 and 9). Consistent with this idea, the comparison of pairs of numbers that are separated by relatively numerically smaller distances is associated with greater brain activation in the IPS than is the case for pairs separated by comparatively larger distances (Ansari, Dhital, & Siong, 2006; Ansari et al., 2005; Kaufmann et al., 2005; Pinel et al., 2001). This effect has been interpreted as a signature of symbolic numerical magnitude processing in the brain.

In addition to the frequently used number comparison tasks, passive tasks such as functional Magnetic Resonance Adaptation (fMR-A) - in which participants solely attend to the presentation of stimuli without any overt task demand - have been used to investigate the neural correlates of numerical magnitude processing. Convergent with activations found in the number comparison task, results of such studies have revealed that areas in and around the IPS habituate to symbolic numerical magnitudes (show decreased activation to repeated numerical magnitudes). Further, following the adaptation of the IPS to a specific numerical magnitude, a distance-dependent recovery to novel numerical magnitudes is observed. Specifically, IPS activation recovers to a greater extent following presentation of novel numerical magnitudes that are relatively distant from the original numerical magnitude compared to when the numerical distance between the adapted and novel numerical magnitude is smaller (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Holloway, Battista, Vogel, & Ansari, 2012; Notebaert, Nelis, & Reynvoet, 2011; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Piazza, Pinel, Le Bihan, & Dehaene, 2007).

Another task that has proved useful for generating behavioral evidence regarding the relation between number and space is the number line estimation paradigm (Siegler & Opfer, 2003). In this paradigm, participants are asked to estimate the spatial position of a number on a physical number line. This task is thought to directly tap into the mechanisms associated with subserving the mapping of symbolic numerical magnitude into space because it involves the mental activity of taking an internal representation of numerical magnitude and mapping it onto a spatial reference frame (i.e., the number line). Recent behavioral studies have shown that children's performance on the number line estimation task correlates with their proficiency in arithmetic and other estimation tasks, memory for numbers, standardized mathematical achievement test scores, and mathematical school grades (Booth & Siegler, 2006; Schneider et al., 2008; Schneider, Grabner, & Paetsch, 2009; Siegler & Booth, 2004; Thompson & Siegler, 2010). Furthermore, interventions that increase the accuracy of children's estimates on the number line cause increases in the children's arithmetic competence (Booth & Siegler, 2008; Siegler & Ramani, 2009). Therefore, it is important to address the question of which regions of the human brain are involved in the mapping process on this task.

The number line task also allows for investigation of differences and commonalities in the brain regions involved in the mapping of discrete symbolic numerical and continuous non-numerical magnitudes onto space. In particular, the task enables the comparison between the brain regions involved in mapping the positions of symbolic numbers on a number line to those involved in estimating levels of luminance on a spectrum from bright white to dark black. Functional neuroimaging studies using symbolic numerical and non-numerical comparison paradigms have indicated that both similar and dissociated regions in the parietal lobe are activated when magnitudes of different kinds are compared. For example, Pinel and colleagues (2004) investigated brain activity while participants decided which of two simultaneously presented numerals was brighter, physically larger, or numerically larger. Judgments of number and area were associated with overlapping responses in the IPS, while comparisons of luminance and size were found to share activation in regions of the occipito-temporal cortex.

This evidence suggests that at least some regions of the parietal cortex are involved in the processing of both symbolic numerical and non-numerical magnitudes. Another fMRI study by Cohen Kadosh and colleagues (2005) used similar comparisons tasks as those that were used in Pinel et al. (2004) and showed overlapping brain representations for size, luminance, and symbolic numerical magnitude in bilateral regions of the parietal cortex. However, in addition to these common effects across different magnitude comparison tasks, the authors found that the left IPS was uniquely engaged in the numerical comparison task: it was the only region that showed a significant neural distance effect for number.

Taken together, these results suggest that differences between symbolic numerical and non-numerical magnitudes may be related to particular locations within the left and right IPS. More specifically, common effects of magnitude processing are predominantly found in regions along the right IPS, while the processing of symbolic numerical magnitudes also involves regions of the left anterior IPS. The use of both a symbolic numerical and a non-numerical line estimation tasks allowed for an examination of whether these effects were unique to the numerical comparison tasks or whether these effects can be generalized to other symbolic numerical tasks.

For these reasons, a number line estimation task with numbers from 0-100 was administered to investigate which brain regions are involved in mapping symbolic numerical magnitudes onto space. The comparison task involved estimation of the luminance of gray swatches on a number line ranging from white to black.

In sum we investigate two related questions in this study. On the one hand, we are interested in uncovering the neural regions involved in mapping number symbols into space and, on the other hand, in establishing whether such brain regions differ as a function of whether the spatial position of symbolic numerical or non-numerical magnitudes are estimated. We predicted that the parietal lobe would play a vital role in mapping symbolic numerical magnitudes onto space. Against the background of the literature from numerical and non-numerical comparison studies, reviewed above, we also expected to find right IPS involvement in both symbolic numerical and non-numerical magnitude processing, and additional left IPS involvement in the processing of symbolic numerical magnitudes.

2.2. Materials and Methods

2.2.1.Participants

Participants were 14 healthy, right-handed adult participants: 7 female (mean age = 24.86 years; SD = 5.40; range = 18 – 33) and 7 male (mean age = 24.29 years; SD = 2.87; range = 19 – 28).

2.2.2.Task Design and Stimuli

Two experimental conditions – number line estimation (NLE) and brightness estimation (BE) - and one control condition were used in this experiment (see Figure 2.1 for example of stimuli).

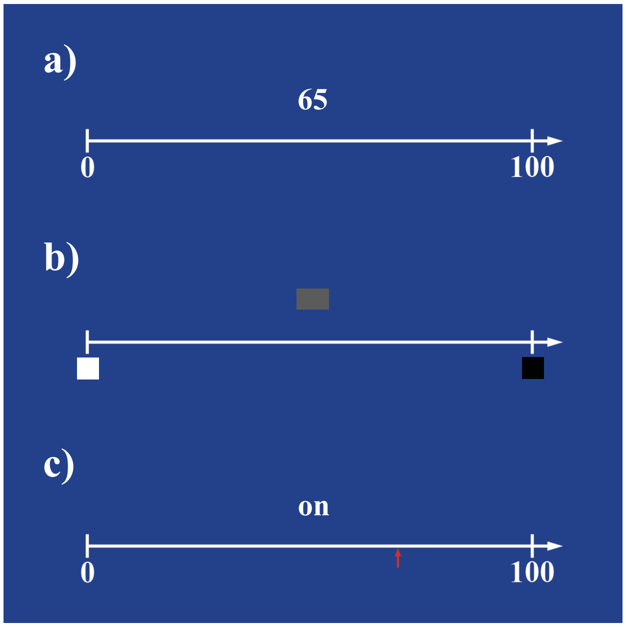

Figure 2.1: Example stimuli used in the three different experimental conditions. A) Number line estimation, b) Brightness estimation and c) word control task. Reprinted

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2.2.2.1.Number Line Estimation (NLE)

A white vertical line was presented on a blue screen to visually map out a spatial reference frame from left to right. At the right end of the line, an arrow was pointing towards infinity indicating that the reference space-line extends further to the right. In addition, at the left end, a small horizontal line marked the beginning of the line. Furthermore, the spatial reference line was supplemented in such a way that two Arabic numerals – 0 at the left-end and 100 on the right-end - were presented as flankers below the vertical line. The purpose of the two numerals was to indicate the spatial-numerical extent of the reference line ranging from 0 on the left to 100 on the right.

Arabic numerals, ranging within 1 – 99 (Table 2.1), were randomly ordered as probes in the NLE condition. Probes were presented for 5000 ms at the center of the screen and above the spatial reference line. Each probe was presented 3 times using 3 different jitter intervals after stimulus presentation. Participants were instructed to indicate the spatial position of the numerical value on the number line by clicking a trackball at the desired location.

Numbers in the NLE	Brightness in the BE	Words in the control
3	⬜	on
7	⬜	in
11	⬜	to
13	⬜	at
21	░	me
28	░	we
33	░	he
36	░	it
42	▒	no
45	▒	so
56	▒	by
57	▒	go
60	▒	do
65	▒	am
74	▓	as
77	▓	my
83	▓	or
85	▓	ox
90	⬛	if
98	⬛	be

Table 2.1: List of stimuli used in the experimental and in the control condition. Note that the brightness values in the BE task correspond to the numerical values used in the NLE task in such a way that the steps between brightness and numerical levels are equivalent. For example, the magnitude difference between the 1st number (i.e., 3) and the 2nd number (i.e., 7) in the list is the same as the magnitude difference between the 1st and 2nd brightness swatch in the list. Reprinted from "Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study," by S. Vogel, 2013, Neuropsychologia, 51(5), p. 982. Copyright Elsevier. Reprinted with permission.

2.2.2.2.Brightness Estimation (BE)

The same visual reference line as in the NLE condition was used for the BE condition. However, instead of 0 and 100 anchoring the line, two square boxes, one filled with the brightness level of white and the other filled with the brightness level of black[1] were presented below the vertical line and were used to indicate the brightness range of the reference line, from white on the left to black on the right. The same procedure as in the NLE condition was used for the BE task. However, instead of Arabic digits, brightness levels (Table 2.1) were presented randomly on the screen at the same location as the numeric probe in the NLE task. Participants needed to indicate with the trackball the spatial position on the reference line at which they would place the presented brightness.

2.2.2.3.Control Condition

The same reference line as in the NLE condition was used in the control condition. In contrast to the two experimental conditions, two-letter words (Table 2.1) were used as probes. The rationale for using two-letter words in the control condition was to equate visual complexity across the word and number conditions. The task was to move the trackball to the location on the line indicated by an arrow, and to click on it. The arrows indicated the locations of correct estimates in the other two conditions, thus requiring the same hand movements in all three conditions. However, in the control condition the

---

[1] All brightness levels were generated with the computer program Borland Delphi. Shades of grey were specified with the RGB color system. Within this format, each color value (R,G and B) was coded within in a range from 0 to 255. Using the formula [(100-n)*255/100] different gray levels (100 in total) were generated, with white (R,G,B = 0, 0, 0) and black (R,G,B = 100, 100, 100) on the two ends of the range.

stimuli were irrelevant to task performance and were only used to equate complexity of visual input.

Please note that the visual indicator of the trackball was reset to the center of the screen (i.e., same location as the presented probe) after each trial. In addition, the spatial locations of the correct answers on the reference line were matched across identical trials between conditions. For example, the correct position on the reference line for the numerical probe 36 was identical to the correct position of the corresponding gray shade (see Figure 2.1 for the correspondence between numerical and brightness values) and the arrow in the word control condition. This standardized procedure ensured that hand movements were matched as much as possible across the three experimental conditions.

Since the word control task did not involve explicit processing of the two-letter words presented in the middle of the screen, additional dummy trials were included in all conditions. On these trials, numbers, brightness stimuli, and dummy words were crossed out with two red lines. Whenever dummy trials appeared on the screen, participants were asked to indicate the presence of such a trial with a button press. The inclusion of these additional trials ensured that participants paid attention to the dummy words in the word control condition and that perceptual processing mechanisms across all tasks were at least roughly comparable.

2.2.3.Procedure

Before entering the scanner, participants were told about the fMRI environment and the experimental task procedure. Once in the scanner, participants were presented 12 blocks – 4 for NLE, 4 for BE, and 4 for the word controls - divided into four functional runs (3 blocks per run). The order of the 12 blocks was counterbalanced across the four runs; thus, the block presentation order from one run to the next was not predictable for participants. Within each block, 15 stimuli for the same task were presented, resulting in a total of 45 trials per run (see also Table 2.1) and 180 trials for the four runs. Stimuli were presented in a pseudo-random order, with the rule that the same stimulus must not be presented on consecutive trials. Between stimuli, a jitter interval of 5,000 ms, 7,500 ms and 10,000 ms was used to optimize the hemodynamic response function (HRF). Jitter time was balanced in such a way that the same jitter-time was never presented on consecutive trials. As a result, the stimuli were presented in an event-related design.

2.2.4.Data Acquisition

Functional and structural imaging data were acquired using a whole-body MRI scanner (3T GE). A standard echo-planar imaging (EPI) $T2^*$ sequence was used in order to measure and quantify the blood-oxygen-level-dependent (BOLD) functional response. In each run, 444 functional volumes were collected. One volume consisted of 36 slices (3.4 mm slice thickness; flip angle: 59°) and were acquired using an interleaved ascending order. Timing parameters for this paradigm were set to a time to repetition (TR) of 2100 ms and a time to echo (TE) of 31 ms. T1 whole-brain high-resolution pictures for each subject were acquired with an axial FSPGR BEAVO sequence with a TR of 8836 ms and a TE of 3504. Each 3D volume consisted of 140 horizontal slices (1.2 mm slice thickness, flip angle: 13°).

2.3. Data Analysis

All functional and structural imaging data were pre-processed and analyzed with the software package Brain Voyager QX 2.3 (Brain Innovation, Maastricht, The Netherlands). Participants' functional runs were first corrected for slice time acquisition (cubic spline, images were acquired in an ascending-interleaved order) and head motion (trilinear/sinc interpolation). Furthermore, a High-Pass filter (GLM-Fourier, 2 sine/cosine cycles) was applied to remove frequencies related to physiological noise, such as breathing and the heart beat. Finally, all functional runs were spatially smoothed using a kernel of 6 mm full width at half maximum (FWHM). Individual's structural 3D images and individual functional runs were co-registered. This was attained by mapping the individual functional runs onto the anatomical 3D image until a maximum of spatial overlap of anatomical landmarks was achieved. To maximize the accuracy of the functional-to-structural alignment, all anatomical images were stripped from the skull and only the remaining brain tissue was used for the co-registration process. After all the functional images were aligned to their corresponding anatomical image, the data were transformed into Talairach space (Talairach & Tournoux, 1988) for group statistical analysis.

Functional events were modeled using random effects (RFX) general linear model (GLM) with the three tasks used as predictors. The design matrix contained, therefore, event-related predictors for the NLE, BE and control conditions. All predictors were convolved with a two-gamma hemodynamic response gamma function (HRF) to model the expected (BOLD) function (Friston et al., 1998).

2.3.1.Tasks > control condition

The initial analysis aimed to investigate brain areas that were significantly modulated by the experimental conditions compared to the word control condition. Contrasts of "[NLE > control]" and "[BE > control]" were calculated separately.

2.3.2.Areas involved in both number line and brightness estimation

To examine regions that showed a significant common neural response to number and brightness estimation, a RFX conjunction analysis was calculated over the contrasts "[NLE > control] ∩ [BE > control]".

2.3.3.Analyses used to investigate distinct activation for number and brightness

To evaluate numerical and non-numerical task specific brain activation patterns, two conjunction analyses were calculated. To investigate number specific activation, the conjunction of "[NLE > BE] ∩ [NLE > control]" was calculated. To calculate brightness specific activation, the conjunction of "[BE > NLE] ∩ [BE > control]" was calculated. These analyses ensured that activation differences between the two experimental estimation conditions (i.e., NLE and BE) were over and above activation of the word control task.

For all analyses, an initial, uncorrected threshold of $p < 0.001$ was used to identify regions that showed a statistical difference. The resulting maps were subsequently corrected for multiple comparisons using cluster size thresholding (Forman et al., 1995; Goebel, Esposito, & Formisano, 2006). In this method, an initial voxel-level (uncorrected) threshold is set. Then, threshold maps are submitted to different correction criteria, based on the estimates of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positives rates. After 1000 iterations, the minimum cluster-size that yielded a cluster-level false –positive rate (α) of 0.05 was used to threshold the statistical maps. Only activations whose size met or exceeded the cluster threshold were allowed to remain on the statistical maps.

2.4. Results

2.4.1.Behavioural Results

Reaction times in the three conditions were subjected to an analysis of variance (ANOVA) with repeated measurements. This analysis indicated a difference in median RT's among the three tasks (NLE = 3367 ms, SD= 266 ms; BE = 3264 ms, SD = 376 ms; Word Control = 3106, SD = 303 ms, (F(2,13) = 5.541, p = 0.015). To identify the source of this effect, we calculated three paired sample t-tests between the conditions. After Bonferroni Corrections for multiple comparisons, this analysis revealed a difference between the NLE and control reaction times (t(13) = 3.661, p = 0.003). The contrast between NLE and BE conditions was non-significant (t(13) =1.491, p = 0.160), as was the contrast between BE and Word conditions (t(13) = 1.679, p = 0.117).

We also compared the mean PAEs (percent absolute errors) for the three conditions. The PAEs were 2.43 (SD = 0.71) for the NLE condition, 17.32 (SD = 7.00) for the BE condition, and 0.41 (SD = 0.17) for the word condition, where participants only needed to duplicate the position of the arrow on the number line. An ANOVA with repeated measurements showed a significant difference across the three conditions (F(2,13) = 70.803, $p < 0.001$). Post-hoc t-tests for paired samples revealed significant differences for all possible combinations: NLE versus BE t(13) = -7.735, $p < 0.001$; NLE versus Control t(13) = 10.896, $p < 0.001$; BE versus Control t(13) = 9.056, $p < 0.001$).

2.4.2.fMRI Results

2.4.2.1.Number and brightness versus control

The aim of the first analysis was to identify brain regions that showed stronger activation for the numerical and brightness estimation tasks than for the word control. The numerical estimation task revealed greater activations than the control task in frontal, parietal and occipital areas (see Figure 2.2, activations displayed in red). Activations within the parietal lobe were restricted to the IPS in both hemispheres and to the left posterior superior parietal lobe (PSPL, more specifically the precuneus). Similarly, the brightness estimation task produced greater activations within frontal, parietal and occipital regions than the control (see Figure 2.2, activation displayed in blue). In this contrast however, parietal activations in the IPS were more pronounced in the right hemisphere, covering the IPS and the PSPL (precuneus). See Tables 2.2 and 2.3 for Talairach coordinates of the contrasts.

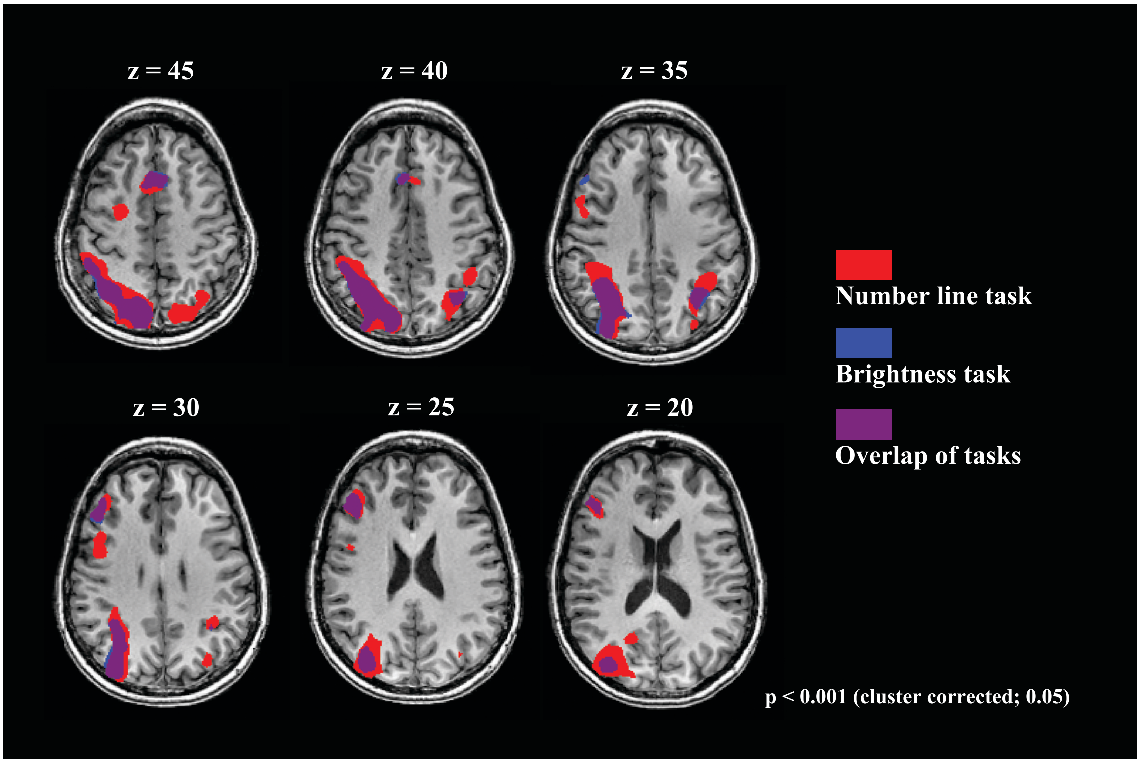

Figure 2.2: Activations of the "Number line task > word control" and the "Brightness task > word control" are displayed in six transversal sections of the brain. Number related activations are shown in red while Brightness related activations are shown in blue. Overlapping regions are shown in puple. Reprinted from "Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study," by S. Vogel, 2013, Neuropsychologia, 51(5), p. 984. Copyright Elsevier. Reprinted with permission.

	Hemisphere	Stereotaxic coordinates		
		X	Y	Z
Precuneus	R	8	-77	48
Intraparietal Sulcus	R	29	-62	36
Middle Occipital Gyrus	R	35	-77	21
Middle Frontal Gyrus	R	32	1	51
Superior Frontal Gyrus	R	8	10	48
Superior Frontal Gyrus	R	41	37	27
Cuneus	L	-16	-95	9
Precuneus	L	-13	-80	48
Intraparietal Sulcus	L	-31	-68	42
Middle Frontal Gyrus	R	47	13	33

Table 2.2: List of those areas that showed a significant difference between the number line estimation task and word control task (i.e., NLE > control). Coordinates are given in Talairach space (Talairach & Tournoux, 1988). Activations are reported at a threshold level of p > 0.001 (0.05 corrected on cluster level). Reprinted from "Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study," by S. Vogel, 2013, Neuropsychologia, 51(5), p. 984. Copyright Elsevier. Reprinted with permission.

	Hemisphere	Stereotaxic coordinates		
		X	Y	Z
Intraparietal Sulcus	R	32	-56	39
Sub-Gyral	R	29	1	54
Precuneus	R	8	-80	48
Intraparietal Sulcus	L	-34	-59	36
Medial Frontal Gyrus	L	-4	19	45
Lingual Gyrus	R	14	-89	0
Middle Frontal Gyrus	R	48	31	30

Table 2.3: List of those areas that demonstrated a significant difference between the brightness estimation task and the word control task (i.e., BE > control). Coordinates are given in Talairach space (Talairach & Tournoux, 1988). Activations are reported at a threshold level of p < 0.001 (0.05 corrected on cluster level). Reprinted from "Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study," by S. Vogel, 2013, Neuropsychologia, 51(5), p. 984. Copyright Elsevier. Reprinted with permission.

2.4.2.2.Common activations for number and brightness

To analyze the extent to which the neural correlates of the experimental tasks overlapped, a whole-brain conjunction analysis between "[NLE > control] ∩ [BE > control]" was performed. Results of this contrast showed a significant overlap in the right hemisphere of the parietal cortex and the frontal lobe (see Figure 2.3, activation displayed in blue; for Talairach coordinates see Table 2.4). Activation overlap between NLE and BE tasks in the parietal lobe spanned the right IPS extending to the PSPL, while activation in the frontal lobe was found in the dorsolateral prefrontal cortex (DLPFC) and the right middle frontal gyrus.

2.4.2.3.Number specific activations

The last analysis was designed to reveal brain regions that showed activation specifically modulated to the number line estimation task. For the contrast "[NLE > BE] ∩ [NLE > control]", number specific activations were found in bilateral regions of the anterior IPS and the left PSPL. In addition to the activation clusters in the parietal lobe, right lateralized activations were found in the DLPFC and occipital-parietal junction (see Figure 2.3, activation displayed in red; also for Talairach coordinates see Table 2.5).

To investigate regions specifically modulated in response to brightness estimation, a conjunction of the contrasts "[BE > control] ∩ [BE > NE]" was performed. No significant differences in activation were found.

