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How does the brain represent digits? Investigating the neural correlates of symbolic number representation using fMRI-Adaptation

Celia Goffin, *The University of Western Ontario*

Supervisor: Ansari, Daniel, *The University of Western Ontario*

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Abstract

How does the brain represent numerical symbols (e.g., Arabic digits)? Activity in left parietal regions correlates with symbolic number processing. Research with functional resonance imaging adaptation (fMRI-A) indicates that the intraparietal sulcus (IPS) exhibits a rebound (increase in activation) effect when a repeatedly presented number is followed by a new number. Importantly, this rebound effect is modulated by numerical ratio as well as the difference between presented numbers (distance). This ratio-dependent rebound effect could reflect a link between symbolic numerical representation and an approximate number system (ANS). In this doctoral dissertation, fMRI-A is used to investigate mechanisms underlying symbolic number representation.

The first study investigates an alternative to the ANS hypothesis of symbolic number representation: could the positional relations between ordered symbols (e.g., letters, numbers) explain activity observed in the parietal cortex for number symbols? The predicted distance-dependent rebound effect is exhibited in bilateral IPS for number symbols. This effect is not found for letters (which, like numbers, can be represented using an ordered sequence – the alphabet). The contrast between numbers and letters reveals greater activity for numbers in the left inferior parietal lobule. The hypothesis that general ordinal mechanisms underpin neural parametric recovery in the IPS is not supported.

What does the development of symbolic number representation look like in the brain? In the second study, I replicate Vogel et al. (2015; n=19) with a larger sample (n=45) of 6-14-year-olds. While Vogel et al. found a correlation between age and the ratio-dependent rebound effect in the left IPS, my data suggest an age-invariant, ratio-dependent rebound effect in bilateral IPS. Therefore, findings from Vogel et al. were not replicated.

The final study asks: does handedness of participants play a role in the neural lateralization of symbolic number representation? Right-handers demonstrate the predicted left-lateralized rebound effect within the IPS. When left- and right-handed groups are compared, results do not suggest group differences in laterality. These findings do not support the hypothesis that handedness plays a role in neural lateralization of symbolic number processing.

Results from these studies are discussed in terms of theoretical implications for symbolic numerical representations in the brain.

Keywords

Symbolic number, number representation, intraparietal sulcus, numerical cognition, functional magnetic resonance imaging, adaptation, development

Summary for Lay Audience

Representing numerical information symbolically (e.g., with Arabic digits) is integral to modern society. Learning to understand number symbols involves learning the digit ‘3’ means 3 items (e.g., •••). This understanding is a necessary step towards learning more complex math. The use of number symbols is too recent an invention for our brains to have been evolved for this function. So how does the human brain learn to represent numerical symbols?

Using functional magnetic resonance imaging (fMRI), we can measure brain activity while people look at numbers. Research using fMRI has found that part of the brain, the intraparietal sulcus (IPS), is of particular importance for representing numbers. However, there are many outstanding questions surrounding the mechanisms underlying symbolic number representation. In this thesis, fMRI was used to address some of these outstanding questions.

In the first study, we examined whether brain activity looked similar for number symbols and letters. We found that letters and numbers did not display the same patterns of activity in the brain. However, a follow-up study where participants completed computer tasks outside of the MRI indicated that letters and numbers did show similar patterns in response time data.

The second study examined how children develop an understanding of number symbols. Children ages 6-to-14 looked at symbolic numbers using fMRI. We found that children demonstrated a similar pattern of activity in the IPS across the entire age group. This response was similar to that observed in previous studies with adults.

In the last study, we were interested in whether, through practicing to write numbers, the handedness of people may be related to how numbers are represented in the brain. Typically, in neuroimaging research, left-handed people are excluded from participating in order to reduce the noisiness of the data. We compared brain activity in response to number symbols in a group of left-handed participants to right-handed participants. Handedness of participants was not found to be related to brain activity for number symbols.

This research helps us to better understand how, over the course of learning and development the brain comes to be able to understand number symbols.

Co-Authorship Statement

This doctoral thesis was completed under the guidance of my supervisor Dr. Daniel Ansari. Dr. Ansari contributed to the conception and design of all studies, the interpretation of the data, and preparation and revision of each chapter. In Chapters 2 and 3, Dr. Stephan Vogel contributed to the design, data analysis and interpretation, as well as the revision of the manuscript. H. Moriah Sokolowski made valuable contributions to the conception, design, data analysis and revision of Chapter 4. Michael Slipenkyj provided important contributions to data collection and analysis for all empirical chapters. I hereby acknowledge that the present thesis represents my own work, however it should be noted that all above-mentioned parties provided valuable contributions in the completion of this dissertation.