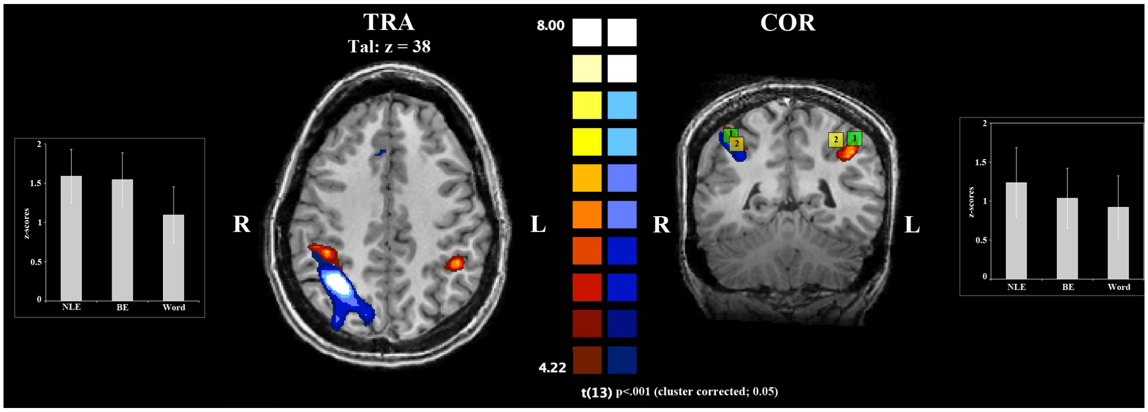

Figure 2.3: The blue areas represent areas that were involved both when participants mapped number and brightness into space. Areas in red displayed number specific regions that were activated only when the position of numbers were estimated. The coronal section displays in addition gravity centers of two metal-analysis of numerical magnitude processing – green square (1): Cohen Kadoh, Lammertyn, & Izard (2008), in yellow square (2): Dehhaene et al. (2003). Reprinted from "Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study," by S. Vogel, 2013, Neuropsychologia, 51(5), p. 985. Copyright Elsevier. Reprinted with permission.

	Hemisphere	Stereotaxic coordinates		
		X	Y	Z
Intraparietal Sulcus	R	32	-56	39
Sub-Gyral	R	29	1	54
Precuneus	R	8	-80	48
Middle Frontal Gyrys	R	47	31	27
Middle Frontal Gyrus	R	5	19	45

Table 2.4: Areas that showed a significant overlap for the number line estimation and brightness estimation task (i.e., [NLE > control] ∩ [BE > control]). Coordinates are given in Talairach space (Talairach & Tournoux, 1988). Activations are reported at a threshold level of $p < 0.001$ (0.05 corrected on cluster level). Reprinted from "Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study," by S. Vogel, 2013, Neuropsychologia, 51(5), p. 985. Copyright Elsevier. Reprinted with permission.

	Hemisphere	Stereotaxic coordinates		
		X	Y	Z
Intraparietal Sulcus	R	38	-38	36
Intraparietal Sulcus	L	-43	-44	39
Middle Temporal Gyrus	R	35	-71	15
Middle Frontal Gyrus	R	23	-5	48
Precuneus	L	-10	-81	51

Table 2.5: Brain regions that demonstrated a significatn number specific activation (i.e., [NLE > BE] ∩ [NLE > control]). Coordinates are given in Talairach space (Talairach & Tournoux, 1988). Activations are reported at a threshold level of $p < 0.001$ (0.05 corrected on cluster level). Reprinted from "Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study," by S. Vogel, 2013, Neuropsychologia, 51(5), p. 985. Copyright Elsevier. Reprinted with permission.

2.5. Discussion

A growing body of neuroimaging work has examined the neuronal correlates associated with the processing of symbolic numerical magnitudes and non-numerical magnitudes (e.g., Ansari et al., 2005; Pinel et al., 1999, 2001). Converging evidence from this literature has indicated that intraparietal sulcus (IPS) of the parietal lobe is critically involved in processing magnitude dimensions of different kinds. Specifically, neuroimaging studies that have pitted the neural correlates of different magnitudes dimensions against each other have demonstrated that overlapping as well as distinct brain regions of the parietal lobe and particularly of the IPS are engaged when symbolic numerical and non-numerical magnitudes are processed. This suggests that the processing of different magnitude dimensions draws upon common as well as upon distinct cortical magnitude representations. Moreover, results of these studies have indicated that especially the left IPS is critically involved in the processing of symbolic numerical magnitudes, suggesting that symbolic numerical magnitude representation draws upon a specific neural architecture and form a special class amongst other magnitude dimensions. To further constrain our knowledge about symbolic numerical magnitude representation in contrast to other non-numerical magnitude dimensions we measured the brain activity of adults who performed a number line estimation and a brightness estimation task. Number line tasks have been previously used in behavioural studies in order to investigate symbolic numerical magnitude representation in children and adults. Therefore, number line estimation may be particularly useful to further investigate how the human brain represents symbolic numerical magnitudes and how such representations overlap or differ from representation of non-numerical magnitudes. To fill this gap, the present study explored neural correlates of the processes of mapping symbolic numerical and non-numerical magnitudes onto space, in particular, mapping of numbers and brightness levels onto horizontally oriented lines.

Results of the present study demonstrated that the parietal lobe plays a critical role in mapping quantities onto space for both discrete symbolic numerical and continuous non-numerical quantities. Results of a conjunction analysis between number and brightness, revealed an extensive activation overlap in the right IPS while participants estimated the position of symbolic numerical and non-numerical magnitudes on an external number line, relative to a control in which participants only needed to click the mouse at positions on the line indicated by arrows. Moreover, a second conjunction analysis, contrasting the brain activation evoked by the number line estimation task with those evoked by each of the other tasks revealed number specific activations within bilateral regions of the anterior IPS. The results of the present study, therefore, demonstrated that the mapping of discrete numerical magnitudes onto space encompasses additional regions of the bilateral anterior IPS, above and beyond the common activation in the right hemisphere for processing numerical and non-numerical magnitudes.

The importance of the parietal lobe in processing symbolic numerical magnitude information has been demonstrated in many studies using different experimental paradigms. These studies indicate that the IPS hosts an abstract and format-independent representation of numerical magnitude (Dehaene et al., 2003). The present data extend this body of evidence by showing that the mapping of numerical magnitudes onto space also engages regions in and around the IPS. The bilateral number specific activations of the anterior IPS that were found in the present study were located in close anatomical proximity to the mean centers of gravity recently identified by meta-analyses of numerical magnitude comparison (Cohen Kadosh, Lammertyn, & Izard, 2008; Stanislas Dehaene et al., 2003; see Figure 2.3 on the right). Thus, the present findings show, for the first time, that mapping numbers onto space is mediated by similar brain regions as those that have been revealed in comparison and number adaptation paradigms.

In addition to the above discussed number specific activations, the present study revealed extensive activation overlap in the right, but not left, IPS for numerical and non-numerical magnitude estimation. Recent investigations into the neural correlates of numerical and non-numerical quantities have suggested that the IPS is not specific to the processing of numerical magnitudes but is also involved in the processing of non-numerical magnitudes (Cohen Kadosh et al., 2005; Dormal et al., 2008; Dormal & Pesenti, 2009; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Walsh, 2003).

The present study goes beyond the notion of a common magnitude code. Specifically, the mapping of number and brightness onto an external spatial reference space co-activated a strictly right-lateralized network within the IPS, whereas a bilateral activation in the IPS was found for numbers only. Similar hemispheric dissociations for the processing of discrete numerical and continuous non-numerical magnitudes have been implicated by functional imaging studies using magnitude comparison tasks. One such study employed number, luminance and size comparison tasks (Cohen Kadosh et al., 2005). The left IPS was more strongly activated in the numerical comparison condition, whereas the right IPS was engaged to the same extent across all three comparison tasks, suggesting lateralization effects for the processing of numerical and non-numerical magnitudes.

Similarly, Dormal and Pesenti (2009) reported that when participants compared the amount of dots displayed in two linear arrays, the length of two dot arrays and the length of two continuous rectangles, there was significant activation overlap in the right IPS for the length and the number comparison tasks. There also was number specific activation in the right as well as in the left anterior IPS, suggesting that additional areas of the anterior bilateral IPS are recruited when discrete numerical magnitudes are processed.

Another functional imaging study investigated the neural correlates in response to analogue (i.e., disks and dots) and number symbol (i.e., positive and negative integers) processing (Chassy & Grodd, 2012). In the analogue disk comparison condition, participants were asked to decide which of the two presented disks was larger in physical size. Similarly, in the analogue dot condition, participants were asked to decide which of the two presented dot-arrays had the larger amount of dots. Furthermore, in the symbolic conditions, both the positive (e.g., 3 vs. 9) and the negative (e.g., -3 vs. -9) comparisons were used and participants were asked which of the two presented Arabic digits was larger in numerical value. A conjunction analysis of brain responses across formats revealed a right lateralized parietal network, including the IPS and the right superior parietal lobule. Moreover, neural correlates of format specific contrasts suggested that the processing of discrete symbolic numerical information recruited additional areas in the left parietal lobe. These results are consistent with those of the present study.

Yet more evidence for a common right-lateralized activation for the processing of numerical and non-numerical magnitudes has been provided by Dormal and colleagues (2012) who found an activation overlap for the processing of numerosity and duration in the right, but not the left, IPS. Participants in this study were asked to categorize either the number of flashed dot sequences or the display duration of single dots on a screen. Using fMRI, the authors found a large right-lateralized parietal–frontal network for the processing of numerical and non-numerical magnitudes, suggesting a large overlap in the right hemisphere for these quantitative dimensions.

Taken together, the present study and the reviewed literature converge in suggesting a hemispheric dissociation of parietal activation when processing discrete numerical and continuous non-numerical magnitudes. This convergence of evidence across findings with different methods and stimuli, provide strong evidence for hemispheric differences in the processing of numerical and non-numerical magnitudes. By doing so, the present data suggest that these activations are not task specific but may be category specific (discrete vs. continuous) and demonstrate that these differences generalize across number processing paradigms. While the right IPS is commonly activated for processing both numerical and non-numerical magnitudes, symbolic numerical magnitudes are associated with additional recruitment of the left IPS. Strong empirical evidence for such hemispheric differences has also been provided by fMR-A studies, which indicate greater sensitivity of the left hemisphere for processing symbolic than non-symbolic numerical magnitudes (Notebaert et al., 2011; Piazza et al., 2007). The additional involvement of the left IPS in numerical processing may reflect a process of enculturation that leads to specialization for the processing of discrete numerical magnitudes (Ansari, 2007).

2.5.1.Conclusion

Number lines are used to externally represent symbolic numerical magnitudes and are frequently employed in developmental research to examine how symbolic number processing changes over the course of learning and development. However, while a large body of evidence suggests that brain regions in and around the IPS are involved in processing the magnitude information of number symbols, the brain regions that are involved in the mapping of number symbols onto an external reference space such as the number line are currently unknown.

The present study addressed this gap in the literature by probing the brain regions associated with number line estimation. We examined brain regions involved in mapping number symbols onto space, and compared them to the areas involved in mapping a non-numerical dimension – brightness – onto space. Results showed common activation for mapping symbolic numerical magnitudes and brightness onto space in the right IPS. Bilateral anterior regions of the IPS were significantly involved when symbolic numerical magnitudes were mapped onto an external reference space. Therefore, findings of the present study revealed common as well as number-specific activation within regions of the IPS for mapping numerical and non-numerical magnitudes onto space.

Taken together, the study demonstrates for the first time that the number line task is a feasible paradigm for investigating the neural substrate of numerical magnitude processing and its mapping onto space. Moreover, the present data extend our current knowledge of the neural basis of symbolic numerical and non-numerical magnitude processing. The data of the present study particularly highlight the importance of the left IPS for symbolic numerical magnitude representation. This finding is consistent with a growing body of imaging literature that has indicated left lateralized activation of the IPS in fMR-A studies, which have investigated the representation of symbolic numerical magnitudes in the absence of response selection. In the next chapter of this thesis an adjusted child friendly fMR-A design will be tested in order to replicate previous findings of lateralization and to pilot an fMR-A design in order to investigate developmental changes in the way the cortical representation of symbolic numerical magnitudes change over developmental time.

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Chapter 3: Investigating symbolic numerical magnitude representation with functional Magnetic Resonance Adaptation

3.1. Introduction

The unique ability of humans to represent numerical quantities with arbitrary symbols, such as Hindu-Arabic digits, is certainly one of the most intriguing cultural inventions in the history of mankind. The acquisition of symbolic numerical semantics does not only establish a foundation for mathematics, but also significantly transformed the way we interact with the world. Take for example the use of numerals in sport. We use them to keep track of the latest sport results of our favourite team, we use them to measure the time of a marathon runner and to count whether he crossed the finish line 1st, 2nd or 3rd. In the last decade, neuroscientific findings have provided new and exciting insights about the neuronal architecture underlying the processing of basic numerical information. This line of research has proven to be fruitful in order to better understand the typical and atypical neural mechanisms underlying the representation of numerical magnitudes and how individual differences in the neural architecture relate to mathematical proficiency. However, despite this great leap in knowledge relatively little is currently known about the way the human mind and brain represents and processes symbolic numerical information and more research is needed in order to better understand the mechanisms of symbolic numerical magnitude representation in the human brain. The Introduction of this chapter provides a comprehensive literature review related to concerns that have been raised about interpreting findings from active tasks and about functional Magnetic Resonance Adaptation (fMR-A) as a mean to mitigate some of these issues. The last part of this introduction will discuss recent findings about symbolic numerical magnitude representation with fMR-A.

3.1.1.Neural correlates of numerical distance effect

Neuroimaging experiments along with neuropsychological case studies have provided evidence to suggest that the intraparietal sulcus (IPS) of the parietal lobe is a key region for representing and processing numerical magnitudes presented in a symbolic format. For example, neuropsychological assessments with patients who suffered from severe brain damage have demonstrated that lesions in and around the parietal lobe can seriously impair the understanding of numbers, but at the same time do not affect knowledge of other semantic domains such as word meaning (i.e., Cipolotti, Butterworth, & Denes, 1991; Dehaene & Cohen, 1997). These data from patients suggest a special role of the parietal lobe for processing numerical information (Ashkenazi, Henik, Ifergane, & Shelef, 2008).

In the realm of neuroimaging, different experimental paradigms – such as mapping numerals into space (through number line estimation, see Chapter 2), or judging which of two numerals is larger or smaller (e.g., Ansari et al., 2005; Pinel et al., 1999, 2001) – have been used in the past to assess the neural correlates of numerical symbol processing in the human brain. Results of these studies have consistently shown that the IPS of the parietal lobe is activated whenever numerical symbols are manipulated.

As mentioned above, a frequently used paradigm to investigate the neural basis of numerical magnitude representation is the numerical comparison task. In this task participants are asked to judge, which of two numerals is numerically larger or smaller. Behaviourally, the discrimination of the two numbers evokes a very robust and reliable effect - the numerical distance effect (NDE), which reflects a highly replicable inverse relationship between the reaction time (also between the error rates) and the numerical distance between the two numerals that are compared (see Figure 1.3 Moyer & Landauer, 1967). In other words, participants take more time and are more error prone to decide that the number 6 is larger than the number 5 (i.e., the numerical distance is 1) compared to judging that 9 is larger than 5 (i.e., the numerical distance is 4). Another effect that was reported by Moyer and Landauer (1967) is the numerical ratio effect, which relates to the ratio of the numbers being compared. For instance, participants are slower to compare numbers with large ratio (e.g., 8 versus 9, is a numerical ratio of 0.89) compared to numbers that express a small ratio (e.g., 1 versus 2, a numerical ratio of 0.5). The numerical distance as well as the numerical ratio effect have since been taken as evidence for an underlying mental representation of numerical magnitude, in which numbers are organized along an internal continuum – the mental number – which is thought to be organized either logarithmically (Dehaene et al., 2003) or linearly (Gallistel & Gelman, 2000; see Figure 1.2).

Pinel and collegues (1999) were among the first to investigate the neural correlates of the numerical distance effect in the human brain. Specifically, the authors asked eleven right-handed volunteers to decide whether a presented number word or a presented Arabic digit is numerically larger or smaller compared to the reference value "5". The measured neural activity was decomposed into three factors: notation (Arabic digits or Number words), numerical distance from the reference number "*5*" (close: i.e., 4 and 6, and far: i.e., 1 and 9) and motor responses (left or right hand) and analyzed accordingly. The result of this analysis revealed a neuronal signature in the parietal lobe (but also in other regions of the brain) that mirrored the behavioural distance effect in such a way, that the inferior parietal lobule was more strongly activated for numerically small distances compared to trials where the numerical distance was relatively large. The larger activation in small distance trials was interpreted to indicate a larger neuronal representational conflict (i.e., larger overlap in the representational space) for numerals that are close in space compared to numbers that are farther apart. The neural correlates of the symbolic numerical distance effect have since been replicated in different experimental studies across different laboratories (Ansari et al., 2005; Bugden, Price, McLean, & Ansari, 2012; Holloway & Ansari, 2010; Holloway, Price, & Ansari, 2010; Pinel et al., 1999, 2001).

3.1.2.Number Representation or response selection?

However, in recent years some researchers have raised important and valid concerns about the interpretation of number related activations primarily found in regions of IPS. Some have argued that number related activations in the parietal lobe may not necessarily originate from an underlying representation of numerical magnitude, but may rather be explained by alternative cognitive processes such as response selection (Göbel & Rushworth, 2004). Indeed, there is a large body of evidence to demonstrate that the parietal lobe is engaged in the integration of sensory-motor information (Culham & Kanwisher, 2001; Culham & Valyear, 2006) in order to construct behaviours such as selecting the appropriate response amongst multiple alternatives (Andersen & Buneo, 2002). These data suggest a possible alternative explanation for number related activation in the IPS, specifically in tasks in which response selection mechanisms are engaged.

In an fMRI study Göbel and collegues (2004) tested this hypothesis in order to understand whether number related activations in the parietal lobe are indeed confounded by activations elicited by response-selection. Twelve right-handed adults were asked to perform a single-digit and double-digit number comparison task, in which participants had to judge whether the presented numeral was larger or smaller compared to a reference number (i.e., the number 5 in the case of single-digit comparison and the number 65 in the case of double-digit comparison). Furthermore, subjects performed two non-numerical tasks in which they were asked to decide whether numerical or non-numerical stimuli contained a vertical line (numerals were adjusted for this task accordingly). Against baseline, the number comparison tasks engaged a large network across both hemispheres including the parietal lobe. However, when the brain activity of the number comparison tasks was pitted against the brain activity evoked by the control tasks (i.e., vertical line judgments), no significant number specific activation on the whole brain level was found. Since all tasks in the study were carefully matched for task difficulty, the results provided strong evidence to suggest that number related activation in the IPS may be related to response selection mechanisms instead of numerical magnitude representation. Moreover, the authors also investigated areas of the brain that showed a significant correlation with individual differences in reaction time irrespective of the task. Results of this analysis showed that the brain activation of the IPS (amongst other areas) was highly correlated with reaction time, suggesting a tight association between the IPS and response selection mechanisms. Together, the results of this fMRI study provide strong evidence to suggest that activations found in the IPS in numerical tasks cannot be easily explained by numerical magnitude representation alone. The data also highlight the possibility that regions of the IPS are not solely dedicated to the processing of numerical magnitude, but rather subserve non-numerical cognitive functions during numerical tasks. This hypothesis raises the rather general question, whether neural activations found in other numerical tasks are indeed related to numerical processes or whether activation pattern in the IPS represent other non-numerical cognitive functions, or a mixture of the both.

3.1.3.Functional Magnetic Resonance Adaptation (fMR-A)

More recently, functional neuroimaging paradigms have been developed that allow for the measurement of brain responses to a particular category of stimuli (i.e. numbers) in the absence of explicit response selection. One of these paradigms is referred to as functional Magnetic Resonance Adaptation (fMR-A). In general, fMR-A (also called repetition suppression) draws upon the inherent property of a neuronal population to attenuate the neural activity after being repeatedly exposed to a specific stimulus dimension (Grill-Spector & Malach, 2001; Grill-Spector, Henson, & Martin, 2006). Using fMRI it has been shown that a plateau in signal reduction (i.e., adaption) is reached after 6 to 8 stimulus repetitions (Grill-Spector et al., 2006). After adaptation, the stimulus dimension of interest is systematically changed to assess the sensitivity of the adapted neuronal population to the varied attribute. If the adapted neuronal population is invariant to the particular attribute change, adaptation remains and no signal recovery is observed. If, however, the neuronal population is sensitive to the changed attribute, a recovery from adaptation can be measured by a significant increase in signal intensity (Grill-Spector & Malach, 2001). The functional property of fMR-A therefore allows for the assessment of both the repetition suppression effect (decrease in activation as a function of stimulus repetition) and the neuronal recovery effect (increase in activation following a change in the stimulus) post adaptation. Both have been used successfully in a variety of cognitive domains to investigate the underlying neural representation of different stimulus dimensions (for a review see Grill-Spector et al., 2006). Importantly, neural adaptation effects can be measured by passively exposing individuals to the stimuli dimension of interest. Besides a basic level of attention no additional active engagement (e.g., response selection) of the participants is required.

An important aspect of fMR-A is its passive nature, which minimizes the impact of potential confounds such as response selection, which, as demonstrated through the literature review above, can have significant implications for the interpretation of neuroimaging data. Therefore, fMR-A is well suited to assess the degree to which the IPS is involved in symbolic numerical magnitude representation independently of overt response selection mechanisms. In the context of studying the brain representation of symbolic number, fMR-A is used to attenuate the brain responses to a certain numerical value by presenting a continuous stream of the same numerical value on the computer screen. After the adaptation phase a new stimulus of different numerical value (hereafter called numerical deviant) is presented and either the repetition suppression effect or the neural recovery effect in the neural signal is assessed. In accordance with previous findings it is assumed that adaptation effects should be modulated by numerical distance or by numerical ratio. In other words, numerical deviants with a relative small ratio (large numerical distance) to the adaptation numeral should elicit a larger neural signal recovery effect compared to deviants that are relatively large in ratio (close in numerical distance). Regions that show such a pattern of ratio dependent increase in signal recovery may be assumed to be involved in encoding the semantics of numerical symbols.

3.1.4.Neural signal recovery effect in the IPS in response to changes in number

Naccache and Dehaene (2001) were the first to report evidence for a repetition suppression effect in the parietal lobe in response to the presentation of numerical symbols and number words. The authors measured the brain activity of healthy adults, while the participants performed a numerical priming experiment. Participants were thereby exposed to a numerical target and had to decide whether the target is larger or smaller compared to the reference number (i.e., 5). The target was preceded by a masked prime, which was either the same number or a different number compared to the target. For example, if the target was the number 9, the prime could be the same (i.e., the number 9) or a different (e.g., 6) numerical value. By systematically manipulating the prime-target relation the authors demonstrated a numerical repetition suppression effect in bilateral regions of the bilateral IPS for the same number pair compared to a different number pair. In other, words activity in the IPS was reduced when a number was preceded by the same number than when the target was preceded by a different number. This effect was shown independently of stimulus notation (i.e., number symbol or number words), suggesting that the IPS is engaged in the semantic processing of numerical magnitude independent of notation format. While this finding implicates a numerical magnitude related suppression effect in the neural signal of the IPS, the study does not preclude the possibility that the active part of this paradigm influenced the brain signal and that response selection processes may modulate the brain signal to a certain extent. Thus, this study does not provide conclusive evidence for a numerical magnitude representation that is independent of response selection. Moreover, it is somewhat unclear from the paper to which extent perceptual similarities within the same number condition influenced the observed repetitions suppression effect. In other words, in instances in which the target number (e.g., target is Arabic digit 9) was preceded by the same number (e.g., prime is Arabic digit 9) the neural suppression might have been influenced by perceptual similarities rather than semantic meaning.

Another way to investigate the neural representation of numerical magnitudes in fMR-A is to measure the neural signal recovery and its modulation by numerical distance or ratio. Piazza and colleagues (2004) were the first to investigate the ratio dependency of the signal recovery in response to the presentation of non-symbolic numerical magnitudes in adults. The authors presented a continuous stream of dot arrays on the computer screen containing the same number of dots (i.e., 16) while varying non-numerical dimensions (size of the dots, location of the dots, density etc.). Since number was the only constant category throughout the presentation, participant's brain response was exclusively adapted to the number of dots in the array (to its numerical magnitude). The continuous presentation of the "16" dots was randomly interspersed by the presentation of numerical deviants that differed in numerical ratio (i.e., close = 13/20; medium = 10/24; far = 8/32) from the adaptation number. This critical manipulation enabled the authors to explore regions in the brain that exhibited a ratio dependent neural signal recovery effect in response to the presentation of numerical deviants. A whole brain analysis revealed that only one region of the cortex expressed a numerical ratio dependent signal recovery: the left and the right IPS in the parietal lobe. In other words, the neural signal recovery in response to the presentation of numerical deviants was larger for dot arrays that were numerically farther away (i.e., 8/32) compared to arrays that were relatively close in number (i.e., 13/20) to the adaptation numeral "*16*" (Note that a larger neural activation indicates a larger signal recovery and therefore a greater dissimilarity in the neural encoding of the stimuli. This is in contrast to the activation found in the comparison task in which a larger activation has been interpreted to indicate a larger representational similarity.). This result suggested, for the first time, that regions of the IPS process non-symbolic numerical magnitudes in the absence of overt task requirements (i.e., participants were only instructed to pay attention to the stimuli presented on the screen). Moreover, the ratio dependent modulation of the neural recovery effect suggests an approximate neural representation of non-symbolic numerical magnitude obeying Weber's law (Dehaene, 2003; Nieder, 2005).

In view of these findings, the authors argued that numerical magnitudes are represented in the IPS as continuous Gaussian probability distributions that are either logarithmic compressed (i.e., the width of the distributions is the same for each numerical magnitude and the representational overlap of numerical magnitudes varies as a function of a logarithmic arrangement) or linear (i.e., the width of the distributions is scaled by the size of the numerical magnitude and the representational overlap varies as a function of the width of the distributions that are linearly arranged). Interestingly, similar characteristics of neural tuning (i.e., the Gaussian distribution of numerical magnitude representation) have been recently reported from single cell recording in monkeys in the prefrontal and parietal cortex (Nieder & Miller, 2003, Nieder, Freedman & Miller 2004; Nieder, 2002). Therefore, this evidence corroborates the idea of an approximate representation of non-symbolic numerical magnitude in the parietal cortex.

In another fMR-A study Piazza et al. (2007) investigated the neural rebound effect in response to symbolic and non-symbolic deviants. Participants were instructed to fixate and to pay attention to the quantity of the presented dot arrays and the presented numerals (note that in this study the nature of the task was revealed to the participants). The brain response of the participants was either adapted to non-symbolic dot-arrays or to numerical symbols, using small numerical values (i.e., 17, 18 and 19) or large numerical values (i.e., 47, 48 and 49). After this adaptation period, numerical deviants were presented that varied in numerical distance (i.e., close and far). For example, the numerical deviant 20 was close to the adaptation numerals 17, 18 and 19, but far from the adaptation numerals 47, 48, and 49 while the number 50 was close to the adaptation numerals 47, 48 and 49 but far to the quantities 17, 18 and 19. Moreover, the numerical deviants were either presented in the same notation (i.e., non-symbolic to non-symbolic; symbolic to symbolic) or across notations (i.e., non-symbolic to symbolic; symbolic to non-symbolic) allowing for the investigation of cross-notation adaptation effects as well as for numerical distance. The Results of this fMR-A study showed notation independent and numerical distance related neural recovery effects across multiple regions of the brain, including the IPS in the parietal lobe. Importantly, both notations showed a numerical distance related neural recovery effect at which far distances elicited a stronger recovery compared to close distances in bilateral regions of the IPS. This finding suggests that non-symbolic and symbolic numerical magnitudes might follow the same representational characteristic – that of ratio dependency - and, therefore, the authors interpreted this finding as evidence for a common (i.e., notation independent) approximate representation of numerical magnitude in the IPS.

However, a region of interest (ROI) analysis, focusing on the parietal clusters, suggested a hemispheric asymmetry in the precision with which numerical quantities may be coded in the IPS. Specifically, the authors reported an interaction of adaptation notation, deviant notation, and numerical distance in the left hemisphere only. This interaction revealed that there was a large recovery from adaptation for small distances when dot-arrays were presented among Arabic digits in the left IPS, but not so in the right IPS. Since even small numerical changes in the dot deviants resulted in a large recovery signal within the left IPS, the authors suggested that this effect, which was only present in the ROI analysis, is indicative of a more precise representation of numerical symbols in the left hemisphere. Overall, this study provides evidence to suggest that the IPS hosts a format independent (i.e., symbolic and non-symbolic) approximate representation of numerical magnitude. At the same time hemispheric differences in the precision between the processing of symbolic and non-symbolic numerical magnitudes were reported. However, hemispheric differences were only observed in a post-hoc ROI analysis making strong claims about lateralization effects problematic.

While there is some evidence to suggest that non-symbolic and symbolic numerical magnitudes may share a common approximate representation of numerical magnitude, different numerical symbols such as number words (i.e., five) or Arabic digits (i.e., 5) are used to convey the meaning of numerical magnitudes. A fMR-A study by Cohen Kadosh et al. (2007) investigated commonalities and differences in brain activation of different symbolic numerical notation formats. Three different experimental conditions were used in this study. In the digit condition the adaptation stimuli and the deviants were Arabic numerals, in the pure word condition the adaptation stimuli and the deviants were number words and, finally, in the mixed condition the Arabic numerals and the number words were intermixed. Furthermore, the authors manipulated the numerical distance of the presented numerals in such a way that the preceding numerical value was either the same numerical value or a different numerical value. Results of this study showed that the left IPS was sensitive to changes in numerical value (i.e., stronger recovery effect for the different vs. the same value condition) across all notation conditions. On the other hand the right IPS exhibited a significant modulation in the Arabic notation condition but not in the number word and mixed notation condition. This result may indicate that notation dependent and notation independent symbolic numerical representation may coexist in the brain. It points towards the left IPS as an important region for representing numerical symbols independent of the symbolic numerical notation format and towards the right IPS as a region that may be modulated especially by Arabic numerals. However, it should be noted that activation differences observed in the main effect of numerical value (i.e., larger activation for different numerical values compared to same numerical values) may be also explained by changes in the physical shape (its appearance on the screen) of the stimuli instead of a change in the numerical value per se. In other words, in the same condition the same number symbol (although in different font) was used whereas in the different value condition an entirely new symbol was presented. The activation differences found in this study may therefore not be related to changes in numerical magnitude but to changes in the perception of visual shapes.

3.1.5.Evidence for symbolic numerical magnitude signal recovery effects

The fMR-A studies discussed above focused on different notation formats (symbolic and non-symbolic) in order to investigate the neural correlates related to the processing of numerical magnitudes. In addition, some of the studies manipulated only one ratio level, that is, contrasting the activation of same number pairs against the activation elicited by different numbers pairs. A more stringent way to investigate ratio dependent modulation of the signal recovery effect post adaptation is to use different ratio levels. An experiment by Notebaert and colleagues (2011) was the first to test a parametric ratio dependent modulation in the signal recovery effect, focusing on differences and commonalties in the neural correlates associated with the semantic processing of small and large Arabic numerals. In this study, the neural response of adult participants was either adapted to the number “6”, in the small number condition, or to the number “32” in the large number condition. After the adaptation phase, numerical deviants were presented that systematically differed in numerical ratio from the habituation numbers. By analyzing the extent to which the neural signal parametrically changes (a linear ratio-dependent increase in the signal recovery) after the presentation of different numerical deviants, the authors were able to demonstrate a ratio-dependent neural rebound effect in the left IPS for both the small and the large number condition. More specifically, the neural rebound effect in the left IPS was linearly scaled by the ratio in which the numerical deviants differed from the adaptation number (see Figure 3.1). Results of this study provided strong evidence that the left IPS is sensitive to the processing of symbolic numerical magnitude in the absence of any overt task demand. No other brain region was found in which the brain activity was modulated by numerical ratio, suggesting a high specificity with which the left IPS is engaged in the representation of symbolic numerical magnitudes. In addition, no difference between the processing of small (i.e., numbers in the range from 3 to 12) and large numbers (i.e., numbers in the range from 16 to 64) were found in this study, providing evidence that the activation of the left IPS is invariant to the processing of small and large numbers. Together, these results provide strong evidence that the brain activation of the left IPS is modulated by the numerical ratio of symbolic numbers independently of the size (i.e., small or large) of the numerical value. In contrast to active paradigms that often show widespread neural activation in different areas of the brain (e.g., distance effects in number comparison tasks are often found in other regions of the brain including the IPS), the results of this study suggest a high spatial specificity (the IPS was the only region in this study to be significant modulated by numerical ratio) with which the semantic of Arabic numerals may be encoded in the left IPS.

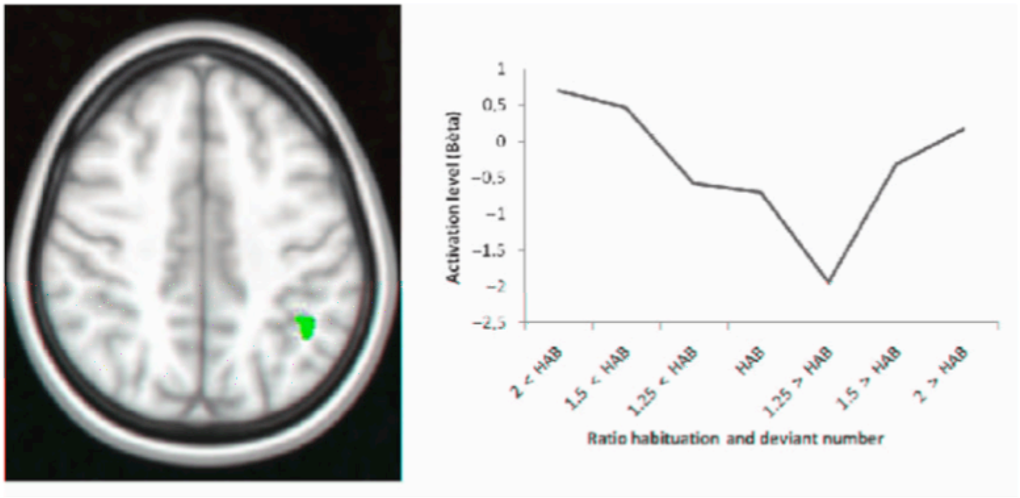

Figure 3.1: The figure illustrates the numerical ratio dependent neural signal recovery in the left IPS (Notebaert et al., 2011). Activation plot on the right demonstrates the signal recovery effect, which is scaled by the ratio between the numerical deviant and the adaptation numeral (i.e., 6). The left picture shows the anatomical location of the brain region (i.e., IPS) that showed a significant ratio dependent modulation (left hemisphere depicted on the right). Reprinted from “The Magnitude Representation of Small and Large Symbolic Numbers in the Left and Right Hemsiphere: An Event-related fMRI Study,” by K. Notebaert et al., 2011, Journal of Cognitive Neuroscience, 23(3), p. 627. Copyright Massachusetts Institute of Technology. Reprinted with permission.

Thus, the data from this study provide evidence to suggest a possible left hemispheric specialization for the semantic representation of Arabic numerical symbols. In line with the study of Piazza et al. (2007), who found more precise encoding of symbolic magnitudes in the left IPS, and with Cohen Kadosh et al. (2007), who demonstrated an adaptation for the processing of number words and Arabic digits in the left IPS, this finding indicates a possible hemispheric lateralization of symbolic numerical magnitude processing. Since symbolic numerical knowledge is transmitted via culture it may be the case that the cortical specialization of symbolic number representation is driven by symbolic numerical experience - a process that Ansari (2007) defined as enculturation of symbolic knowledge.

One way to examine the effect of symbolic numerical experience on cortical specialization is to investigate the brain activation in individuals that have differential experiences with symbolic numerical notation formats. A study conducted by Holloway, Battista, Vogel and Ansari (2012) investigated the neural recovery signal effect of numerical deviants in a group of bilingual readers, who were familiar with the Arabic and the Chinese notation system of numbers (ideographs), and a control group, who was able to read Hindu-Arabic numerals exclusively. Notably, although the Chinese readers were to understand the numerical meaning of the Chinese ideographs the extent to which Chinese readers were exposed to this notation system is considerably less compared to the Arabic notation system which is nowadays the most prominent numerical system in China (Ifrah, 1985; Menninger, 1992). This design allowed the authors to investigate several important key aspects. First, the passive nature of fMR-A enabled the investigation of symbolic numerical magnitude processing in the absence of explicit response selection mechanisms. Second, since individuals from the control group were only able to read Arabic numerals but were unable to understand the numerical meaning of Chinese ideographs, the study was able to examine perceptual and semantic differences in the way numerical symbols are processed in the brain. Finally, the differential experience of individuals with different notation formats between the groups enabled the authors to test the hypothesis to which extent different symbolic numerical expertise biases the cortical specialization of symbolic numerical representations in the brain.

To test these predictions the authors adapted the brain response of the participants to the numerosity “six” by using either the Arabic digit 6 or the corresponding Chinese ideograph (i.e., 六). The numerical deviants varied as a function of ratio in both conditions and participants performed a color detection task in order to assure a minimum of awareness in the scanner. When analyzing the neural signal recovery effect related to the presentation of Arabic numerals, the authors were able to find a parametric ratio-dependent modulation of the left IPS across both groups. In contrast, for the Chinese ideographs a ratio-dependent modulation of the right IPS was found in the bilingual readers, whereas the fusiform gyrus was activated in the control group. These results indicate that the parietal lobe is engaged in the semantic and not in the perceptual processing of numerical symbols. No parietal activation was found in the condition in which participants were not able to read the meaning of the numerical symbols (the Chinese ideographs in the control group). Furthermore, as predicted the Chinese group showed activation in different areas of the parietal lobe depending on the notation system. The less familiar Chinese ideographs activated the right IPS, while the familiar Arabic digits activated the left IPS. This result points to an important interaction between experience and cortical specialization that is expressed in hemispheric lateralization. Together, these results demonstrate that the activation of the IPS is modulated by semantic knowledge and that the left hemispheric activation of the IPS may be related to an experience-based specialization of processing the meaning of numerical symbols. As such, hemispheric lateralization in the parietal lobe may be related to the degree of proficiency with which symbolic numerical magnitudes are processed and are therefore consistent with the notion that the left IPS becomes specialized for the representation and processing of number symbols over the course of learning and development.

3.1.6.Summary of the Introduction

Overall, the data reviewed above demonstrate that parietal brain activations observed in number comparison tasks cannot be exclusively explained by response selection mechanisms. There is now a growing body of evidence that shows that the neural signal recovery in the IPS is modulated in response to changes in numerical magnitudes in the absence of overt task demands. The neural signal recovery in response to the presentation of numerical deviants is ratio dependent indicating that the activation of the IPS is an intrinsic property of the way the human brain represents symbolic numerical magnitudes. In addition, results of fMR-A studies that have focused on symbolic numerical magnitude processing have shown hemispheric differences in the way the IPS processes semantic information conveyed by numerical symbols in adults.

Some of the data suggest that lateralization may be related to experience and that the development of symbolic numerical expertise leads to a specialization of the left IPS to represent symbolic numerical magnitudes.

Given the reviewed literature from above it is apparent that one of the remaining open questions is a developmental one. While fMR-A studies in adults have indicated a hemispheric specialization of the left IPS to represent the semantic meaning of numerical symbols, the developmental trajectory of hemispheric lateralization remains opaque. Consequently, there is a need for developmental studies that aim to investigate changes in the cortical specialization associated with the representation of symbolic numerical magnitudes over developmental time. The main purpose of the experimental study reported in the present chapter is to set the experimental groundwork for using fMR-A in children in order to further unravel ontogentic changes in the cortical representation of symbolic numerical magntiudes. The expenses (moneywise and timewise) related with the testing of children are substantial and, therefore, a careful evaluation about the appropriateness of the experimental procedure is economic and useful. As such there is a need to establish a solid profile in adults before going on to test predictions about developmental changes. Thus the present study aims to test a shortened version of the fMR-A paradigm that has been previously used in the study by Notebaert et al. (2011) and Holloway et al. (2012).

Two main changes were introduced to adjust the paradigm for the use with children. First, instead of detecting a color change in the active control task, children were instructed to detect the presence of a smurf character (see Figure 3.2 c; smurfs are fictional cartoon characters) that is hiding behind the numbers. Second, the paradigm was split into 4 short functional runs instead of 1 or 2 functional runs. Splitting the paradigm into shorter runs ensured a rest period for the children as well as a period of feedback and motion assessment to adjust parameters if necessary. Consistent with the literature reviewed above, we hypothesized to find a numerical ratio-dependent modulation of the IPS in response to the presentation of numerical deviants. In addition we argued, that a ratio-dependent sensitivity of the IPS would be either bilateral or lateralized to the left IPS. Furthermore, in order to extend our knowledge of numerical processing in the IPS and to add greater anatomical specificity to our analysis, two different group brain alignment procedures – Talairach space and Cortex Based Alignment (CBA) – were tested.

3.2. Materials and Methods

3.2.1.Participants

Twenty right-handed (handedness assessed by self-report) healthy adults (8 men, mean age = 26.6, age range = 21 - 37, and 12 women, mean age = 23.6, age range = 21 - 26) participated in this fMRI experiment. No history of neurological or psychiatric disorder were reported from the subjects. Participants were all native English speakers and were unaware of the purposes of the study. Written informed consent was obtained from all participants' prior participation. The experimental procedure was approved by the University of Western Ontario's Health Science Research Ethics Board (HSREB).

3.2.2.Stimuli

The aim of the present study was to replicate and extend findings reported by Notebaert et al. (2011). Therefore, stimuli parameters from this study were reproduced and matched as closely as possible. All Stimuli were created in Adobe Photoshop CS4 and consisted of black (R-G-B color values: 0, 0, 0) colored Hindu-Arabic numerals, printed on a silver gray background (R-G-B color values: 192, 192, 192) (see Figure 3.1). Within the MRI scanner stimuli were back projected onto a computer screen using the software E-prime 2.0 (resolution = 800 x 600 pixels; color bit depth = 16). Participants viewed the presentation of the stimuli via a mirror system which was attached to the MRI head-coil.

Consistent with the study by Notebaert et al. (2011), we used fMRI adaptation to habituate participants brain response to the numerical value "*six"* by presenting a continuous stream of the Hindu-Arabic numeral "*6*" onto the screen. The presentation of the habituation numeral (i.e., "*6*") was randomly interspersed after 5, 6, 7, 8 or 9 repetitions (with a mean of 7 repetitions across runs) by deviant numerals (i.e., "*3*", "*4*", "*5*", "*8*", "*9*", "*12*"), catch trials (the smurf trial), or null trials (i.e., the numeral "6"). The numerical deviants varied systematically in numerical ratio to the habituation numeral "*6*" (see Table 3.1). The catch trials consisted of a numeral (i.e., "*3*", "*4*", "*5*", "*6*", "*8*", "*9*", and "*12*") and an additional picture of a Smurf (see Figure 3.2 c).

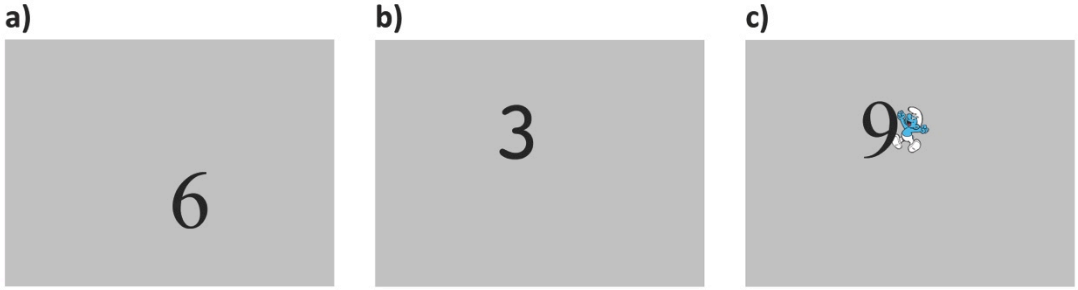

Figure 3.2: Examples of stimuli used in the experiment. Note that the location and the font of the stimuli differ across stimuli. This procedure counteracts low-level visual adaptation effects. a) example of a habituation stimuli "*6*"; b) example of a numerical deviant; c) example of a catch trial with smurf.

Numerical deviant	3	4	5	8	9	12
Ratio to habituation numeral	2.0	1.5	1.2	1.3	1.5	2.0

Table 3.1: Deviant numerals and their ratio to the habituation numeral "6". Numerical ratio was calculated by dividing the larger number over the smaller number.

Critically, in order to avoid confounding low-level perceptual adaptation effects, which could potentially influence the adaptation signal recovery, the font (Times New Roman and Courier New; size 40pt) and the spatial location (one of six possible locations 2 degrees from the center of the display; x/y center-position of the six locations was 435/300, 365/300, 375/325, 425/325, 375/275 and 425/275) of all numerals were randomized across all trials. Furthermore, the presentation of the numerals was pseudo-randomized in such a way that the same location did not appear in immediate succession.

3.2.3.Experimental Procedure

The habituation numeral, the deviant numerals, the catch trials and the null trials were all presented in each of the four functional runs. Each run consisted of the presentation of Hindu-Arabic symbols, which were interleaved by blank screens. The numerical symbols appeared for 200ms while each of the blank screens remained for 1200ms. The continuous presentation stream (i.e., adaptation phase) consisted of a series of adaptation trials of the numeral "*6*" followed either by a deviant trial (18 per run), a catch trial (8 per run) or a null trial (i.e., the presentation of the numeral 6 was continued; 4 per run) (see Figure 3.3).

Deviant trials consisted of numerals that deviated systematically in numerical ratio from the adaptation number (see Table 3.1). Presentation of the numerical deviants was randomized throughout the run, resulting in 3 trials per numerical deviant and per functional run. Eight Catch trials (i.e., the Smurf) were randomly dispersed throughout the run. Participants were asked to press a response key whenever they "…see a Smurf presented on the computer screen". Finally, the null trials consisted of the continued presentation of the numeral "*6*", which is identical to the adaptation number. As such participants were not aware of the presence of the null trials. The inclusion of null events is important since they allow for the estimation of a signal baseline against which ratio dependent signal recovery effects can be quantified. Consistent with the deviants and the Smurf trials, the presentation of the null trials was randomized throughout all runs. Each functional run lasted 6 minutes and 16 seconds.

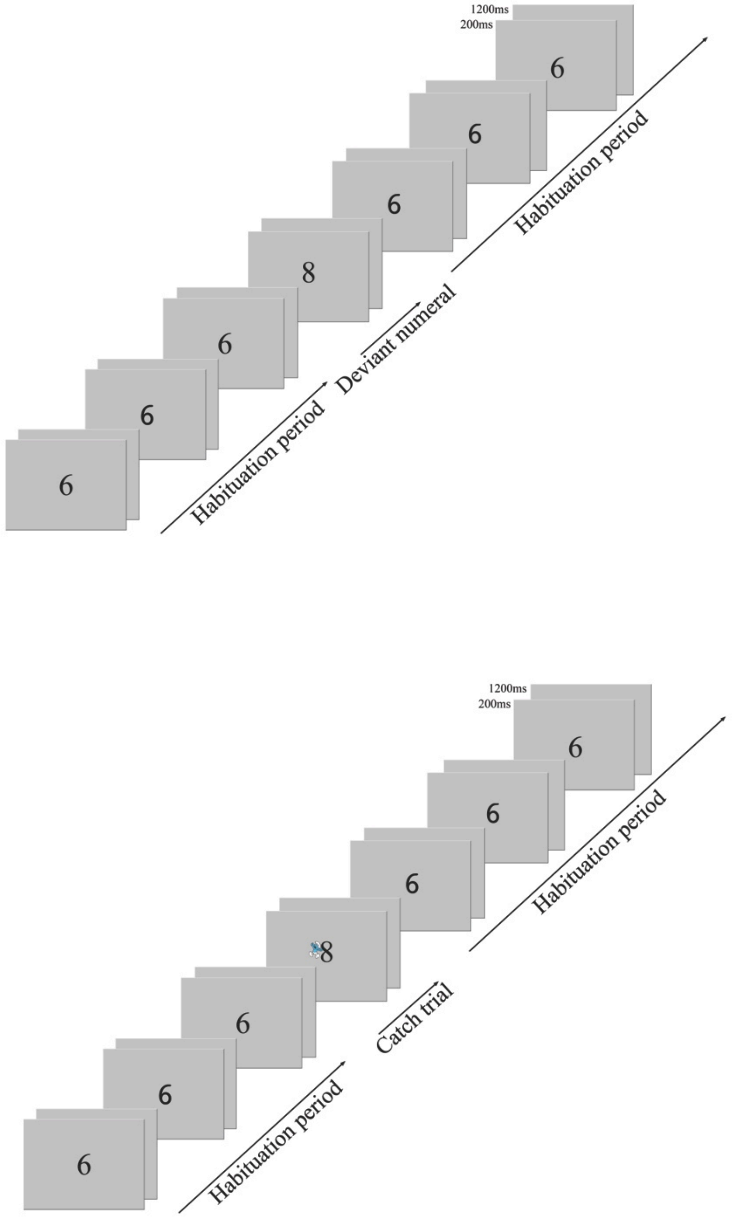

Figure 3.3: Structure and timing of stimuli presentation in the present adaptation design. The first picture shows an example of a numerical deviant trial following the habituation period. The second picture shows an example of a Catch trial containing a smurf. Participants were asked to press a button when they saw a smurf on the screen.

3.2.4. General Procedure

All participants were familiarized with the fMRI environment prior to the scanning session. Each participant was prompted to pay attention to the computer screen at all times in order to catch all the Smurfs and to press a pre-specified button with the right index finger whenever a Smurf appeared on the screen. As such participants were not familiar with the numerical nature of the experiment per se. Therefore, the only overt active task requirement within the experimental was to catch the Smurf's.