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Chapter 1

1 General Introduction

1.1 Why study numbers?

The use of symbols to represent numerical information is vital to modern society. Whether it is the representation of time, a recipe, finances or dosage instructions for medicine, humans depend on number symbols (e.g., Arabic digits) for performing countless activities. It follows then, that impairment in numerical abilities is associated with negative outcomes. Indeed, this is what has been found in a large body of studies. For example, having poor math skills is associated with a lower likelihood of graduating high school and attending college (Parsons & Bynner, 2006). Having lower math skills is also associated with lower rates of employment (Rivera-Batiz, 1992), lower income (Brian Butterworth, Varma, & Laurillard, 2011) and higher physical and mental health risks (Duncan et al., 2007; Hibbard, Peters, Dixon, & Tusler, 2007; Parsons & Bynner, 2006). Unfortunately, math learning disabilities affect approximately 3-6% of the general population (Shalev, 2004). Additionally, approximately 10-20% of the population struggles with math at a level that negatively affects their use of numerical information for important tasks, such as dealing with decisions about health care or personal finances (Gross-Tsur, Manor, & Shalev, 1996). Given the importance of mathematical aptitude, having a solid foundation in symbolic number representation – the language on which math is based – is crucial. An understanding of the mechanisms that form these symbolic number representations then, stands to benefit not only the scientific community but society in general.

In this chapter I will begin by summarizing a dominant theoretical view held in the field of numerical cognition that endeavors to explain how humans learn numerical symbols. I will then present research that questions this central theory, and provide a brief overview of what we know about the neural correlates of symbolic number representation. Following this, I will outline the research questions and methods of the empirical chapters of the current dissertation, and how the empirical research reported in these chapters speaks to the representation of symbolic number.

1.2 An evolutionary account of symbolic number representation

The use of symbols to represent numerical magnitudes (e.g., number of items in a set, levels of a thermometer, number of sounds etc.) is a uniquely human ability, however, the concept of numerical magnitude has been argued to play a role in the life of many species. It is easy to imagine that the ability of an animal to choose the larger food source, or the pathway with fewer predators is highly adaptive. Following this logic, it has been argued that the ability to approximately process numerical magnitudes has been selected through evolution (Dehaene, Dehaene-Lambertz, & Cohen, 1998). The basis of this ability is theorized to be the approximate number system (ANS; Dehaene, 1997). A key quality of the ANS is the noisy manner with which numbers are represented. Numbers in this system are thought to be arranged on a mental number line. According to the ANS account, each number on this number line has an associated distribution around the real location of that number (i.e., the noise; Figure 1.1b). Therefore, the presentation of a given number does not lead to the precise activation of a specific position on the number line. Instead, when a number is presented there is a spread of activity around the exact magnitude. This means that there is overlap in the activated representations of numbers that are numerically close to one another. This overlap could be viewed as confusion between different numerical magnitudes which increases as a function of their proximity to one another as well as their relative size. These overlapping distributions of the numbers are thought to result in the ratio or distance effect (Moyer & Landauer, 1967). The ratio effect is so named because as the ratio between the two numbers gets larger, the time to decide which of the presented magnitudes is larger increases, while the accuracy of the comparative judgements decreases. In essence, comparative judgements of number can be explained by Weber’s Law: the noticeable difference between two numbers decreases as a function of their relative size (i.e., their ratio; Figure 1.1). The distance effect is related to the ratio effect and manifests as a decrease in reaction time and an increase in accuracy as the distance (i.e., numerical difference) between two numbers increases. For example, with a set of two dots and a set of six dots, six would be chosen as the larger magnitude more quickly and more accurately than if the sets being compared consisted of four dots and six dots (for another example see Figure 1.1a). The distance effect predicts that the comparison of magnitudes two and three should be just as difficult as the comparison of four and five. However, since the ratios between these pairs of magnitudes differ, the ratio effect predicts a lower reaction time for the former magnitudes in comparison to the latter. Hence the ratio effect provides a better model of the relative difficulty of comparing two numbers (Moyer & Landauer, 1967). This distance/ratio modulation of reaction time and accuracy is considered a signature of the ANS.