3.2.5. fMRI Data Acquisition

Structural and functional data were acquired in a 3-Tesla Siemens Tim Trio whole-body MRI scanner. A 32-channel Siemens head coil was used. The functional images were collected by using a blood oxygen level dependent (BOLD) sensitive T2* weighted echo planar (EPI SE) sequence. The functional images were acquired in an ascending - interleaved order covering the whole brain with 38 slices per volume (3mm thickness, 64 x 64 matrix, repetition time (TR): 2000ms, echo time (TE): 52ms, flip angle: 78 °).

For each functional run 188 Volumes were collected, resulting in a total length of 6 minutes and 16 seconds per run. High-resolution T1 weighted images were collected using a MPRAGE sequence (1 x 1 x 1 mm, TR: 2300ms, TE: 4.25ms, flip angle: 9 °).

3.2.6.Imaging Analysis

3.2.6.1.Data Preprocessing

The acquired structural and functional imaging data were analyzed with the software package Brain Voyager QX 2.3 (Brain Innovation, Maastricht, The Netherlands). All preprocessing steps were carried out for each individual separately. The functional imaging data were first corrected for slice scan time acquisition (ascending - interleaved) by using a cubic-spline interpolation algorithm. Furthermore, a high-pass (GLM – Fourier) frequency filter with a cut off value of 2 sines/cosines cycles was applied in order to remove low frequency signals from the data such as signals derived from the heartbeat. Finally, participant's motion parameters were corrected using a Trilinear/sinc interpolation approach (see Table 2 for a list of individual motion parameters).

3.2.6.2.Brain normalization

Each individual brain is different in its size, circumference and spatial characteristics. These individual differences cause difficulties when one seeks to compare the spatial location of brain activation or brain structure between children and adults. In order to compensate for natural differences in brain anatomy, and to allow multi-individual analysis on the group level, individual brain data are typically transformed into a standardized spatial reference space. A popular reference space that is used in many functional and structural neuroimaging studies is the Cartesian based Talairach coordinate system, which is based on the work of the neurosurgeon Jean Talairach who defined the stereotaxic coordinates upon post-mortem measurements of a sixty-year-old

French female. This one-subject brain template is used as a reference space to which individual brains are mapped onto in order to adjust for individual differences in brain structure.

3.2.6.2.1.Talairach Space

The acquired anatomical 3D images were first stripped from the skull and the resulting “peeled” brain template was used to align the 3D anatomical image with the functional images of the scan. Removing the skull from the brain tissue results in a more accurate spatial overlap between the anatomical 3D image and the functional run. Subsequently, the 3D images and the functional runs were transformed into Talairach space (Talairach & Tournoux, 1988) for group statistical analysis. This was achieved in two consecutive steps. First, the anatomical image was transformed in to ACPC-plane position, using the landmarks of the Anterior Commissure (AC) and the Posterior Commissure (PC). Thereafter, we manually defined the brain tissue borders (gray matter) of each individual brain (the most anterior, the most posterior, the most superior, the most inferior, as well as the brain tissue furthest to the left and to the right), which were then transformed into Talairach space (Talairach & Tournoux, 1988) by applying a Trilinear interpolation algorithm. Finally, all functional data were spatially smoothed with a 6-mm Gaussian kernel.

3.2.6.2.2.Cortex Based Alignment (CBA)

While Talairach approach has shown to be useful in the past, it also exerts critical limitations. First, as mentioned above the Tailairach coordinates are based on a subject number of N = 1 and it can be considered questionable whether the brain of a sixty-year-old women is the best choice to serve as a template for brain normalization (for a detailed discussion see Mazoyer, 2008). Second, the algorithms for warping individual brains onto a common reference space are based on a linear rigid body transformation that causes a great deal of anatomical distortions. Lastly, the transformation procedure creates only a coarse alignment of brain structure. This misalignment may produce misleading results in group comparisons between children and adults. However, it should be acknowledged that the standard approach of transforming functional and anatomical data into Talairach space offers some important advantages. One of them is the standardized and coordinate based reference system, which allows for a direct comparison of spatial activation patterns across different studies by using the x, y, z Cartesian coordinates of the Talairach space.

Cortex Based Alignment (CBA) is a promising alternative standardizing procedures that has the potential to compensate for some of the limitations inherent in Talairach transformations (Goebel, Esposito, & Formisano, 2006). This approach uses the cortical curvature information of individual brains in order to align human brains dynamically into a common reference frame. More specifically, the gyral/sulcal folding pattern of each individual brain is obtained by creating a 3-dimensional reconstruction of the brain surface, which is then used to align the cortex of individual subjects. This procedure is carried out in multiple steps (see Figure 3.4).

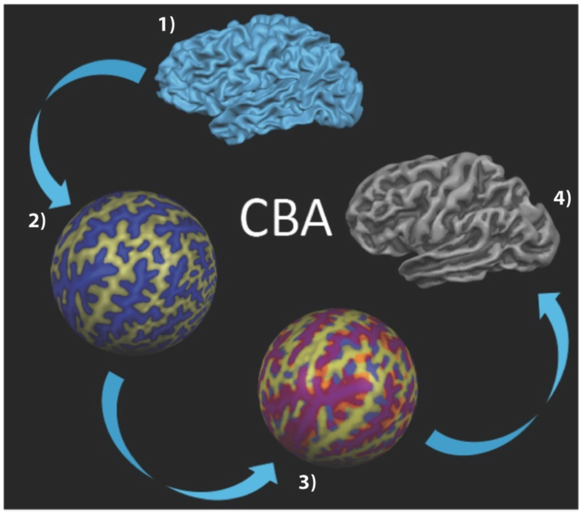

Figure 3.4: Procedure steps (counter clockwise, starting at the brain on the top) of the CBA method, which were carried out for each individual in the present data set. 1) The brain on the top represents an example of a surface reconstruction of one individual brain. 2) Each individual brain reconstruction is transformed into an individual sphere containing the surface information of the gyri/sulci pattern in different colors (blue and yellow). This spherical transformation step is performed with every individual brain for each hemisphere separately. 3) The resulting spheres of each individual are then dynamically aligned – displayed in the sphere on the bottom of the image – in an iterative procedure across the entire group. 4) The brain on the right displays the resulting standardized brain across the group. Statistics are calculated on this group based cortex reconstruction of the brain.

In a first step a 3D reconstruction of the cortex – the mesh – displaying cortical gyral/sulcal information is created, using an automatic segmentation procedure that is applied to the contrast information contained in the anatomical scan of the brain. Erroneous segmentations are subsequently corrected by a time-consuming manual segmentation that compensate for mistakes produced by the automatic segmentation. Second, the 3D mesh reconstruction of the brain is morphed into a spherical representation, providing a parameterizable frame for cross-individual alignment based on non-rigid alignment. The individual gyral/sulcal curvature information is thereby preserved in the spherical representation. Third, the actual alignment involves an iterative method of coarse-to-fine matching in which different smoothing levels of the curvature information are used to maximize the inter-individual alignment. Subsequently, the information gained from the anatomical alignment procedure is applied to the functional data sets across individuals. For statistical purposes a standard General Linear Model (GLM) approach can be used to analyze the data on a now standardized cortex reconstruction of the group.

Taken together, Cortex Based Alignment possesses certain advantages. First, the alignment procedure improves statistical group results due to reducing anatomical variability. Talairach transformation can create large mismatches between corresponding anatomical landmarks. Spatial smoothing of the functional data usually compensates the anatomical mismatch of brain normalization. The reduced anatomical variability of CBA allows statistical analyses on functional data on which no spatial smoothing was applied. Therefore, the analyses are based on the raw - undistorted signal that might contain important additional information that is otherwise distorted by spatial smoothing procedures. Finally, CBA takes the folding pattern of individual brains into account. As a consequence, the spatial relation between the vertices is preserved and the localisation of brain activation is more refined. For instance, two distinct brain activations that are on opposite walls of a given sulcus may appear as one single locus of activation using Talairach transformation. On the other hand, the conservation of the folding pattern in CBA takes the true spatial surface distance of these activations into account and, therefore, allows for a fine-grained spatial resolution.

3.2.7.Statistical Analysis

In order to investigate the influence that numerical deviants exerted on brain signal recovery after adaptation, numerical deviant stimuli were collapsed into three number ratio bins: larger ratio, 2.0 (deviants 3 and 12), medium ratio, 1.5 (deviants 4 and 9), small ratio, 1.33 (deviants 5 and 8) and ratio 1 (null event: number 6) and entered as a parametric regressor - predicting a linear increase in activation according to ratio - into a general linear model (GLM). The catch-trials were entered as additional predictor of no interest into the same GLM. Finally, all functional events were convolved with a two-gamma hemodynamic response function (HRF) in order to predict the blood oxygen level dependent (BOLD) function (Friston et al., 1998).

The main purpose of the subsequent statistical analyses is to identify regions that showed a systematic ratio dependent neural recovery in response to the presentation of numerical deviants on the whole brain level. In other words, we expected a parametric modulation (i.e., increasing signal recovery with an increase in ratio from small to large ratio) in areas of the brain that are sensitive to the semantics of numerical symbols. To identify these regions we pitted the activation modeled by the parametric effect against baseline (the adaptation period). Thus, only regions that showed a significant ratio dependent increase in activation above baseline activity were revealed.

Note that the same GLM and the same statistical analyses were applied to the two different brain normalization methods described in the sections above. However, in the CBA procedure unsmoothed functional data were used for statistical analyses instead of the 6-mm smoothed data in Talairach space, which has been shown to result in more confined group clusters of brain activation (Goebel et al., 2006). The statistical maps derived from these analyses were first thresholded with an uncorrected p value of 0.005. A subsequent cluster correction procedure was applied to correct for multiple comparisons and to adjust Type I error to a level of $p < 0.05$. This is achieved by an iterative “Monte Carlo Simulation”, which estimates the minimum size of a functional cluster to be significant on the basis of functional data from the study (for more detailed information about this procedure the reader is referred to Chapter 2, page 50 and 51 of the present work).

3.3. Results

3.3.1.Behavioural Results

Results of the behavioural data revealed that participants were highly accurate (mean Accuracy (AC) = 98.24; SD = 5.59) in detecting the interspersed catch trials (8 per functional run). Because of the passive nature of the present experimental paradigm, accuracy of the catch trials are the only way to assess a minimum level of sustained attentiveness towards the presentation of the numerical stimuli. Therefore, a high level of accuracy in detecting the smurfs is an imperative for all participants to be included into the study. In order to be included into the analysis subjects had to detect at least 6 out of the 8 smurfs presented in a functional run (75%). A calculated analysis of variance (ANOVA) revealed no significant difference (F(3, 57) = .851; n.s.; mean AC = 98.4%; 5.0; max – min: 100% - 78.12%) in accuracy between the four functional runs. This shows that the attentiveness of individuals was similar across the 4 experimental runs.

Furthermore, reaction time (RT) data were recorded to estimate mean reaction times for detecting the smurf trials. On average participants needed less than half a second (mean RT = 477.11ms, SD = 85.57ms) in order to confirm the presence of a smurf on the computer screen. In order to analyze RT differences across the four runs we calculated an ANOVA for repeated measurements. Analyses revealed a significant difference (F(3,75) = 3.513; p = 0.035) in RT across the four runs. Within-subject contrasts showed that RT's differed significantly between the first and the last run (F(1,19) = 6.817; p = 0.017) and between the third and the last run (F(1,19) = 4.909, p = 0.039). This data suggest that participants RT's became successively slower, very likely indicating an increase in the level of fatigue with the time spend in the scanner.

3.3.2.fMRI Results

3.3.2.1.Parametric effect of numerical deviants

The main aim of the analysis was to identify regions of the human brain that showed a numerical ratio dependent neural recovery in response to the passive presentation of numerical symbols. In other words, we asked the question which areas of the human cortex elicited a numerical sensitivity for the presentation of a novel number compared to the habituation numeral (i.e., "*6*"). To answer this question statistically, a parametric regressor was entered into the model in order to investigate those regions that showed a significant numerical ratio dependent parametric modulation above baseline activation. The next two sections describe the statistical results of the analysis based on the Talairach and CBA approach.

3.3.2.2.Results from the Talairach analysis

The results of the contrasts [parametric effect > baseline] based on the Talairach brain revealed that the neural activity of two regions in the parietal lobe was modulated by numerical deviants (see Figure 3.5). More specifically, regions of the bilateral IPS elicited a ratio dependent modulation in response to the presentation of numerical deviants (see Figure 3.6). This result is highly consistent with previous studies, which were able to demonstrate that regions in and around the IPS show a ratio dependent modulation in response to the passive presentation of numerical magnitudes (Notebaert et al., 2011; Holloway et al., 2012).

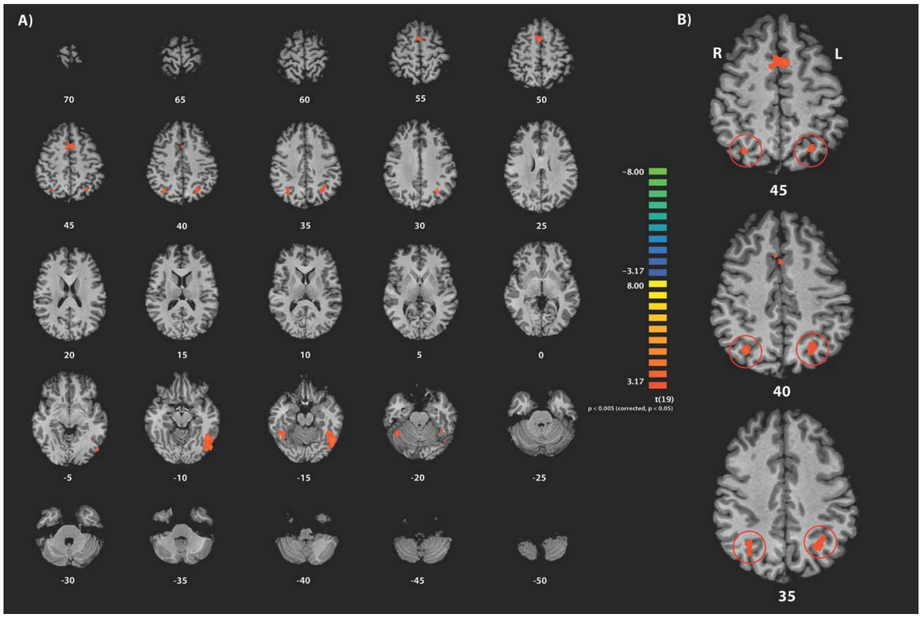

Figure 3.5: A) Regions that exhibited activation that scaled parametrically with the ratio of the deviant to the habituation number, displayed in 25 axial slices of a Talairach standardized brain. The top left image is the most superior part, while the bottom right image displays the most inferior slice of the brain. Numerical values printed below each brain slice, denote the z-coordinate of the Talairach frame. Threshold of this contrast was set to $p < 0.005$ uncorrected (corrected on cluster level 0.05). B) Three magnified images highlighting the ratio dependent modulation of the IPS (red circle).

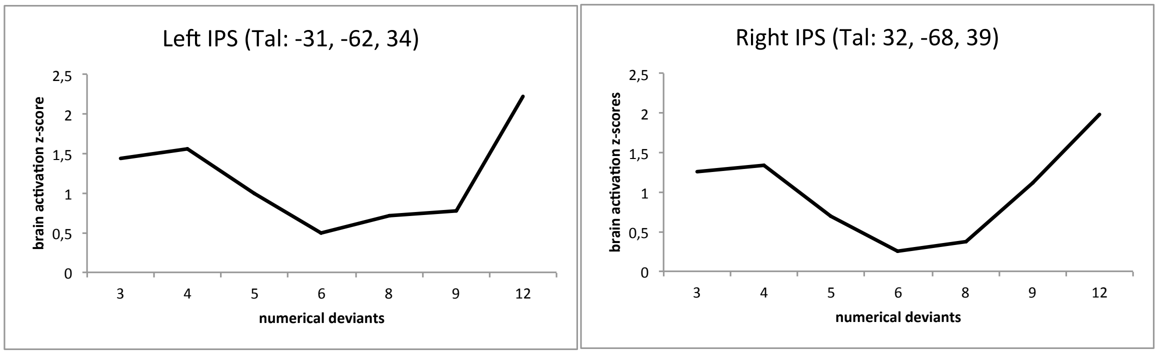

Figure 3.6: The two graphs in this figure illustrate the numerical ratio dependent modulation of brain signal recovery as a function of the deviants and the adaptation number in the left and right IPS. Brain estimates were calculated from a separate GLM in which each numerical deviant was entered as a separate predictors.

An additional post-hoc citoarchitectonic probability analysis based on the JuBrain Cytoarchitectonic Atlas Viewer (Mohlberg et al., 2012) showed that the Talairach coordinate of the peak-voxel of the right IPS was located with a probability of 22.959% in the region of the horizontal segment IP3 (hIP3) of the intraparietal sulcus (IPS), with a probability of 19.949% in area PGa and with a probability of 4.483% in the region PGp of the angular gyrus of the inferior parietal lobe (see Figure 3.6). Furthermore, the focal signal recovery of the left IPS was located with a probability of 59.116% in the region of the horizontal segment IP1 (hIP1) and with a probability of 40.884% the region of the horizontal segment IP3 (hIP3) of the parietal cortex (see Figure 3.7). Besides these parametric activations in the parietal lobe, additional ratio dependent activations were found in the fusiform gyrus of the temporal lobe, and the superior frontal gyrus/anterior cingulate gyrus (ACC, see also Figure 3.5 A and Table 3.2).

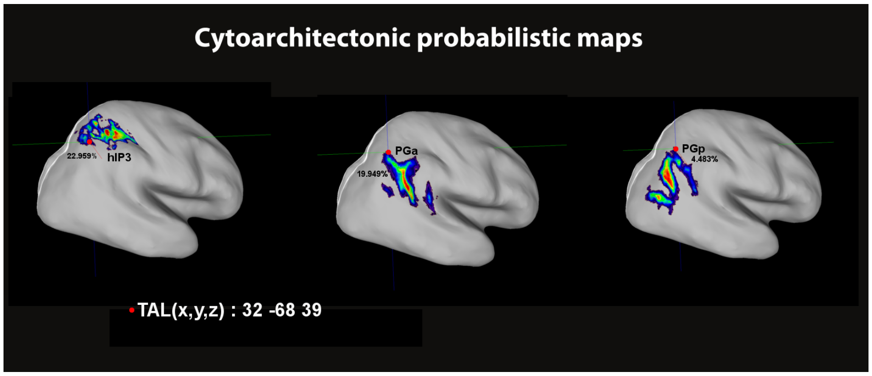

Figure 3.7: Cytoarchitectonic probabilistic maps showing the anatomical location oft the focal activation oft the right hemisphere in the parietal cortex.

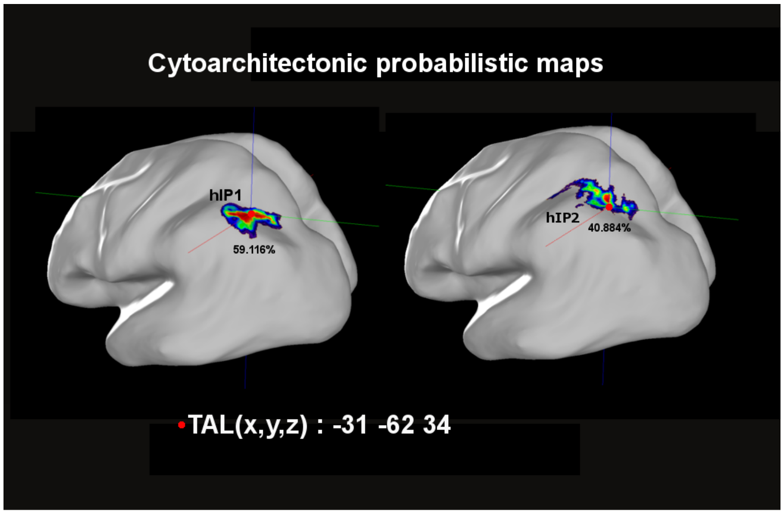

Figure 3.8: Cytoarchitectonic probabilistic maps identifying the anatomical location of the activation oft the left hemisphere of the parietal cortex.

Cluster Label *	**Tal. coordinates**			**Hemisphere**	**Lobe**	**Brodman Area**	**size**	**t-value**	**p-value**
	x	**y**	**z**						
Fusiform Gyrus	41	-47	-18	R	Temporal	37	991	4.280	< 0.001
Intraparietal Sulcus/Precuneus[**]	32	-68	39	R	Parietal	19	738	4.093	< 0.001
Superior Frontal Gyrus	-1	4	54	L	Frontal	6	1752	4.215	< 0.001
Intraparietal Sulcus/Precuneus[***]	-31	-62	34	L	Parietal	39	1273	4.230	< 0.001
Fusifrom Gyrus	-49	-59	-15	L	Temporal	37	4682	4.849	< 0.001

[*] Talairach Daemon application was used to label anatomical locations according to Talairach coordinates (Lancaster et al., 2000).

[**] This structure was labeled as hIP3 according to the JuBrain Cytoarchitectonic Atlas (Mohlberg et al., 2012).

[***] This structure was labeled as hIP1 according to the JuBrain Cytoarchitectonic Atlas (Mohlberg et al., 2012).

Table 3.2: Peak activation and statistical information of brain activation clusters, which showed a ratio dependent sensitivity towards numerical deviants.

3.3.2.3.Results from Cortex Based Alignment analysis

In order to further investigate the effects of numerical deviants on brain activation in cortex-based aligned space, the same contrast (i.e., parametric effect > baseline) as in the analysis above was calculated. Results of this analysis revealed three main regions, which were modulated by numerical ratio (see Figure 3.6). On the left hemisphere a cluster in the parietal lobe and in the inferior temporal lobe survived the statistical threshold set in this study (p = 0.005 uncorrected (corrected on cluster level p = 0.05). In the right hemisphere a single cluster in the parietal lobe survived the thresholding. Interestingly, in contrast to the Talairach procedure no frontal activation was found.

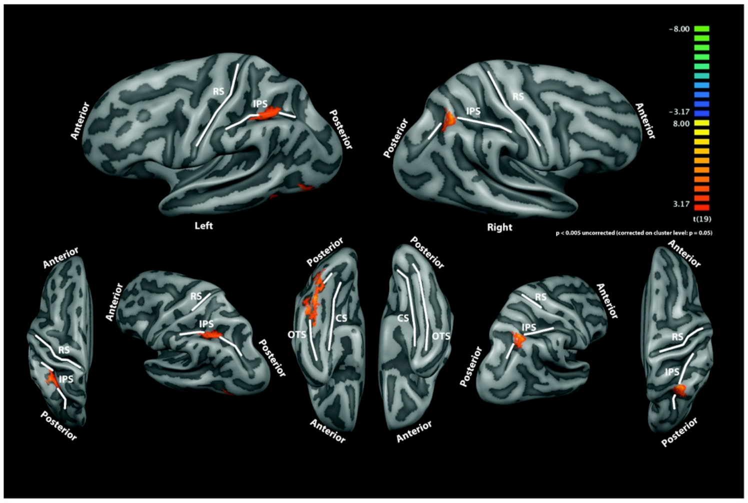

Figure 3.9: Results from Cortex Based Alignment (CBA) statistical analysis (threshold: p = 0.005 uncorrected (corrected at cluster level p = 0.05). Significant brain activations are presented from different angles and views on a group based brain reconstruction. Prominent anatomical landmarks are displayed for orientation: IPS = Intraparietal Sulcus; RS = Rolandic Sulcus; OTS = Occipitaltemporal Sulcus; CS = Collateral Sulcus.

3.4. Discussion

Functional neuroimaging studies along with neuropsychological case studies have provided strong evidence that the intraparietal sulcus (IPS) located in the parietal lobe encodes the semantic numerical meaning of numerical symbols. A good portion of this evidence has been derived from numerical comparison tasks, in which participants were asked to decide which of two numerals is larger or smaller. These studies have demonstrated that the neural activity of the IPS is inversely related (i.e., greater activation for smaller distances) to the numerical distance of the two numbers being compared. This activation pattern has since been taken to index the neural correlates of symbolic numerical magnitude processing in the human brain (Ansari et al., 2005; Bugden & Ansari, 2010; Holloway et al., 2010).

However, legitimate concerns have been cast as to whether brain activations in number comparison tasks are directly related to the semantic processing of numerical symbols per se or whether such activations may be reflective of other cognitive mechanism known to activate regions of the IPS - such as response selection (Goebel et al., 2004). New evidence from fMR-A, which allows for the investigation of symbolic numerical magnitude processing in the absence of overt numerical tasks demands, has now demonstrated that the neural signal in the IPS is modulated by numerical ratio even when no explicit numerical task is required (Cohen Kadosh et al., 2007; Holloway et al., 2012; Notebaert et al., 2011; Piazza et al., 2007). These findings suggest that the IPS is a critical region for encoding the semantic meaning (i.e., symbolic numerical magnitudes) of numerical symbols.

The study discussed in this chapter was intended to test the suitability of this experimental paradigm in children in order to investigate developmental changes of cortical specialization underlying the processing of symbolic numerical magnitude in a next step (see Chapter 4). Furthermore, the second purpose of this study was to increase our understanding of the brain systems underlying symbolic number processing by probing whether findings associated with the processing of symbolic numerical magnitudes in the IPS can be generalized across two different brain normalization procedures - Talairach space and Cortex Based Alignment.

Overall, the present study was successful in replicating previous neuroimaging findings that have demonstrated significant adaptation effects in adults in response to the presentation of deviating symbolic numerical magnitudes. Specifically, the study described in this chapter demonstrated that regions of the left and right IPS show significant neural signal recovery effects following the presentation of novel numerals (i.e., numerical deviants) that differ from the adaptation number (i.e., 6) in numerical ratio. Importantly, the increase in neural signal recovery was scaled by the numerical ratio between the numerical deviants and the adaptation reference number (i.e., 6), suggesting that numerical ratio is a significant predictor for brain activity associated with symbolic numerical magnitude representation. Ratio dependent neural signal recovery in the IPS has been recently demonstrated by studies with a similar experimental design (Holloway et al., 2012; Notebaert et al., 2011). The present study with adults replicated these findings with an experimental paradigm that has been adjusted for the use with children. In more detail, instead of using a single or two long adaptation runs, as was used in Notebaert et al. (2011) and Holloway et al. (2012), the experimental paradigm of the present study used 4 short functional adaptation runs in order to investigate signal recovery effects. The successful replication with this altered paradigm demonstrates that the ratio dependent recovery effect can be obtained by varying parameters of the experimental design, indicating that adaptation is independent of specific paradigm's settings and that the ratio dependent signal recovery is a stable and robust measurement. Furthermore, the findings indicate that neural signal recovery effects can be replicated across multiple laboratories, further strengthening the reliability of this design. As such, the presented results suggest that the current experimental design is suitable for the use with children and that it can be applied to investigate developmental changes in the way the human brain represents symbolic numerical magnitudes.

Another aim of the present work was to probe two different brain normalization procedures. This was done in order to tests whether different analysis methods reveal converging results and to test whether one method should be preferentially used to analyse the data. Results of this comparison demonstrated that both methodological approaches reveal similar findings in the regions of the parietal lobe. Using the same significance level across both methods demonstrated that the brain activity of the left and right IPS was modulated by numerical ratio. The converging results indicate a strong similarity across both methods and further demonstrate the robust nature of the signal recovery effect in regions of the IPS. However, also interesting differences between the two methods arose. Normalizing individual brains into Talairach space demonstrated significant neural signal recovery effects in the frontal lobe. Such activation was absent in the Cortex Based Alignment analysis, which only revealed significant rebound effects in the parietal lobe. Consequently, it could be argued that the Tailairach space approach might be more sensitive in detecting additional regions that are modulated by numerical ration. On the other hand, the absence of this finding in the CBA analysis suggests that findings of the parietal lobe are the most robust and, therefore, further strengthening the specificity of parietal findings in symbolic numerical magnitude processing.

Overall, the data of this study converge with a growing body of evidence demonstrating that the activation of the IPS is modulated by numerical ratio in response to the passive presentation of symbolic numerical magnitudes (Holloway et al., 2012; Notebaert et al., 2011). Therefore, the present work indicates that numerical ratio dependent activation in the IPS is highly reproducible across different experimental settings and across different laboratories. The next chapter will use the experimental design tested in this study to investigate developmental changes in the cortical specialization associated with symbolic numerical magnitude representation.

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Chapter 4: Developmental changes in the cortical representation of symbolic numerical magnitudes.

4.1. Introduction

Human beings possess the unique ability to process and represent numerical magnitudes - the total amount of items within a given set - through the use of numerical symbols such as Arabic numerals. The acquisition of symbolic numerical knowledge in childhood is crucial for the development of mathematical abilities. Over the last decade functional brain imaging studies have aimed to unravel the neural correlates of symbolic numerical magnitude representation in the brain. Results from studies with adults investigating the neural correlates of numerical symbol processing, have demonstrated that the neural activity of the intraparietal sulcus (IPS), located in the parietal lobe, is modulated by symbolic numerical magnitude information (for reviews see Ansari, 2008; Cohen Kadosh, Lammertyn, & Izard, 2008; Dehaene, Piazza, Pinel, & Cohen, 2003; Nieder & Dehaene, 2009; see also chapter 2 and 3 of the present thesis). This body of evidence has suggested that the IPS is critically engaged when the semantic meaning (e.g. the numerical magnitude) of numerical symbols is processed. While our knowledge about symbolic numerical magnitude representation in the adult brain has greatly increased over the last decades, the neural processes underlying the development of symbolic numerical magnitude representation in the child's brain remain elusive.

Despite these important advances in our understanding of how the adult brain represents symbolic numerical magnitudes, little is currently known about the way symbolic numerical magnitudes are processed and represented in the child’s brain, and how the neural correlates of symbolic numerical magnitude processing change over developmental time. There does exist a sparse body of neuroimaging evidence of studies that have investigated developmental changes in the neural correlates of symbolic numerical magnitude representation. Broadly summarizing, these studies have pointed towards a developmental, functional specialization of the IPS for representing the semantic meaning of numerical symbols (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon et al., 2009; Holloway & Ansari, 2010; Houdé, Rossi, Lubin, & Joliot, 2010; Kaufmann et al., 2006).

One of the first neuroimaging studies to investigate the neural correlates of symbolic numerical magnitude representation was conducted by Ansari and colleagues (2005). The authors measured the functional brain activity of children and adults while both groups performed a symbolic number comparison task (see also chapters 1 and 3 for a detailed description of the number comparison task) in a magnetic resonance imaging scanner. Both groups were asked to decide which of two simultaneously presented single digits is numerically larger. The numerical distance of the numerals being compared was systematically manipulated in order to investigate developmental changes in the neural correlates associated with the numerical distance effect (for a detailed discussion on the numerical distance effect see chapters 1 and 3 of the present thesis). Consistently with previous work in adults, the results of this study revealed a significant numerical distance effect on neural activation of the parietal lobe of adults. On the other hand, activations in children were predominantly found in regions of the prefrontal cortex. This intriguing group difference was argued to suggest an ontogenetic reorganization of the underlying neural architecture, shifting from prefrontal regions of the child's brain to parietal regions (especially the IPS) in adults. As such, the results of this study demonstrated an age-related functional specialization of the IPS that may be related to a change in the underlying representation of symbolic numerical magnitudes. One possible explanation for the functional specialization of the IPS is a developmental change in the efficiency with which the human brain associates numerical magnitudes and their symbolic referents (i.e., the degree of automaticity with which numerical magnitudes are associated with their corresponding symbols). In other words, the mapping (i.e., the associative connection) between an initially arbitrary shape and its culturally mediated semantic meaning (i.e., the numerical content; the numerical magnitude) may be refined over developmental time, increasing the efficiency with which the semantic meaning of numerical symbols is retrieved during tasks such as number comparison. In addition to age-related changes in the parietal cortex, the decreased activation in the prefrontal cortex of adults may be indicative of a reduced engagement of cognitive control mechanisms (e.g., working memory), which might play a crucial role in earlier stages when the mapping between numerical magnitudes and the numerical symbol is established (Cantlon, 2012; Andreas Nieder & Dehaene, 2009).

Corroborating evidence for a developmental shift in the fronto-parietal network underlying the processing of symbolic numerical magnitudes was provided by another developmental study, which revealed similar numerical distance related activation in the prefrontal cortex of children (Kaufmann et al., 2006) and significant numerical distance related activation in parietal regions of adults (Kaufmann et al., 2005). As was indicated by the results of the study by Ansari and collaegues (2005), these findings point towards an age-related change in the neural substrates that sub-serve the comparison of symbolic numerical magnitudes. Thus, indexing a widespread engagement of prefrontal regions in children, and a focal activation in regions of the parietal lobe, specifically the IPS, in adults.

Another developmental fMRI study by Cantlon et al. (2009) measured the brain response of 6-year olds, 7-year olds and adults while performing a symbolic and a non-symbolic numerical comparison task in the scanner. In the symbolic task participants were asked to decide which of two simultaneously presented numerals is larger, in the non-symbolic task participants were asked to judge which of two simultaneously presented dot-arrays contains more dots. In this study numerical ratio (for a detailed discussion on the numerical ratio effect see chapters 1 and 3 of the present thesis) was manipulated in such a way, that half of the trials consisted of small ratio pairs (i.e., 2 4; 4 8; 8 16 = ratio 0.5), whereas the other half consisted of large ratio pairs (i.e., 3 4; 6 8; 9 12 = ratio 0.8). The main results of this fMRI study demonstrated a greater activation in bilateral regions of the inferior frontal gyrus across both notation formats (i.e., symbolic and non-symbolic) in children. On the other hand, adults exhibited stronger activation across both notation formats in the left superior parietal cortex. In addition to this main effect of age on brain activity, a significant ratio dependent effect was found in the superior parietal cortex in adults but not in children who exhibited a numerical ratio dependent activation in regions of the inferior frontal cortex. Convergent with previous studies the findings of this study suggest a functional specialization of parietal regions for the representation of numerical magnitudes that may be invariant to the notation format (i.e., symbolic and non-symbolic). However, it should be stressed that both conditions were collapsed in the analysis and it is, therefore, not apparent whether ratio dependency was truly driven to the same extent by both conditions (i.e., symbolic and non-symbolic).

The developmental neuroimaging findings described above provide compelling evidence that the neural correlates associated with the symbolic numerical distance effect shift from a distributed prefrontal network in children to a functionally specialized region in the IPS in adults. However, recent imaging work in adults has demonstrated that IPS activations found in numerical comparison paradigms may not be solely related to the semantic encoding of numerical symbols (Göbel, Johansen-Berg, Behrens, & Rushworth, 2004; Göbel & Rushworth, 2004; see also Chapter 3 of the present Thesis). The finding that activation patterns in the IPS may not be related to numerical magnitude representation per se, has significant implications for findings that demonstrated developmental changes in the neural correlates in number comparison tasks. Moreover, it is well known that developmental neuroimaging studies are very sensitive to age-related performance differences in reaction time and accuracy, consequently leading to a potential confound between developmental changes and changes that are attributable to changes in task performance (Poldrack, 2000). For example, in the Ansari et al. (2005) study and in the study of Kaufmann et al. (2005, 2006) large behavioural performance differences between the groups of children and adults were observed, which may have obscured developmental differences in brain activation. Put differently, in these studies it is impossible to know whether the differences in brain activation observed between children and adults were truly a function of age or a consequences in the difference with which children and adults were able to perform the task. As a consequence, performance differences may be very powerful predictors of brain activation and it is not unreasonable to assume that age related differences in brain activation observed in previous number comparison studies may be related to differences in task performance rather than developmental differences in symbolic numerical magnitude representation.

The importance of minimizing performance confounds in developmental studies has been demonstrated in a developmental fMRI study by Holloway and Ansari (2010). In this study children and adults performed a symbolic and non-symbolic numerical comparison task. In the first condition two numerals were presented on the screen and participants had to decide which number is numerically larger. In the non-symbolic condition two arrays of squares were presented and participants had to judge which of the two arrays contained more squares. In addition to these numerical tasks, both groups performed two control tasks (one for the symbolic and one for the non-symbolic condition) in which participants had to decide whether the presented stimuli contain a diagonal line. By subtracting the control tasks from the experimental tasks the influence of confounding factors such as response selection was minimized.

In a first analysis the authors performed a whole brain conjunction across both notation formats (i.e., symbolic and non-symbolic), without subtracting activation from the control tasks (thereby not removing any variance related to non-numerical factors such as response selection and the perceptual aspects of the stimuli). This analysis showed significantly greater activation in bilateral regions of the IPS in adults compared to children. However, the same contrast controlled for confounding variables (by subtracting away the control conditions from each experimental condition) revealed only activation in the right superior parietal lobe, whose activity was modulated by both symbolic and non-symbolic comparison conditions to a larger extent in adults compared to children. This result suggests that a large portion of age-related activation differences in the IPS can be attributed to non-numerical dimensions and highlights the importance for conditions that control for performance differences. Moreover, a post-hoc analysis of the brain activation measured in this region demonstrated that both conditions – the symbolic and the non-symbolic - exhibited a numerical distance effect in adults, however, in children a numerical distance effect was only found in the non-symbolic condition but not in the symbolic condition, suggesting that the IPS in children was involved in processing numerical semantics of non-symbolic stimuli but not of symbolic numerical stimuli. In general, the results demonstrate the importance of stringent control tasks to reduce the influence of confounding variables. The focal activation identified by the stringent contrast revealed important insights on developmental processes underlying the representation of symbolic and non-symbolic numerical magnitude. It showed that activations found in the IPS cannot be solely attributed to response selection mechanisms. Since the control condition involved a similar response selection as the experimental condition, subtracting the activation of this condition from the experimental condition eliminated variance that one might attribute to response selection. Consequently, developmental activation differences found in this study may be attributed to changes in the underlying representation of numerical magnitudes.

While the use of active control tasks is a legitimate way to reduce confounding variables such as response selection, an even more stringent way to eliminate performance confounds is to use experimental paradigms that do not afford explicit task requirements. For example, functional Magnetic Resonance Adaptation (fMR-A) has been successfully used in adults to investigate the neural correlates of numerical magnitude representation in the absence of response selection demands (the reader is also referred to chapter 3 of present work). These studies were able to demonstrate that the IPS in adults is sensitive to the manipulation of numerical magnitude, and that the neural signal recovery extracted from the IPS is modulated by the numerical ratio between the adaptation numeral and the numerical deviant (Holloway, Battista, Vogel, & Ansari, 2012; Naccache & Dehaene, 2001; Notebaert, Nelis, & Reynvoet, 2011; Piazza et al., 2004, 2007).

Recent evidence from these fMR-A studies has revealed a striking anatomical specificity with which symbolic numerical magnitudes may be represented in the adult brain (Holloway et al., 2012; Notebaert et al., 2011). For instance, using fMR-A Notebaert and colleagues (2011) investigated the neural signal recovery in response to small (e.g., 3,4,5) and large numbers (e.g., 16, 20, 26). Participant’s brain response was first adapted either to small (i.e., the Arabic digit 6) or large (i.e., the Arabic numeral 32) numerical values. The repeated presentation of these adaptation numerals was then interspersed with the presentation of numerical deviants that systematically differed in numerical ratio from the adaptation numerals. A whole brain analysis revealed that the left IPS was the only region that expressed a significant ratio dependent recovery effect independent of the number condition (i.e., large numbers 16, 20, 26 or small numbers 3,4,5). In other words, the signal recovery of the left IPS was larger for numbers that were further away from the adaptation number compared to numbers that were relatively close to the adaptation number. The findings of this fMR-A study revealed a striking anatomical specificity with which numerals may be represented in the adult brain. Typically brain activations found in active tasks are widespread and a whole set of significant activations can be found throughout the cortex (see for example Pinel et al., 1999, 2001). In contrast, the fMR-A study by Notebaert et al. (2011) revealed a highly specific activation of the left IPS. The ratio dependent neural recovery effect found in this study, suggests a greater representational overlap for symbolic numerical magnitudes that are close in numerical value compared to numerals that are separated by a larger numerical distance. In other words, the neural signals of numbers that are close in numerical distance elicit a greater similarity in the neural signal (i.e., less deviation from the adaptation signal) than numerals that are farther apart. Thus, the data presented by Notebaert et al. (2011) suggest a striking specificity with which the semantics of numerals may be represented in the left IPS in the absence of overt decision and response requirements.

Converging evidence comes from another fMR-A study that compared the brain activity of participants capable of reading Chinese Ideographs (e.g., 六) and Arabic numerals (e.g., 6) to a control group that was only able to read Arabic numerals (Holloway et al., 2012; see also chapter 3 of the present thesis). Results of this cross-linguistic study demonstrated a significant ratio dependent rebound effect in the left IPS for Arabic numerals across both groups (i.e., the Chinese and the control group). On the other hand, the less familiar Chinese ideographs evoked a right lateralized IPS recovery effect in the Chinese group, whereas, no parietal signal recovery was found in the control group who was not able to read the Chinese ideographs. Consistent with the previous study by Notebaert et al., (2011), the findings Holloway et al. (2012) point towards the importance of the left IPS for symbolic numerical magnitude representation, especially when highly used numerical symbols, such as Arabic numerals are processed. Specifically, the results of this study indicate that lateralization effects may be experience-dependent, as it shows that differences in the familiarity with numerical notation formats elicit differences in hemispheric activation.

Together, the results of the studies described above point towards a left hemispheric specialization of the IPS for representing the semantic meaning of numerical symbols in adults. However, these findings are in contrast to the findings reported in chapter 3 of the present thesis, which demonstrated a bilateral modulation of the signal recovery in regions of the IPS. As such, the issue of lateralization remains inconclusive and more studies are required to further constrain our knowledge of hemispheric specialization related to the representation of symbolic numerical magnitude. Since the association between numerical magnitudes and their symbolic referents is learned over the course of development, one way to further understand lateralization in the human brain during numerical symbol processing is to investigate ontogenetic changes in the cortical representation of symbolic numerical magnitude representation.

The literature on fMR-A studies in adults, reviewed above and in the previous chapters of this thesis, provides evidence to suggest that the left IPS is engaged when symbolic numerical magnitudes are processed in the absence of overt task demands (though see Chapter 3 for data that suggest bilateral processing of number symbols in adults). In contrast, evidence from developmental studies has not yet painted a clear picture on whether hemispheric specialization does occur over developmental time. The few studies that have investigated the development of symbolic numerical magnitude representation have used active tasks such as number comparison. For example, while the study by Cantlon et al. (2009) found developmental differences between children and adults for the processing of symbolic and non-symbolic numerical magnitude in the left superior parietal lobe, the study by Holloway and Ansari, (2010) found developmental differences in the right IPS. However, it should be noted that quite different approaches were used in these studies to analyze the data and to control for potential confounds such as response selection, which might explain inconsistencies in hemispheric lateralization across different developmental studies. As such more research is needed in order to further investigate the possibility of hemispheric differences in cortical specialization.

Besides our limited knowledge about the developmental trajectory of cortical specialization and hemispheric lateralization, there are important methodological limitations in the developmental studies reported above. Thus far developmental imaging studies have primarily focused on group comparisons between adults and children. This dichotomy as well as the heterogeneity of the ages within the groups of participants labelled 'children' may have lead to an underestimation of subtle developmental differences that drive the hemispheric specialization for the processing of numerical symbols. In other words, by collapsing data from children of a wide age range, some of the developmental changes that occur within such an age range may have been obscured in previous studies. Investigations using cross-sectional data of different age groups may provide a more refined picture of how the human brain represents symbolic numerical magnitudes over developmental time. Since one might expect to see subtle changes (such as lateralization) in the underlying functional architecture associated with symbolic numerical knowledge acquisition, this fine-grained approach may reveal important ontogenetic chances that are overlooked in coarse group comparisons.

In order to overcome these limitations and to further increase our understanding about the underlying ontogenetic changes in brain specialization, the present study used a fMR-A paradigm that was successfully tested in adults in chapter 3 of the present thesis. The passive nature of fMR-A allows for an investigation that eliminates, or at least reduces, explicit task demands. To investigate the cortical specialization associated with the representation of symbolic numerical magnitude over developmental time, we attenuated the brain activity of children – ranging from 6 years of age to 14 years of age - through the repeated occurrence of the Arabic numeral “*6*” on a computer screen. Symbolic numerical deviants were randomly interspersed in order to measure ratio dependent changes in the neural signal recovery. For this study, several predictions can be articulated:

First, it is currently unknown at what time point in life a cortical representation of symbolic numerical magnitude, measured at the level of fMR-A, is fully developed. On one hand, representations of symbolic numerical semantics in the parietal lobe could be established before the age of six. If this assumption were true, one would predict to see a quite stable and significant ratio dependent modulation of the neural signal recovery in the IPS in response to the presentation of numerical deviants across all ages. Consequently, this hypothesis predicts that the ratio dependent effect is similar across the entire sample and does not correlate with age. On the other hand, if the cortical specialization of symbolic numerical magnitude representation has not been fully established by the age of six and does continue to manifest itself over developmental time, we would expect to see significant developmental changes in ratio dependency of the signal recovery effect in regions of the IPS that positively correlate with age. In other words, we would predict the emergence of an increased ratio dependent signal recovery effect over developmental time.

Second, fMR-A studies with adults have suggested a left lateralized specialization for representing symbolic numerical magnitudes in the human cortex in adults (Holloway et al., 2012; Notebaert et al., 2011). In relationship to these findings two predictions can be made in connection with the predictions discussed above. In the first potential scenario, that is the prediction of a fully developed symbolic numerical cortical representation at the age of 6, one would expect to find a fully established cortical specialization of the left IPS. In the second scenario, that is the prediction that the cortical specialization continues to develop beyond the age of 6, one would expect to see an emerging left hemispheric specialization over developmental time. In addition to this prediction and in relation to results presented by Holloway et al. (2012), who revealed right lateralized activation in the IPS for the presentation of Chinese ideographs, which are symbols that are used to a lesser degree and thus perhaps less fluently, one might predict an early involvement of the right IPS that either decreases with developmental time or remains stable over the age-range covered in this study. As such it is entirely possible that representations of symbolic numerical magnitude emerge from a more complex interplay of the two hemispheres over developmental time.

4.2. Material and Methods

4.2.1. Participants

In total we invited 33 healthy children to participate in this study. Out of these 33 participants, nineteen children (7 males and 13 females; ages: 6-14 years) achieved our cut-off criteria for excessive motion (no more than 3mm overall deviation from the 1^{st} volume acquired and no more than 1.5mm deviation between subsequent volumes) in at least 2 out of 4 functional runs within the scanner. In each age cell a minimum of two children were included for each year (i.e., two 6-

year-olds, two seven-year-olds, etc.). This age range was chosen to sample an adequate age range in order to investigate developmental changes of symbolic numerical magnitude representation. All participants were right-handed (as measured by the Edinburgh Handedness Inventory; Oldfield, 1971) and had normal or corrected to normal vision. For participating, children were given a total of fifty dollars in the form of gift cards to a local toy store (twenty-five dollars for each of the two testing sessions, see below for details on these two sessions) as well as a picture of their brain from the fMRI session. Informed consent was obtained from the parents, as well as assent from the children. The procedures of this study were approved by the Human Subjects Research Ethics Board at the University of Western Ontario.

4.2.2.Stimuli

The stimuli (see Figure 3.2) for the present study were created in Adobe Photoshop CS4 and consisted of black (R-G-B color values: 0, 0, 0) colored Hindu-Arabic numerals. Numerals were displayed on a silver gray background (R-G-B color values: 192, 192, 192) with a font size of 40pt. The presentation software Eprime 2.0 was used to project the stimuli onto a computer screen (resolution = 800 x 600pixles, color bit depth = 16) mounted in the MRI scanner. Participants viewed the presentation via a mirror system attached to the MRI head-coil.

4.2.3.Experimental Procedure

The experimental procedure was first tested in adults (the reader is referred to chapter 3 of the present thesis). fMRI adaptation was used in order to habituate participant's brain response to the numerical value "six". This was achieved by presenting the Hindu-Arabic digit "*6*" repeatedly on the computer screen. The length of the continuous presentation was systematically varied between 5 and 9 repetitions, with an overall mean of 7 repetitions across the functional runs. Importantly, in order to minimize potential low-level perceptual adaption effects, the font (Times New Roman and Courier New) as well as the spatial location of the numerals (one of six possible locations 2 degrees from the center of the display; x/y center-position of the six locations was 435/300, 365/300, 375/325, 425/325, 375/275 and 425/275) was systematically varied throughout the experiment. In addition, the same spatial location did not appear in immediate succession. After the adaptation phase, different numerical deviants (i.e., the numbers "*3*", "*4*","*5*","*8*","*9*", and "*12*"), catch trials (i.e., numerals with a "Smurf"), and null trials (i.e., the adaptation number "*6*") were presented on the screen.

Importantly, the numerical deviant trials consisted of numerals that differed systematically in ratio from the adaptation number "*6*" (see Table 3.1). This systematic manipulation in ratio was used to investigate ratio dependent neural recovery effects in response to the presentation of the numerical deviants. The catch trials consisted of a numeral (i.e., the numbers "*3*", "*4*","*5*","*8*","*9*", and "*12*") and a picture of a Smurf (see Figure 3.2). The location of the smurf was varied and it appeared either on the left-upper, left-lower, right-upper or right-lover corner of the numeral. Participants were instructed to attend to the screen at all times and to press a predefined button with their right index finger whenever: ". . .a Smurf appears on the computer screen". The purpose of the catch trial was to assure a minimum of attentiveness of participant's towards the presentation of the numerals in the scanner. Participants were instructed to press a button when a smurf appeared on the computer screen. The null trials (i.e., the continued presentation of the number "*6*") were used to estimate the baseline signal of the neural recovery effect. The null trials were entered in the parametric predictor in order to assess ratio dependent deviations from this baseline. As such the participants were unaware of the presence of the null trials. As with the numerical deviants and the catch trials, the null trials were randomized across the run.

Four functional adaptation runs were administered per participant. Each run consisted of presentations of Hindu-Arabic digits interspersed with a blank screen (see Figure 3.3). The numeral appeared for 200ms on the screen, the blank screen was displayed for 1200ms. The continuous presentation of the number "6" (i.e., the adaptation phase) was randomly interrupted by the presentation of a numerical deviant (18 per functional run), or a catch trial (8 per functional run) or a null trial (4 per functional run). Each run lasted 6 minutes and 16 seconds. Experimental stimuli were presented in an event-related fashion with a jittered interval of 5000 – 9000 msec with a mean of 7500msec in order to oversample the hemodynamic response function (HRF).

4.2.4.General Procedure

All children were familiarized with the fMRI environment in a training session on a day sometime before the actual scanning. In the beginning of the session the experimenter used a photo book, which was specifically created for training purposes at the Numerical Cognition Laboratory[1] in order to explain the nature and the procedure of MRI. A mock 0T-scanner was then used to practice the fMRI scanning procedure. In this mock scanner, the children watched a movie and performed a short training of the paradigm. To avoid any potential training effects, letters were used instead of numbers to simulate the adaptation task in the scanner. Movements were monitored visually and immediate feedback was given when the child moved too much.

At the scanning day, children were again familiarized with the procedure, using the same photo book as in the training session. In addition, children were prompted to pay attention to the computer screen at all times so that they make sure "...to catch all the Smurfs hiding between the numbers". As such, participants were unaware of the numerical nature of the experiment. The only active task requirement was to catch the Smurfs. Children were allowed to explore the MRI environment for a short period of time, before they were slowly positioned into the scanner.

4.2.5.fMRI Data Acquisition

Structural and functional data were acquired in a 3-Tesla Siemens Tim Trio whole-body MRI scanner. A 32-channel Siemens head coil was used. The functional images were collected by using a blood oxygen level dependent (BOLD) sensitive T2* weighted echo planar (EPI SE) sequence. The functional images were acquired in an ascending - interleaved order covering the whole brain with 38 slices per

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[1] Link to the online fMRI photo book: ***http://www.numericalcognition.org/?page_id=1129***

volume (3mm thickness, 64 x 64 matrix, repetition time (TR): 2000ms, echo time (TE): 52ms, flip angle: 78°). For each functional run 188 Volumes were collected, resulting in a total length of 6 minutes and 16 seconds. High-resolution T1 weighted images were collected using a MPRAGE sequence (1 x 1 x 1 mm, TR: 2300ms, TE: 4.25ms, flip angle: 9°).

4.2.6.Imaging Analysis

The entire data set was analyzed with the brain imaging software package Brain Voyager QX 2.3 (Brain Innovation, Maastricht, The Netherlands). Preprocessing steps for the functional and anatomical data sets were carried out for each participant individually. All functional images were corrected for slice-scan time acquisition (ascending – interleaved - using a cubic-spline interpolation algorithm), and high-pass (GLM – Fourier) frequency filtered with a cut off value of 2 sines/cosines cycles in order to remove low frequency signals from the data. In addition, participants' motion parameters were corrected using a Trilinear/sinc interpolation approach. To ensure a high data quality, stringent motion criteria were used. In order to be included into the analysis, participants motion must not exceed more than 3mm overall drift from the first volume acquired and must not exceed a volume-to-volume peak jump of 1.5mm for a given functional run. Furthermore, a minimum of two good functional runs (meeting the criteria described above) were required from each subject to allow their inclusion in the final analysis.

Anatomical 3D images were first stripped from the skull (using the implemented brain peeling tool in BV) and the resulting "peeled" brain template was used to align the 3D anatomical image with the functional images of the scan. This was carried out fully automaticly in two consecutive steps. The initial alignment brings the anatomical and the functional data sets in close proximity (this is achieved by an automatic procedure implemented in BV using the header-information contained in the data set). The second step uses a gradient-driven affine transformation in order to fine tune the alignment between the functional and anatomical image. The quality of the automatic alignment was manually checked for each participant and if necessary corrected by hand. For group analysis, the 3D images and the functional runs were then manually transformed into Talairach space (Talairach & Tournoux, 1988) using a Trilinear interpolation algorithm implemented in the software package Brain Voyager.

4.2.7.Statistical Analysis

All subsequent statistical analyses were performed on the group data set in Talairach space. In order to investigate the influence that numerical deviants exerted on the brain signal, deviant stimuli were collapsed into four number ratio bins - larger ratio, 2.0 (deviants 3 and 12), medium ratio, 1.5 (deviants 4 and 9), small ratio, 1.33 (deviants 5 and 8) and ratio 1 (null event: number 6; the baseline). The bins were then entered as a parametric regressor into a general linear model (GLM) to reveal regions that showed a parametric increase in signal recovery scaled by numerical ratio. Moreover, to explain additional variance in the data both the smurf catch-trials as well as the participant's individual motion parameters were entered as predictors of no-interest into the same GLM. Finally, all functional events of the GLM were convolved with a two-gamma hemodynamic response function (HRF) in order to predict the blood oxygen level dependent (BOLD) function (Friston et al., 1998) in a random effect (RFX) analysis.

The first statistical analysis carried out aimed to identify those regions in the brain that showed a ratio dependent neural signal recovery across the entire group, and therefore were independent of developmental time. In other words, this analysis asked the question which areas of the brain showed a ratio dependent increase in activation relative to baseline in response to the presentation of numerical deviants across the whole sample. To answer this question the parametric regressor of the modeled GLM was contrasted against baseline (adaptation period) activation.

The second question aimed to investigate whether regions of the IPS exhibited an age related change in the strength of the ratio dependent neural signal recovery effect. For this we performed a whole brain correlation analysis between age and the fit of the parametric regressor.

For both analyses, only those voxels whose activation reached a minimum threshold of $p < 0.005$, uncorrected (cluster corrected at $p = 0.05$) were considered to be significant. For cluster correction a Monte-Carlo simulation implemented in BV was used to estimate the minimum cluster-size that reduces the Type-I error to an expectable level of $p = 0.05$. The minimum size of a cluster is thereby estimated by an iterative simulation procedure based on the functional set used in the study (for more detailed information about this procedure the reader is referred to chapter 2, page 51 of the present thesis).

4.3. Results

4.3.1. Behavioural Results

In order to be included into the study participants had to catch a minimum of 6 out of 8 smurf catch trials. This criterion ensures an objective measurement of minimum attentiveness of the participants towards the stimuli presentation in the scanner. The children included into the study showed therefore a high accuracy in catching the smurfs (Mean = 93.5%; SD = 7.4; max-min = 100% - 75%). It took the children on average of 643.6ms (SD = 137.0ms; max-min = 910.1ms – 470.3ms) to catch the smurfs. No further analyses were conducted with the behavioural data.

4.3.2. Imaging Results

To investigate the effect of ratio dependent neural signal recovery across the entire group, the parametric regressor was contrasted against baseline activation. Analysis of this contrast revealed 5 clusters that reached the predefined threshold, and, therefore, showed a significant ratio dependent increase in neural recovery in response to the presentation of numerical deviants. Importantly, one of the regions was situated in the parietal lobe and more specifically in the right superior parietal lobe (see Figure 4.1). A post-hoc citoarchitectonic probability analysis based on the JuBrain Cytoarchitectonic Atlas Viewer (Mohlberg, Eickhoff, Schleicher, Zilles, & Amunts, 2012) showed that the Talairach coordinate of the peak-voxel was located with a probability of 44.615% in the region of the horizontal segment IP3 (hIP3) and with a probability of 4.025% in area 7A of the superior parietal cortex (see Figure 4.2).

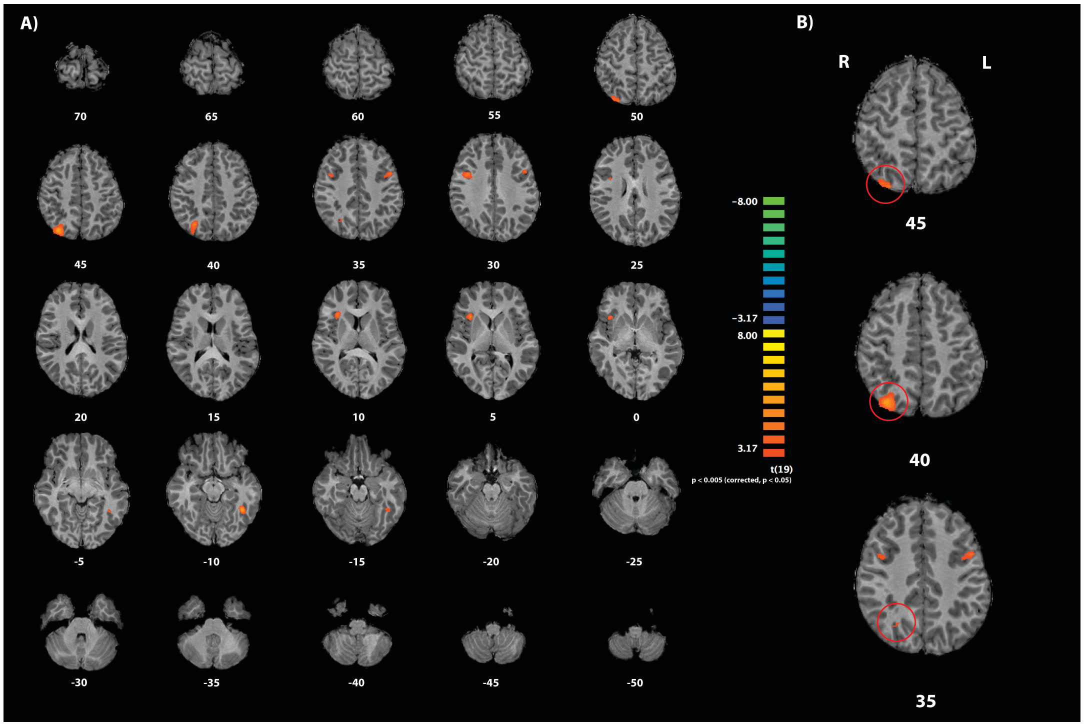

Figure 4.1: Statistical maps illustrating the numerical ratio dependent brain activations found across the entire group: a) Superior to inferior axial brain slices covering the whole brain. Slices are labeled according to Talairach coordinates along the z-axis; b) three brain slices highlighting the activation of the right IP3.

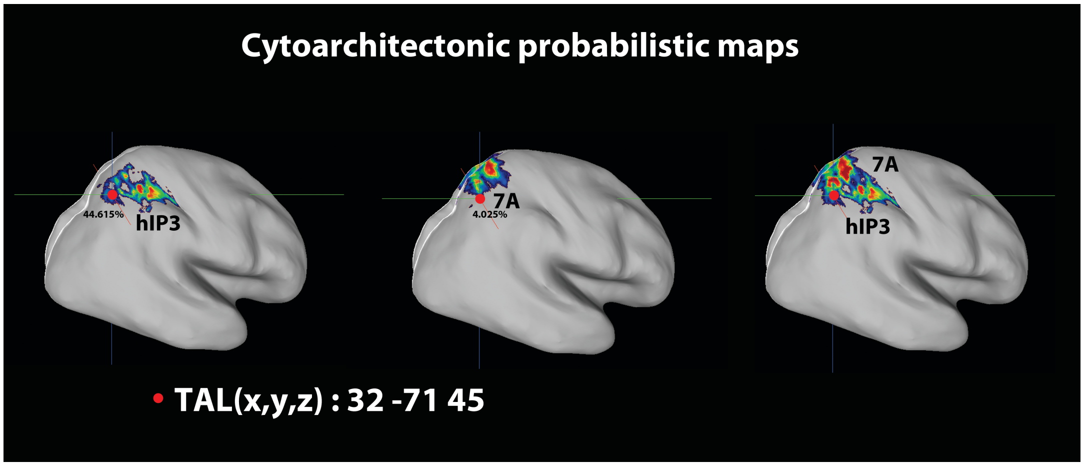

Figure 4.2: Cytoarchitectonic probabilistic maps identifying the anatomical location of the activation found in the right hemisphere of the parietal cortex.

In addition to the activation found in the parietal lobe, the analysis demonstrated significant parametric recovery effects in the right precentral gyrus of the frontal lobe, the right Insula, the left middle frontal gyrus of the frontal lobe and in the left fusiform gyrus of the temporal lobe (see also table 4.1). Note that the cluster size of the right IPS was the largest of the identified areas.

Cluster Label [*]	**Tal. coordinates**			**Hemisphere**	**Lobe**	**Brodman Area**	**size**	**t-value**	**p-value**
	x	**y**	**z**						
Precentral Gyrus	38	4	30	R	Frontal	6	736	4.751	< 0.001
Superior Parietal Lobule[**]	32	-71	45	R	Parietal	7	2241	5.653	< 0.001
Insula	32	19	6	R	Sub-lobar	13	886	5.553	< 0.001
Middle Frontal Gyrus	-46	7	33	L	Frontal	9	468	5.066	< 0.001
Fusifrom Gyrus	-40	-47	-9	L	Temporal	37	787	6.469	< 0.001

[*] Talairach Daemon application was used to label anatomical locations according to Talairach coordinates (Lancaster et al., 2000).

[**] This structure was labeled as hIP3 according to the JuBrain Cytoarchitectonic Atlas (Mohlberg et al., 2012).

Table 4.1: Talairach coordinates of activation peaks that showed a significant ratio dependent parametric modulation across participants independent of age.

The second whole brain analysis of the present study aimed to investigate age related changes in the neural signal recovery in response to the presentation of numerical deviants. For this a correlation between age and the parametric predictor was calculated across the whole brain. The results of this analysis revealed a region in the left parietal lobe (peak-voxel Talairach coordinates (x,y,z): -43 -65 42; cluster size = 529 voxel) that showed a significant positive correlation between age and the extent of the ratio dependent neural recovery effect (Figure 4.3). In other words, this region of the inferior parietal lobe showed an increased ratio dependent modulation with age. A post-hoc cytoarchitectonic probability analysis revealed that the Talairach coordinates of the peak correlation were situated with a probability of 62.712% in the horizontal segment of IP1 (hIP1; see Figure 4.4).

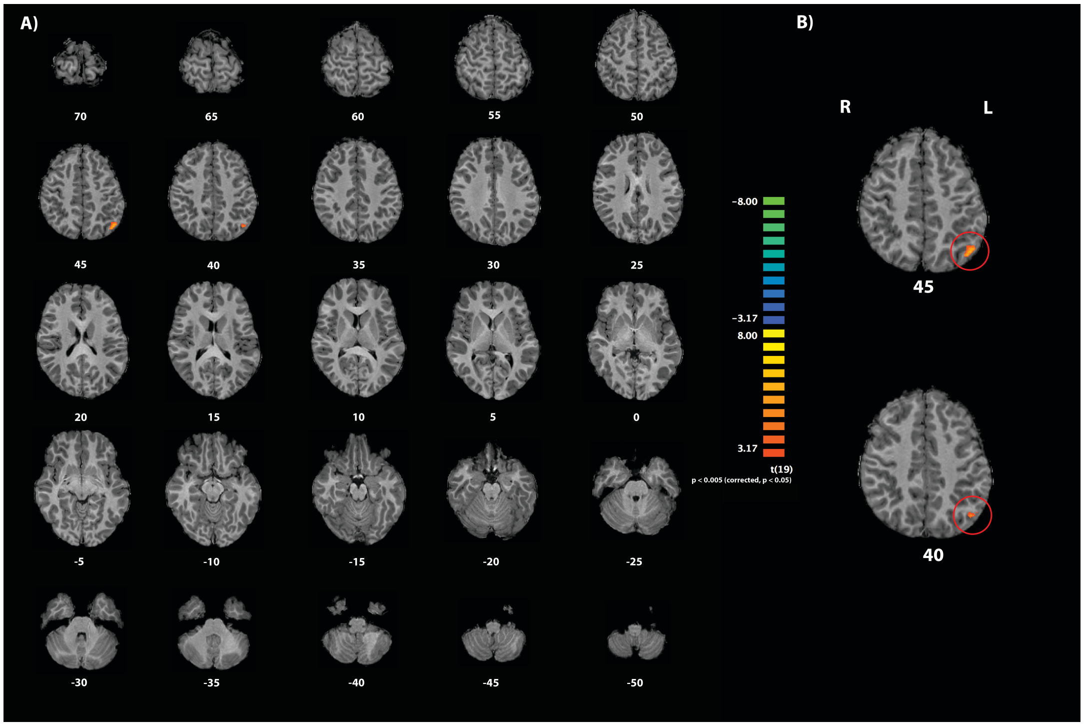

Figure 4.3: Activation map showing the significant correlation between age and the parametric effect in the left IPS.

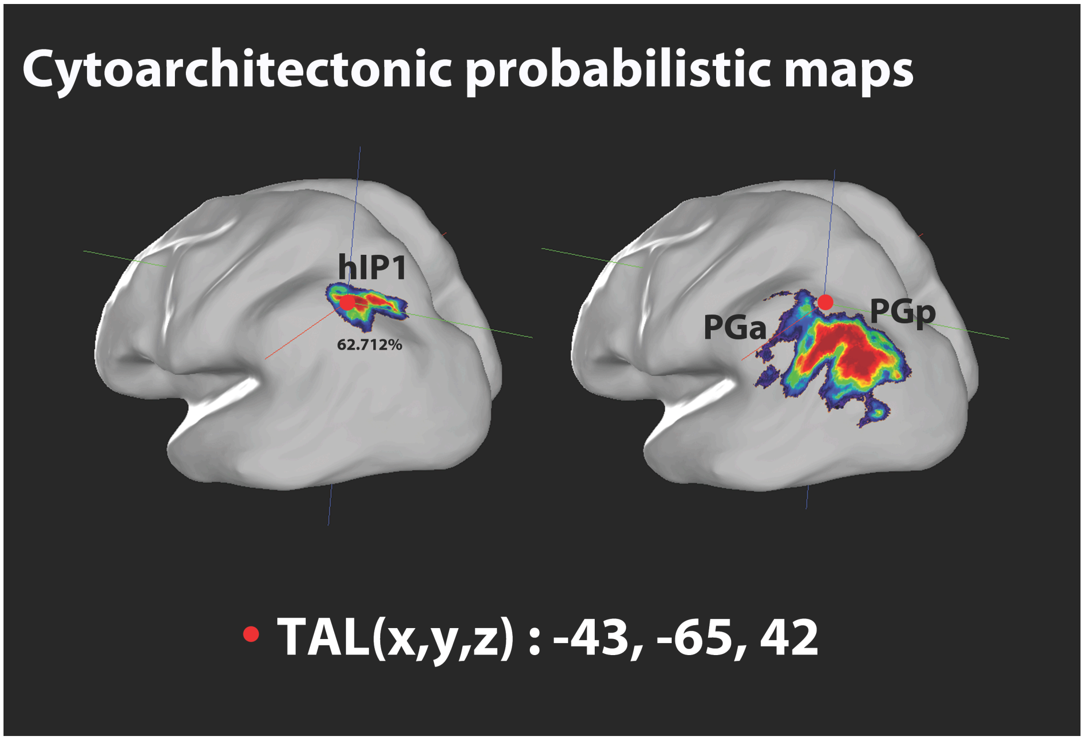

Figure 4.4: Cytoarchetectonic probabilistic maps identifying the anatomical location of the activation found in the left hemisphere of the parietal cortex.

4.4. Discussion

Over the past years a growing body of research has explored the neural principles underlying the representation of symbolic numerical magnitude in children and adults. Despite the great advances that have been made in the field, relatively little is currently know about the way the human brain represents symbolic numerical magnitudes over developmental time. The few developmental imaging studies that have explored changes in the cortical representation of number have implicated a functional shift in the underlying neural architecture from a greater reliance on prefrontal regions in children to a relatively greater reliance on parietal regions in adults (Ansari et al., 2005; Cantlon et al., 2009; Kaufmann et al., 2005, 2006). Evidence from these studies converges with a large body from the adult literature that has demonstrated that the intraparietal sulcus (IPS) of the parietal lobe is involved in processing the semantic meaning conveyed by number symbols such as the Arabic digits (Cohen Kadosh et al., 2008; Dehaene et al., 2003; Holloway et al., 2010; Pinel et al., 1999, 2001). This indicates a cortical specialization of the IPS for the processing of symbolic numerical magnitudes over developmental time. The majority of the evidence derived from developmental neuroimaging studies relies on active paradigms, such as number comparison, in which the brain activity associated with the processing of symbolic numerical magnitudes is contrasted between children and adults. A particularly difficult problem related to this account is the inherent presence of performance differences between different age groups (greater reaction time and lower accuracy in children compared to adults). These performance differences may greatly confound brain activations measured in paradigms in which participants are asked to decide, one stimulus over the other. As a consequence, interpretational inferences about developmental changes in brain activation are particularly difficult and caution is needed when associating changes in the neural architecture with changes in cognitive functioning. As such it is currently unclear whether developmental changes in brain activation relate to differences in the cortical representation of symbolic numerical magnitude per se, or alternatively, to non-numerical processes such as response selection.

The aim of the present functional Magnetic Resonance Imaging study was to overcome this problem and to investigate developmental changes in the cortical representation of symbolic numerical magnitude while minimizing the influences of non-numerical confounding variables. For this, an adjusted child friendly version of an fMR-A design (adopted from the study by Notebaert et al., 2011) was used. This paradigm was successfully tested in adults (reported in chapter 3 of the present thesis) and demonstrated that signal recovery of the IPS in adults is modulated by numerical ratio. In order to evaluate developmental changes related to the semantic processing of symbolic numerical magnitude while minimizing confounds of response selection, the brain signal of a group of children ranging from 6 to 14 years of age was deliberately attenuated to a specific symbolic numerical magnitude value (the number "*6*"). Numerical deviants differing in numerical ratio from the adaptation numeral "*6*" were randomly interspersed and the numerical ratio dependency - as an index of symbolic numerical magnitude processing – of the neural recovery signal was investigated.

Using a parametric regressor to predict numerical ratio dependent neural signal recovery effects in a whole brain analysis, demonstrated that the brain activation of the right IPS was significantly modulated by the presentation of numerical deviants across the entire age-range. In other words, the fit of the parametric regressor significantly predicted the neural activity in the right IPS independent of age. This finding is consistent with fMR-A studies in adults, which have demonstrated that the neural activity in regions of the IPS is modulated by symbolic numerical ratio (Holloway et al., 2012; Notebaert et al., 2011; see also the results of chapter 3 of this thesis), suggesting that the right IPS of children is engaged in representing symbolic numerical magnitudes. The finding of a numerical ratio dependent signal recovery in the right IPS across the entire group (the youngest participants were 6 years of age) suggests a relatively early, potentially with an onset before the age of 6, involvement of the right IPS for processing the semantic meaning of symbolic numerical magnitudes. Interestingly, there is emerging evidence from neuroimaging studies with young children and infants that have reported an early engagement of the right parietal lobe in response to non-symbolic numerical magnitudes (Cantlon, Brannon, Carter, & Pelphrey, 2006; Hyde, Boas, Blair, & Carey, 2010).

For instance, Hyde and colleagues (2010) used functional Near-infrared Spectroscopy to investigate the brain response of 6-month-old infants related to changes in non-symbolic numerical magnitudes. Specifically, using habituation the brain response of infants was adapted to the non-symbolic numerical magnitude "*16*" by presenting a sequence of images that contained different arrays of shapes. While controlling for confounding variables such as surface area and density, the adaptation period was randomly interrupted by the presentation of numerical deviants that contained either "*8*" or "*32*" items (i.e., a numerical ratio of 0.5 to the adaptation value). This systematic change in non-symbolic numerical magnitude allowed the authors to measure the brain response in relation to the presentation of numerical deviants. Focusing on parietal and occipital regions, results of this study showed that the brain signal of the right parietal lobe was significantly modulated by changes in non-symbolic numerical magnitude (i.e., numerical deviants elicited a larger Oxyhemoglobin concentration signal compared to the adaptation phase, indicating a neural signal recovery in response to the presentation of numerical deviants). In contrast, the left parietal lobe showed no such modulation in the brain signal in relation to the adaptation phase (baseline). This finding indicates that the neural activity of the right parietal lobe in 6-month-old infants is significantly modulated by changes in the numerical magnitude conveyed by non-symbolic numerical stimuli. Thus providing strong evidence that the right parietal lobe is involved in the discrimination of non-symbolic numerical magnitudes early on in life.

Consistent findings come from an fMR-A study, which demonstrated that the neural signal recovery of the IPS of very young children is modulated by changes in non-symbolic numerical magnitudes. More specifically, Cantlon and colleagues (2006) adapted the brain response of 4-year-old children and adults to images containing different arrays of "*16*" dots. Non-numerical dimensions were again carefully controlled. The continuous presentation of "*16*" dots was randomly interspersed with the presentation of numerical deviants containing "*8*" or "*32*" dots (i.e., ratio of 0.5 to the adaptation number). When analyzing the data the authors found significant evidence that the signal recovery in the right IPS in children is modulated by numerical ratio. This region of the right IPS overlapped topographically with a region that was found to be active in adults. Together with the finding from Hyde et al., (2010), these findings indicate that the right IPS is sensitive to non-symbolic numerical magnitude manipulation early on in life and that the neural signal recovery of the IPS is modulated by numerical ratio. The engagement of the right IPS in the present study might be therefore explained by an early engagement of a system that extracts rudimentary information about the numerical meaning that is conveyed by numerical symbols. In other words, the right IPS may responsible for an early mapping between a system that represents non-symbolic numerical magnitudes early on in life and a system that represents numerical symbols. However, since the present study did not directly investigate this association (symbolic and non-symbolic processing in children younger than 6) this argumentation remains speculative. To further elucidate this possibility direct empirical testing in young children using symbolic and non-symbolic numerical magnitude stimuli is needed.

In contrast to the age invariant numerical ratio dependent effect in the right IPS, a whole brain correlation analysis associating the numerical ratio dependent parametric regressor with age demonstrated a significant increase in the signal recovery effect in the IPS of the left hemisphere as a function of the children's chronological ages.

As such, this finding suggest a developmental change in the way the left IPS responds to the presentation of numerical deviants that differ in numerical ratio from the adaptation numeral "*6*". Numerical ratio dependent neural signal recovery effects in the IPS have been previously found in adult fMR-A studies, which have especially demonstrated a specificity with which the left IPS responds to symbolic numerical magnitudes in the absence of response selection (Holloway et al., 2012; Notebaert et al., 2011). However, the evidence reported in chapter 3 of the present thesis suggests otherwise since the specificity of the left IPS to represent symbolic numerical magnitudes was not replicated. As such, the issue of hemispheric specialization may be not as straightforward as has been suggested by earlier fMR-

A studies. Nevertheless, the findings of the present study extend the result of hemispheric specialization as it suggests that the functional reliance on left lateralized activation in the IPS may be an outcome of ontogenetic cortical specialization. Moreover, it indicates that the cortical representation of symbolic numerical magnitude may be driven by experience and that left-lateralized encoding of symbolic numerical magnitudes may become estranged from a right-lateralized representation of non-symbolic numerical magnitudes over developmental time (Lyons, Ansari, & Beilock, 2012). Experience dependent lateralization has been indicated in the study by Holloway et al. (2012) in which left IPS activation was found in response to familiar Arabic digits and right IPS activation in response to less familiar Chinese ideographs in a group of Chinese readers, indicating a potential hemispheric modulation in response to the experience with numerical notation formats. It is therefore possible that the developmental change observed in the current study is related to the experience children gain with the Arabic notation format. Thus, it should be considered that the observed developmental changes in this study might be in fact related to a continued refined understanding of the semantic information that is conveyed by numerical symbols. As such the acquisition of symbolic numerical magnitude could be argued to be a process that goes well beyond a simple mapping account between symbolic and non-symbolic representation, but rather encompasses the integration of other non-magnitude related dimensions such as ordinality (i.e., the knowledge that number 5 comes before the number 6 but after the number 4) in order to construct symbolic numerical knowledge (Lyons et al., 2012; Lyons & Beilock, 2011).

While previous developmental neuroimaging studies have found a consistent shift from frontal to parietal regions, the present study did not find a negative correlation between chronological age and the neural signal recovery effect in prefrontal regions of the brain. While the absence of an effect is difficult to interpret, this null result nevertheless may indicate that observed frontal activations may be less related to symbolic numerical magnitude processing, but rather to task-related activation differences between children and adults. This interpretation also underscores the problem of coarse group comparison between children and adults in developmental studies as well as the age heterogeneity within these groups. The cross-sectional approach of the present study in contrast allows for a more fine-grained evaluation of age dependent effects on brain activation and therefore draws a more accurate picture of the developmental trajectories associated with the representation of symbolic numerical magnitudes.

In addition, results about hemispheric differences in developmental studies have been quite inconsistent. This inconsistency might be due to the fact that most developmental imaging studies have used these coarse group comparisons in addition to active numerical paradigms, which in combination may have washed out consistent hemispheric developmental differences in the way the child brain represents symbolic numerical magnitude. Controlling for these variables may in fact draw a more refined picture of how the IPS of the two hemispheres interact in order to generate symbolic numerical magnitude understanding. However, more research is needed in order to test these possibilities and to further unravel the nature of symbolic numerical magnitude representation.

Overall, the results of the present study demonstrated that numerical ratio and age modulated the brain response in the left IPS. In addition, a region in the right parietal lobe was found to exhibit a stable and therefore age-independent numerical ratio dependent recovery effect across the entire sample. Together the findings of the present study provide evidence that that neural activity in the IPS of children is modulated by the mere presentation of numerical symbols and that its neural activity changes as a function of developmental time.

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Chapter 5: Final Discussion

5.1. Integration of the findings presented in this thesis

While there is accumulating evidence to suggest that a variety of different animal taxa, including non-human primates, birds, fish and amphibians, are able to approximate and differentiate non-symbolic numerical magnitudes (such as deciding which of two dot arrays is larger), the ability to use numerical symbols to represent numerical magnitudes (i.e., the total amount of items in a given set) is a unique human quality. Despite the relevance numeracy has in our modern societies, to date relatively little is known about the ways the human brain represents the semantic meaning of numerical symbols. Even less is known about how the child's brain represents symbolic numerical magnitudes and how the neural correlates of symbolic numerical magnitude representation change over developmental time. In order to further constrain our current understanding, I conducted a series of functional Magnetic Resonance Imaging (fMRI) studies in children and adults with the aim to investigate how the human cortex represents symbolic numerical magnitudes. The next sections will discuss the results of these functional imaging studies by relating them to our existing knowledge of how the human brain represents symbolic numerical magnitudes.

5.1.1.The neural correlates of symbolic numerical and non-numerical magnitudes.

A large body of research from neuropsychological case studies as well as from neuroimaging studies has provided converging evidence that the intraparietal sulcus (IPS) is a key region for processing and representing the semantic meaning (i.e., numerical magnitude) conveyed by numerical symbols (for reviews see Cohen Kadosh, Lammertyn, & Izard, 2008; Dehaene, Piazza, Pinel, & Cohen, 2003). In addition, there is increasing evidence that the IPS of the parietal lobe is not exclusively engaged in processing symbolic numerical magnitudes, but is also activated whenever non-numerical magnitudes such as brightness, space or time are estimated (for a discussion see Walsh, 2003). Some of the neuroimaging studies that have compared the neural correlates associated with the processing of symbolic numerical magnitudes to the neural correlates associated with the processing of non-numerical magnitudes have found commonalities as well as differences in the way the human cortex represents these different magnitudes. Specifically, there is growing evidence to suggest that the left IPS is involved in processing symbolic numerical magnitudes over and above common activations with non-numerical magnitude dimensions (Cohen Kadosh et al., 2005; Dormal, Andres, & Pesenti, 2008; Doraml, Dormal, Joassin, & Pesenti, 2012; Dormal & Pesenti, 2009; Pinel, Piazza, Le Bihan, & Dehaene, 2004).

The first study of the present thesis (reported in chapter 2) aimed to further constrain our current understanding related to the processing of symbolic numerical magnitudes by contrasting the neural correlates of symbolic numerical magnitudes and non-numerical magnitudes processing. To investigate this question, this study used fMRI to pit the brain activation associated with the mapping of symbolic numerical magnitudes into space against the brain activation associated with mapping non-numerical magnitudes (brightness) into space. Specifically, using a number line estimation task, a group of adult participants was asked to indicate the correct position of symbolic numerical magnitude probes (e.g., 45) and non-numerical brightness swatches (e.g., ■) on a spatially extended line (ranging from 0 to 100 in the numerical condition and from white to black in the non-numerical condition). Using this experimental paradigm, which has previously generated useful knowledge about the mental representation of symbolic numerical magnitudes in children and adults (e.g., Schneider, Grabner, & Paetsch, 2009; Siegler & Opfer, 2003), this study was well suited to further validate the generalizability of previous results that have shown commonalities and differences in the way the human brain represents symbolic numerical and non-numerical magnitudes. Moreover, the number line estimation task was well suited to investigate which regions of the brain are specifically linked (i.e., over and above other non-numerical magnitudes) to the processing of symbolic numerical magnitude. As predicted, the results of this fMRI study demonstrated differences as well as commonalities in the way the human cortex estimates symbolic numerical and non-numerical magnitudes. Consistent with other findings the result of this study showed that the estimation of symbolic numerical magnitudes as well as the estimation of non-numerical magnitudes co-activated large portions of the right IPS within the parietal lobe. This finding suggests that a common network of the right parietal lobe is devoted to the processing of different magnitude dimensions. While it is possible that the overlapping activations in the right IPS are based on common underlying neural mechanisms, the present work cannot fully exclude the possibility that differences between these tasks were not detected with the performed statistical analysis. In order to test such a possibility additional multivariate analysis such as Multi-Voxel-Pattern Analysis (MVPA) might be useful in the future to further investigate potential differences on the level of representational patterns. For instance, in a recent study Fias, Lammertyn, Caessens and Orban (2007) asked participants in three tasks to decide which of two simultaneously presented numerals is larger, which of two simultaneously presented letters comes later in the alphabet, and which of two simultaneously presented coloured square was most saturated. Results of this imaging study revealed brain responses in regions of the bilateral anterior IPS in the number and letter task, but not for the saturation task. Thus, the results of this study suggested that similar regions in the brain respond to the comparison of discrete dimensions regardless of the format. However, using the same dataset and a multivariate approach (i.e., Multi-Voxel-Pattern Analysis (MVPA), using a support vector machine) in order to further investigate representational similarities or differences between these dimensions, Zorzi, Di Bono and Fias (2011) demonstrated that distinct sets of voxel discriminate between numerical and non-numerical categories within the anterior IPS.

Moreover, besides the common right lateralized activation of the parietal lobe additional number specific activations were found in bilateral regions of the anterior IPS. These regions were significantly more activated in the symbolic numerical magnitude condition compared to the non-numerical magnitude condition and the control condition. The additional greater engagement of the left anterior IPS for estimating the correct position of symbolic numerical magnitudes compared to estimating the position of non-numerical magnitudes indicates that the left IPS of the parietal cortex is devoted to the processing of symbolic numerical magnitudes. This finding is consistent with previous data, which have shown that the left IPS is modulated in response to the presentation of symbolic numerical magnitudes in the absence of response selection (Holloway, Battista, Vogel, & Ansari, 2012; Notebaert, Nelis, & Reynvoet, 2011). As such, the present findings further highlight the special role of the left IPS in processing symbolic numerical magnitudes and point towards the special role symbolic numerical magnitudes constitute amongst other magnitude dimensions. Consequently, the study further constrains our current understanding of how the human brain represents symbolic numerical magnitudes by demonstrating that similar and distinct brain regions of the parietal lobe are devoted to the processing of symbolic numerical and non-numerical magnitudes and that these findings are generalizable across different experimental designs, indicating that observed brain activations are not task specific but rather denote an inherent property of how the human brain processes numerical and non-numerical magnitude dimensions.

5.1.2.Probing symbolic numerical magnitude representation in adults

Consistent with previous neuroimaging findings the first study of the present thesis demonstrated a special role of the anterior IPS in processing symbolic numerical magnitudes in adults. As indicated by this study, the left IPS may play a crucial role in representing symbolic numerical magnitudes over and above the processing of non-numerical magnitudes. Converging with this finding are recent results from functional Magnetic Resonance Adaptation (fMR-A) studies that investigated the cortical specialization of symbolic numerical magnitude representation in adults. These studies have demonstrated that the neural signal recovery of the left IPS following adaptation is significantly modulated by numerical ratio in the absence of response selection (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Holloway et al., 2012; Naccache & Dehaene, 2001; Notebaert et al., 2011; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Piazza, Pinel, Le Bihan & Dehaene, 2007). Therefore, indicating that the semantic meaning of numerical symbols modulates the neural activity of the left IPS. This raises an interesting question: How do regions of the human cortex, especially the left IPS, become specialized for the representation of symbolic numerical magnitudes? One possibility is that the acquisition of symbolic numerical magnitude knowledge shapes the way the human brain represents the semantics of numerical symbols and that experience is an important factor. A way to test this prediction is to take a developmental approach. In order to reach this goal the second study of this thesis aimed to pilot an adjusted child friendly fMR-A design (adopted from Notebaert et al., 2011) and to replicate previous findings that have indicated that the neural signal recovery of the left IPS is modulated by numerical ratio in adults (Holloway et al., 2012; Notebaert et al., 2011). As such, this study aimed to further examine the reliability of previous findings which have demonstrated hemispheric differences in the way the adult brain represents symbolic numerical magnitudes, thus, demonstrating that the paradigm is suitable for investigating developmental changes in children.

Moreover, the second aim of this study was to extend our current knowledge of symbolic numerical magnitude representation in the human brain by probing different methodological approaches in brain normalization procedures. To do so, the brain responses of adult participants were habituated to the Arabic digit "*6*" and numerical ratio dependent brain signal recovery effects in response to the presentation of numerical deviants were investigated. Results of this study demonstrated that the mere presentation of numerical ratio dependent deviants modulated the neural signal recovery of bilateral regions of the IPS. As such the paradigm was successful in replicating previous fMR-A studies that have demonstrated numerical ratio dependent adaptation effects in regions of the IPS in adults (Cohen Kadosh et al., 2007; Holloway et al., 2012; Naccache & Dehaene, 2001; Notebaert et al., 2011; Piazza et al., 2004, 2007). The replication of these findings is crucial since only a handful of neuroimaging studies have investigated symbolic numerical magnitude processing using fMRI adaptation thus far. Results of the present study suggest that the numerical ratio dependent modulation of the neural recovery signal in the IPS is a robust effect and can be replicated in different laboratories with different experimental variations.

However, in contrast to previous fMR-A studies which have indicated a high specificity of the left IPS to represent symbolic numerical magnitudes (Holloway et al., 2012; Notebaert et al., 2011), the present data showed bilateral signal recovery effects in the IPS. Therefore, the findings of this study do not support the results of an exclusive left lateralized specialization of the IPS for representing symbolic numerical magnitudes. This indicates that observed lateralization effects revealed in adults might in fact be more complicated than suggested by these previous studies.

Moreover, we analysed the functional imaging data with two different brain normalization procedures – Talairach based and Cortex Based Alignment (CBA). Both procedures yielded similar results, however, the activations in CBA were more strongly restricted to bilateral regions of the parietal lobe. This result indicates that activations found in the IPS are robust and can be generalized over different methods for the normalization of brain structures across participants.

Taken together, the second study of the present thesis was successful in testing a child friendly fMR-A paradigm by showing that the neural signal recovery of the IPS is significantly modulated by numerical ratio in the absence of response selection. However, the issue of IPS lateralization may in fact be more complicated as indicated by previous fMR-A work and more studies are needed to further constrain this question. A developmental approach may be particularly useful in order to shed light on brain lateralization of symbolic number representation.

5.1.3.Developmental changes in the cortical representation of number

While there is substantial evidence from the adult literature that the IPS is involved in representing symbolic numerical magnitudes (Cohen Kadosh et al., 2008; Dehaene et al., 2003), considerably less is currently known about the ways the child brain represents symbolic numerical magnitude and how such representations change over the course of development. The majority of the small body of existent developmental neuroimaging has found an age related shift in the underlying neural architecture from prefrontal regions in children to parietal regions, especially the IPS in adults (Ansari & Dhital, 2006; Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon, 2009; Kaufmann et al., 2005, 2006). While these studies have provided important information about functional changes in the underlying neural architecture, the interpretation of these findings has remained problematic. Specifically, neuroimaging studies in adults have provided convincing evidence to suggest that the neural activity of the IPS in active tasks (such as number comparison) may not be related to numerical processes per se but rather be explained by response selection processes (Göbel, Johansen-Berg, Behrens, & Rushworth, 2004; Göbel & Rushworth, 2004). In developmental studies this confound in active tasks poses a particularly serious problem since developmental data are inherently confounded by age related performance differences. Developmental differences between age groups may therefore be explained by differences in performance rather than developmental changes in the underlying representation of symbolic numerical magnitudes.

In order to tackle this issue, study 3 of the present thesis aimed to investigate the representation of symbolic numerical magnitude over developmental time while minimizing confounding variables such as response selection and performance differences. In addition, developmental studies that have investigated the processing of symbolic numerical magnitude representation have reported mixed findings about the lateralization of representing the semantics of numerical symbols. This divergence in results may be a result of different mechanisms related to different experimental tasks in which participants engage in active decision making processes. As such the use of fMR-A, successfully implemented in chapter 3, may provide new insights into the way the human cortex specializes for the representation of symbolic numerical magnitude.

Using the child friendly fMR-A paradigm piloted in chapter 3, the brain response of children ranging from 6 to 14 years of age was habituated to the symbolic numerical magnitude "*6*". The adaptation sequence was randomly interspersed by the presentation of numerical deviants that differed in numerical ratio from the adaptation number. When analyzing the data, two major results were obtained through this study. First, the right IPS showed an age-independent numerical ratio dependent signal recovery effect in response to the presentation of numerical deviants across the entire group. Second, the left IPS showed a significant correlation between the symbolic numerical signal recovery effect and age.

These finding highlight some important aspects related to the development of cortical representations of symbolic numerical magnitudes. The first finding demonstrated that a region of the right IPS was consistently activated across the entire group, indicating the potential onset of this region before the age of 6 (the youngest children tested in the present study). This might not be surprising given that children in most countries learn the meaning of symbolic numerical magnitudes before the start of formal education. Interestingly, some evidence with infants and young children has demonstrated that the neural activity of the right IPS is sensitive to manipulations of non-symbolic numerical magnitudes early on in life (Cantlon, Brannon, Carter, & Pelphrey, 2006; Hyde, Boas, Blair, & Carey, 2010).

For instance, one of these studies provided evidence to suggest that the neural activity of the right parietal lobe of 6-month-old infants is modulated when non-symbolic numerical deviants are presented after a phase of adaptation (Hyde et al., 2010). While speculative, the findings of the present study may converge with these findings to suggest that the right IPS may be involved in an early mapping process of non-symbolic and symbolic numerical magnitudes. This early mapping may provide an initial scaffold for understanding the semantic meaning of numerical symbols on which additional symbolic numerical information may build.

In contrast to the stable activation of the right IPS, the activity of the left IPS was found to increase with age. This finding converges with findings from the adult literature that has shown similar left IPS activation in fMR-A designs, which are almost identical to the paradigm used in the present study (Holloway et al., 2012; Notebaert et al., 2011). As such, this finding suggests that the left IPS becomes increasingly engaged in representing symbolic numerical magnitudes over developmental time. This additional modulation of the left IPS may indicate an ongoing refinement in the way the human brain represents symbolic numerical information. One possibility is that the representation of symbolic numerical magnitudes goes well beyond the simple mapping between non-symbolic numerical magnitudes and symbolic numerical magnitudes and integrates other numerical information dimensions such as ordinality into a complex representation of numerical symbols. Supporting evidence comes from an increasing body of literature that suggests that the ordinal relationship between numerals is a critical aspect of symbolic numerical knowledge and that ordinality may be an important predictor for symbolic numerical representation in the brain (Franklin & Jonides, 2009; Lyons, Ansari, & Beilock, 2012; Lyons & Beilock, 2011; Turconi, Campbell, & Seron, 2006; Turconi, Jemel, Rossion, & Seron, 2004; Vogel, Remark, & Ansari, 2013).

Another observation deserves some discussion. The present developmental fMR-A study did not reveal a negative correlation between age and activation of the prefrontal cortex as may have been predicted by other developmental studies (Ansari et al., 2005; Cantlon et al., 2009; Kaufmann et al., 2006). In other words, while the present study demonstrated developmental changes in parietal regions of the brain no such changes were observed in regions of the prefrontal cortex. This is surprising given that the most consistent finding in the developmental literature has demonstrated a fronto-parietal shift in relation to the processing of symbolic numerical magnitudes. While null results are difficult to interpret, the result may nevertheless bear some food for additional thoughts. It may well be the case that prefrontal regions of the brain do in fact not play as much of a significant functional role for symbolic numerical magnitude representation as has been suggested by some authors (Cantlon, 2012; Andreas Nieder & Dehaene, 2009), but rather displays functions of domain general mechanisms associated with working memory or cognitive control which are typically associated with activations in the prefrontal cortex (Baddeley, 2003; D'Esposito et al., 1995; Miller & Cohen, 2001). The frontal engagement in developmental studies may therefore by an artefact of task general cognitive operations that are bound to be present in active tasks in which participants are asked to make decision choices. The data of the present study indicate that developmental changes in relation to the semantic representation of symbolic numerical magnitudes are highly restricted to the parietal lobe, especially the left IPS and that therefore the prefrontal lobe may not play a critical role in representing or associating symbolic numerical magnitudes.

Together, the data of this study indicate a complex developmental interplay between the right and left IPS to represent symbolic numerical magnitudes in the human brain. This may be achieved by the integration of different symbolic information such as an understanding of ordinal relationships, non-symbolic numerical magnitudes and others. In addition, the data indicate that the cortical representation of symbolic numerical magnitude specializes over developmental time and that this specialization may be the foundation for number expertise.

5.1.4.Final remarks

In the present doctoral thesis I aimed to further constrain our current knowledge about how the human brain represents symbolic numerical magnitudes. A series of functional imaging studies in children and adults demonstrated that symbolic numerical magnitude is a special category amongst other magnitude dimensions and that specific cortical regions of the human brain become increasingly specialized to represent symbolic numerical magnitudes over developmental time. Experience is a potential candidate that may drive this cortical specialization and the fact that symbolic numerical knowledge is acquired over cultural transmission makes this explanation very powerful. Studying the brain reveals the structural and functional plastic nature of this organ to change with experience and training (Dehaene & Cohen, 2007; Gao, van Beugen, & De Zeeuw, 2012; Johnson, 2001; Lövdén, Wenger, Mårtensson, Lindenberger, & Bäckman, 2013; Steele, Bailey, Zatorre, & Penhune, 2013), revealing that the brain is consistently adapting to environmental needs. Because of this complexity there are many open and challenging questions that need to be addressed in order to understand the nature of symbolic knowledge acquisition and its instantiation in the human brain. The present work provides a small window into this fascinating topic and has added another puzzle piece in order to unravel the representation of symbolic numerical magnitudes in the human brain.

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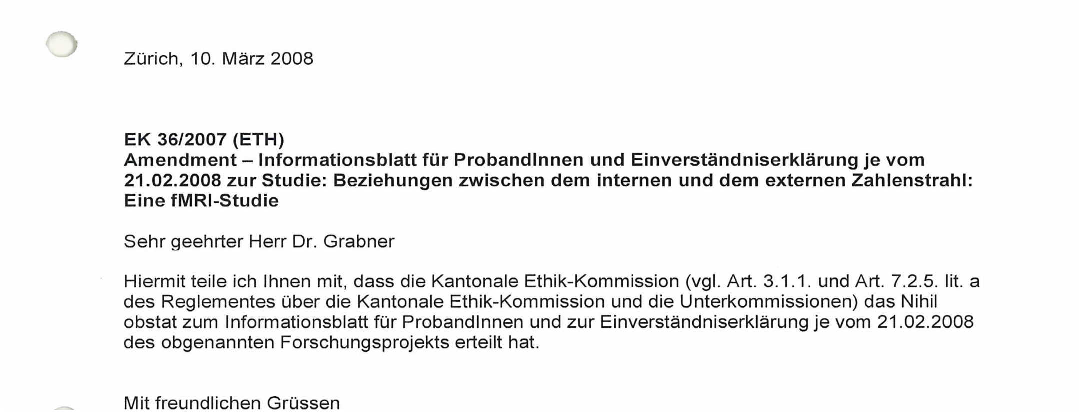
Appendices

Appendix A: Documentation of ethics approval



Zürich, 10. März 2008

EK 36/2007 (ETH)
Amendment – Informationsblatt für ProbandInnen und Einverständniserklärung je vom 21.02.2008 zur Studie: Beziehungen zwischen dem internen und dem externen Zahlenstrahl: Eine fMRI-Studie

Sehr geehrter Herr Dr. Grabner

Hiermit teile ich Ihnen mit, dass die Kantonale Ethik-Kommission (vgl. Art. 3.1.1. und Art. 7.2.5. lit. a des Reglementes über die Kantonale Ethik-Kommission und die Unterkommissionen) das Nihil obstat zum Informationsblatt für ProbandInnen und zur Einverständniserklärung je vom 21.02.2008 des obgenannten Forschungsprojekts erteilt hat.

Mit freundlichen Grüssen

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: Psychology, University of Western Ontario
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: August 17, 2011 **Expiry Date:** April 30, 2013
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised UWO Protocol	Revised objectives and hypothesis, Revised methodology,Revsied references, Revised study instruments	
Letter of Information & Consent	Adult participant	2011/08/09
Revised Letter of Information & Consent	Parent/Guardian	2011/08/09
Assent		2011/08/09
Addition of Co-investigator	L. van Eimeren has been removed as a co-investigator for this study and S. Vogel has been added as co-investigator.	

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.

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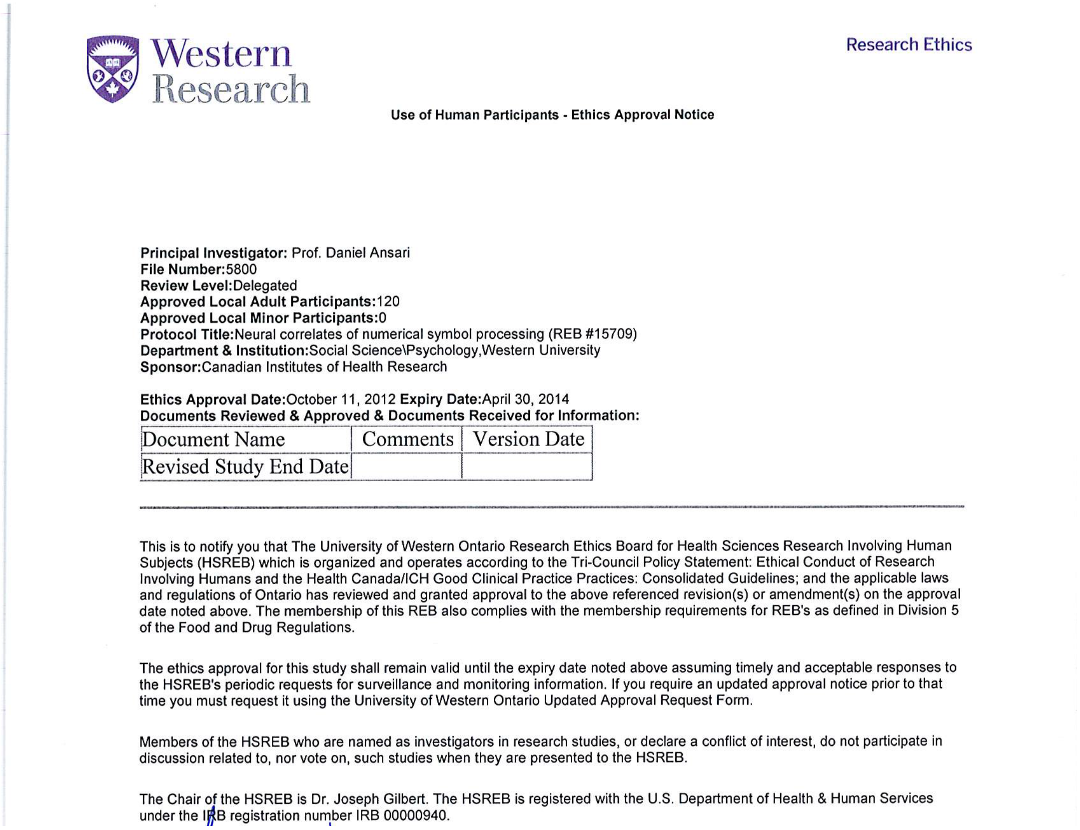

Western Research

Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Prof. Daniel Ansari
File Number:5800
Review Level: Delegated
Approved Local Adult Participants:120
Approved Local Minor Participants:0
Protocol Title: Neural correlates of numerical symbol processing (REB #15709)
Department & Institution: Social Science\Psychology,Western University
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: October 11, 2012 **Expiry Date:**April 30, 2014
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Study End Date		

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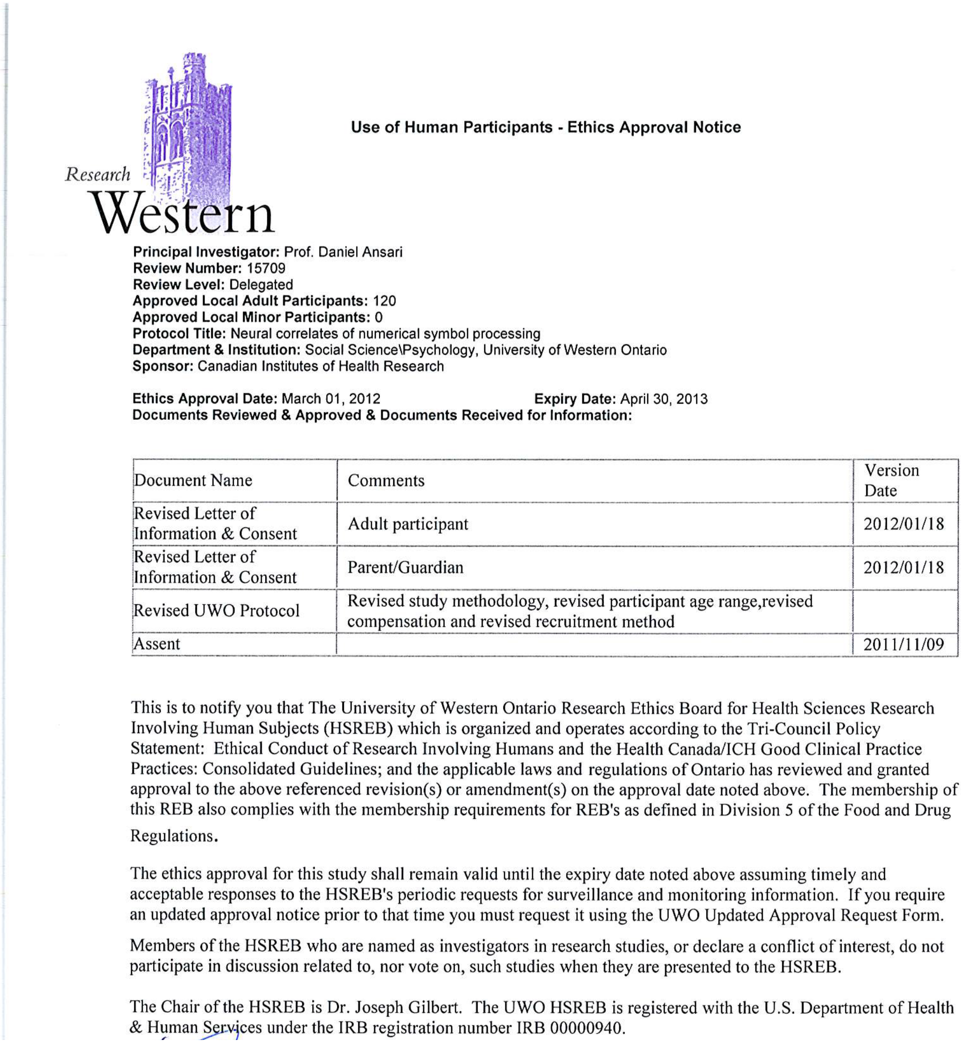

Research Western

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.

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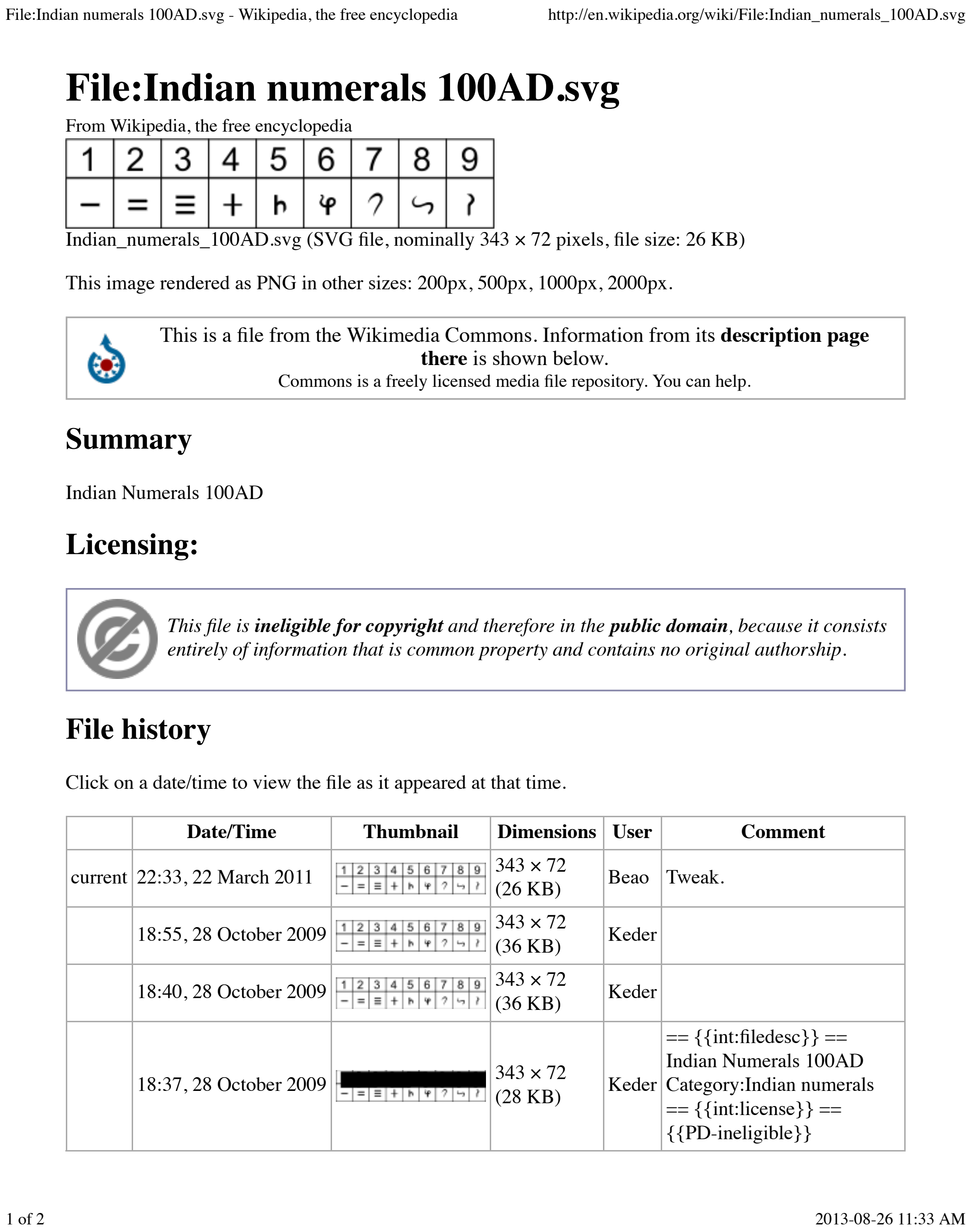

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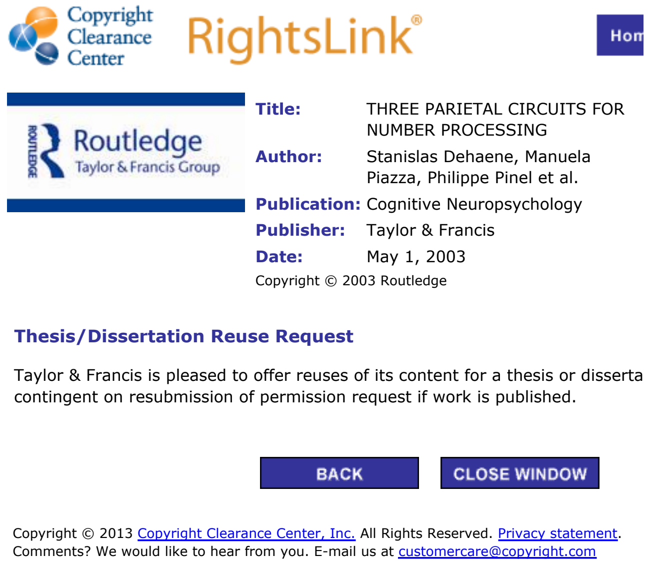

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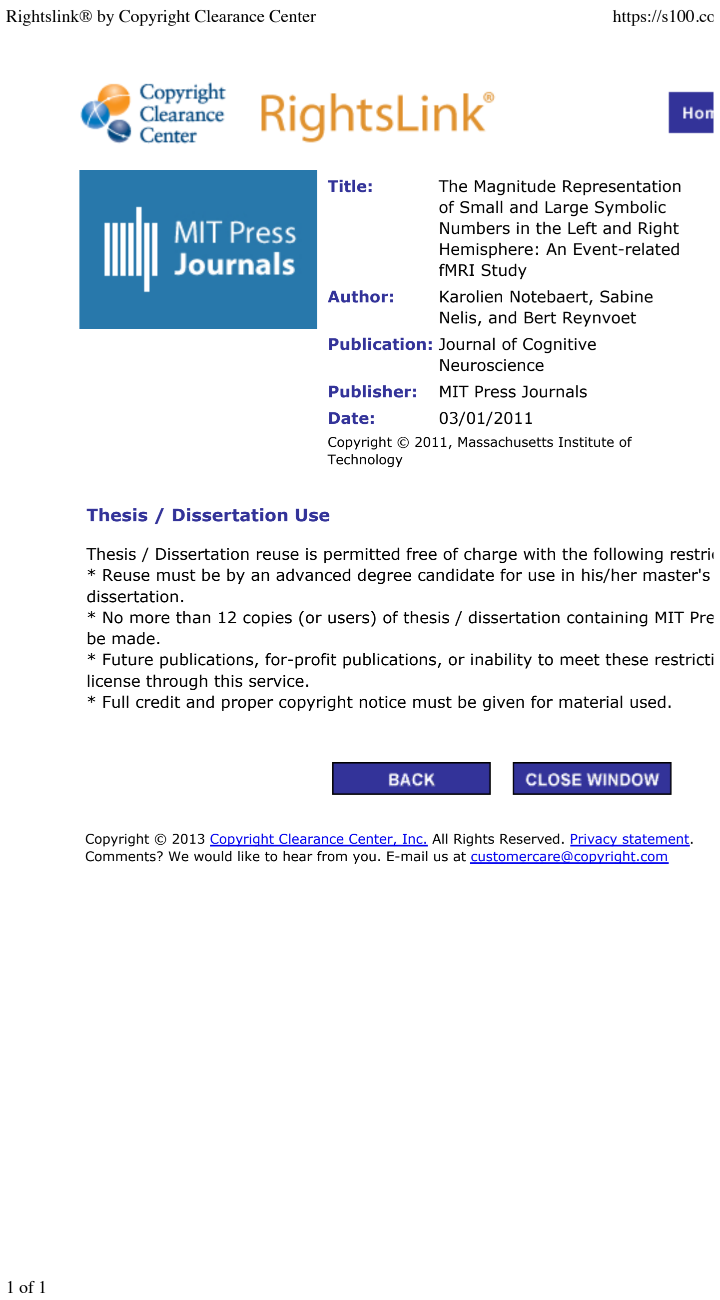

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CURRICULUM VITAE

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European Association for Research on Learning and Instruction (EARLI) Advanced study colloquium, Bruegge, Belgium

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Ontario Graduate Scholarship (OGS)

2011-2012
Ontario Graduate Scholarship (OGS)

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Summer Institute in Cognitive Neuroscience 2011
University of California, Santa, Barbara, U.S.A.

Februrary 2007
Fellow
Spring School Neurosensory and Cognitive Science in the North 2007
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REFFEREED PUBLICATIONS

Vogel, S. E., Grabner, R. H., Schneider, M., Siegler, R. S., & Ansari, D. (2013). Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study. *Neuropsychologia, 51(5), 979–89.*

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Holloway, I. D., Battista, C., **Vogel, S. E.,** & Ansari, D. (2012). Sematic and Perceptual Processing of Number Symbols: Evidence from a Cross-linguistic fMRI Adaptation Sudy. *Jouranl of Cognitive Neuroscience*, *25*(3), 388–400.

Kaufmann, L., **Vogel, S. E.,** Starke, M., Kremser, C., Schocke, M., & Wood, G. (2009). Developmental dyscalculia: compensatory mechanisms in left intraparietal regions in response to nonsymbolic magnitudes. *Behavioral and brain functions : BBF*, *5*, 35.

Kaufmann, L., **Vogel, S. E.,** Starke, M., Kremser, C., & Schocke, M. (2009). Numerical and non-numerical ordinality processing in children with and without developmental dyscalculia: Evidence from fMRI. *Cognitive Development*, *24*(4), 486–494.

Kaufmann, L., **Vogel, S. E.,** Wood, G., Kremser, C., Schocke, M., Zimmerhackl, L.-B., & Koten, J. W. (2008). A developmental fMRI study of nonsymbolic numerical and spatial processing. *Cortex; a journal devoted to the study of the nervous system and behavior*, *44*(4), 376–85.

Kaufmann, L., Ischebeck, A., Weiss, E., Koppelstaetter, F., Siedentopf, C., **Vogel, S. E.,** Gotwald, T., et al. (2008). An fMRI study of the numerical Stroop task in individuals with and without minimal cognitive impairment. *Cortex; a journal devoted to the study of the nervous system and behavior*, *44*(9), 1248–55.

BOOK CHAPTER

Ansari, D., & **Vogel, S.E.** (in press). Cognitive neuroscience of numerical cognition. *In Oxford Handbook of Cognitive Neuroscience (eds. S. Kosslyn & K. Ochsner).*

CONFERENCE ABSTRACTS

Oral Presentations:

Vogel, S.E., Starke, M., & Kaufmann, L. (2008). Neural correlates of ordinality and subtraction in children and adults. *International Society for the Study of Behavioural Development (ISSBD), Würzburg, Germany.*

Vogel, S.E., & Kaufmann, L. (2008). Functional overlap between numerical and spatial magnitude. *The 50th Meeting of the German Psychological Society for Experimental Psychology, Marburg, Germany.*

Vogel, S.E., Starke, M., & Sachse, P. (2006). Informationsaufnahme bei redundanter Nachrichtenberichterstattung. *The 48th Meeting of the German Psychological Society for Experimental Psychology, Mainz, Germany.*

Poster Presentation:

Vogel, S.E., & Ansari, D. (2012). Developmental changes in the brain mechanisms underlying the semantic processing of numerical symbols. *European Association for Research on Learning and Instruction (EARLI), London, U.K.*

Vogel, S.E., Grabner R., Schneider M., Siegler, R., & Ansari, D. (2012). The neural correlates of mapping numerical and non-numerical quantities into space. *Cognitive Neuroscience Society (CNS), Chicago, U.S.A.*

Vogel, S.E., G.R. Price, J. Halberda, R. Ly, and D. Ansari (2011). Cerebral correlates of non-symbolic numerical magnitude processing: the role of surface area. *Human Brain Mapping (HBM), Quebec City, Canada.*

Vogel, S.E., & Kaufmann, L. (2010). Developmental trajectories of numerical and non-numerical processing in the brain: An fMRI study! *Cognitive Neuroscience Society (CNS), Montreal, Canada.*

Starke, M., **Vogel, S.E.,** & Kaufmann, L. (2009). Neural correlates of ordinality processing and simple subtraction in developmental dyscalculia. *The European Workshop on Cognitive Neuropsychology, Bressanone, Italy.*

Vogel, S.E., & Kaufmann, L. (2008). What is special about numerical ordinality? Evidence from fMRI. *Second annual workshop on Concepts, Actions, and Objects, Rovereto, Italy.*

Vogel, S.E., Starke, M., & Kaufmann, L. (2008). Numerische und physische Größenverarbeitung: Eine fMRT Studie. *Gesellschaft für Neuropsychologie (GNP), Tübingen, Germany.*

Vogel, S. E., Starke, M., & Sachse, P. (2006). Textleisten in Nachrichtensendungen: Distractor oder Informationsstütze? *The 45th Meeting of the German PsychologicalSociety for Experimental Psychology, Nürnberg, Germany.*

INVITED TALKS

Vogel, S.E. (2012). Neural correlates of numerical symbol processing in children and adults. *Colloquium talk, Georg-August-University of Göttingen, Germany*

Vogel, S.E. (2009). Introduction to Functional Magnetic Resonance Imaging. *Invited lecture for the course "Biological Psychology II," University of Innsbruck, Austria.*

Vogel, S.E., M. Starke and L. Kaufmann **(2008).** Numerical and non-numerical ordinality processing in children and adults. *Invited talk, The University of Western Ontario, Canada.*

Vogel, S.E. (2008). Introduction to Functional Magnetic Resonance Imaging. *Invited lecture for the course "Introduction to Psychological Diagnoses," University of Tübingen, Germany.*

Vogel, S.E. (2008). Introduction to Functional Magnetic Resonance Imaging. *Invited lecture for the course "Biological Psychology II," University of Innsbruck, Austria.*

Kaufmann, L., **Vogel, S.E.,** & Starke, M. (2008). fMRI with children and its application in the field of numerical cognition. *Invited talk at the "Radiology Retraining," Medical University of Innsbruck, Austria*

TEACHING

Seminar

Term: Winter 2013
Course title: “Pädagogisch-psychologische Diagnostik und Beratung A”
Course number: B.Psy.801 (630982)
University: Georg-August-University Göttingen, Germany

Term: Winter 2013
Course title: “Psychologie des Lernens und Lehrens A”
Course number: M.BW.200 (631511)
University: Georg-August-University Göttingen, Germany

*Term***:** Winter 2013
Course title: “Psychologie des Lernens und Lehrens C”
Course number: M.BW.200 (631508)
University: Georg-August-University Göttingen, Germany

Term: Winter 2010
Course title: “Methodik und spezielle Kapitel der fMRT Applikation”
Course number: 720292
University: Leopold-Franzens-University Innsbruck, Austria

Graduate Teaching Assistant

Term: Winter 2013
Course title: “Mind, Brain and Education”
Course number: Psych3442G-001
University: The University of Western Ontario, Canada

Term: Winter 2012
Course title: “Exceptional Children: Behavioural Disorders”
Course number: Psych2042B-001
University: The University of Western Ontario, Canada

Term: Fall 2011
Course title: “Development of the Mathematical Brain”
Course number: Psych3443F-001
University: The University of Western Ontario, Canada

Term: Winter 2011
Course title: “Introduction to Psychology”
Course number: Psych1000-004
University: The University of Western Ontario, Canada

Term: Fall 2010
Course title: "Mind, Brain and Education"
Course number: Psych3442F-001
University: The University of Western Ontario, Canada
Term: Winter 2010
Course title: "Developmental Cognitive Neuroscience"
Course number: Psych3340G-001
University: The University of Western Ontario, Canada

Term: Fall 2009
Course title: "Developmental of the Mathematical Brain"
Course number: Psych3443F-001
University: The University of Western Ontario, Canada

Supervision

Senior Honors Thesis 2012, entitled "Reliability and Convergent Validity of the Numerical Distance Effect and Priming Distance Effect", awarded the UWO McClelland Award for the best 4th – year honors thesis 2012.

Senior Honors Thesis 2010 entitled "Numerical Magnitude and Order Representations in 1st and 2nd Grade Children" . Student went on to complete graduate work at University College London, UK.

SCIENTIFIC SERVICES

Committee:
Abstract Committee for Human Brain Mapping (HBM) in 2011.

Review Journal Articles:
Mind, Brain and Education

NON-SCIENTIFIC ACADEMIC ACTIVITIES

Organizing Committee of the “Developmental Brown Bag Series 2011/12 “ in the Department of Developmental Psychology at the University of Western Ontario, Canada

President and vice-president of the student union at the University of Innsbruck, Austria – elected for 2 years (2005 - 2007)