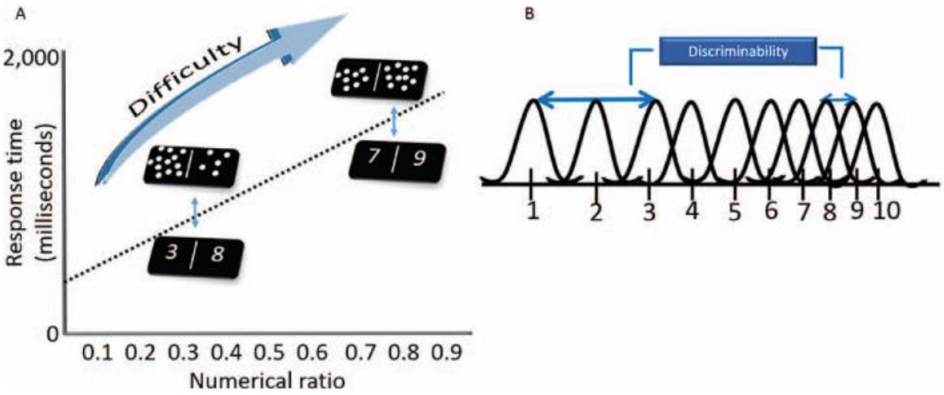

Figure 1.1: Adapted from Leibovich and Ansari (2016), Canadian Journal of Experimental Psychology, APA, p. 2. A. The numerical ratio effect is the finding that participants tend to be faster and more accurate when the ratio between two magnitudes being compared is smaller (e.g., 3/8 = 0.37, an easier ratio) than compared to when it is larger (e.g., 7/9 = 0.77, a more difficult ratio). Similarly, the distance effect is an increase in difficulty as the numerical distance between numbers decreases (e.g., 3 vs. 8 has a distance of 5, while 7 vs. 9 has a distance of 2). B. Proposed approximate representation for magnitudes. Each number has a distribution of noise surrounding its true location on the number line, which follows a logarithmic scale. The distributions surrounding each number overlap.

Research with non-human animals has been suggested to provide the means by which to gain insight into the evolutionary precursors of numerical magnitude representation (i.e., the ANS) in humans. Accordingly, evidence for an ANS has been demonstrated in a wide variety of species, such as rats, pigeons and primates (Dehaene, 1997). For example, Nieder and Miller (2004) used electrodes to record activity from individual neurons within the prefrontal cortex and posterior parietal cortex in two rhesus monkeys to examine the analog representation of number at the level of single neurons. The monkeys were trained to decide whether two sequentially presented arrays contained equal numerical magnitudes. Behaviourally, monkeys demonstrated a distance effect, with larger distances between numerical magnitudes associated with greater response accuracy. In the posterior parietal cortex and prefrontal cortex, groups of neurons responded preferentially to certain numerical magnitudes, and displayed turning curves with distributions that closely fit a logarithmic function (as predicted by Weber's Law). Put differently, neurons in the intraparietal sulcus (IPS) and prefrontal cortex exhibited preferential activity for specific magnitudes. For example, for neurons that exhibited maximum firing for three dots, less activation was observed for two dots, and even less for one dot. These number-encoding neurons had the highest concentration in the dorsolateral prefrontal cortex, with the second highest being in the IPS. This finding of number-selective neurons in the monkey brain supports the idea of the ANS as a phylogenically conserved system for numerical magnitude representation, with a specific neural substrate. Convergent with this notion are also the data showing that the monkeys exhibited a behavioural ratio effect, a signature of the ANS.

Cantlon and Brannon (2006) also demonstrated that primate performance on a non-symbolic task demonstrated the signature of the ANS. Monkeys had to order two presented magnitudes, smallest to largest. Their performance followed a ratio effect; monkeys were faster and more accurate when the magnitudes they were required to order had a smaller ratio (e.g., 0.5) compared to a larger ratio (e.g., 0.67). Results from humans tested with the same paradigm resembled that of the monkeys, and also followed a ratio effect, providing further support for the idea of the ANS as a primitive system, that is present across species.

Research on the numerical capacities of non-human animals has been taken as evidence for an evolutionarily ancient system for representing non-symbolic, approximate magnitudes (i.e., the ANS). Furthermore, human infants have been shown in numerous studies to demonstrate numerical abilities that suggest analog representation (Feigenson, Dehaene, & Spelke, 2004). For example, Izard, Dehaene-Lambertz and Dehaene (2008) used a habituation paradigm to demonstrate ANS representation in infants. In this paradigm, a numerical magnitude was presented repeatedly until the infants' looking times reduced below a pre-specified level. Then, the test magnitude (i.e., a different numerical magnitude) was displayed. If an infant showed increased interest in the display during the test phase, it was taken as evidence that the infant perceived a change in numerical magnitude, thus demonstrating the ability to discriminate that ratio. Using this paradigm, Izard et al., (2008) demonstrated that three-month-old infants were sensitive to large changes in magnitude.

In a related experiment, Xu and Spelke (2000) tested six-month-old infants' ability to discriminate between large, visually displayed, numerical magnitudes using an infant habituation paradigm. Specifically, infants were found to be able to discriminate successfully between displays of 8 versus 16 (a small ratio), but failed to discriminate between 8 versus 12 (a larger ratio). These data may suggest an analog representation in infancy akin to that described above for animals. These findings could be interpreted to suggest that infants' representations of numerical magnitudes are highly noisy and therefore they can only discriminate between magnitudes with a ratio of 0.5 (8 vs. 16) but not between magnitudes with a higher ratio. Moreover, research with infants has revealed that the ability of infants to discriminate magnitudes rapidly increases with age, suggesting that the acuity of their ANS increases over developmental time. At six months, infants are limited to discrimination of a 1:2 ratio (Xu & Spelke, 2000). However, by nine months infants can discriminate a 3:4 ratio (Lipton & Spelke, 2003).

In numerical habituation tasks, infants seem to demonstrate performance that is both consistent with predictions by the ANS and is comparable to that of non-human animals. Therefore, it has been assumed that the ANS is a primitive system, largely preserved across species (Dehaene et al., 1998; Xu & Spelke, 2000). Furthermore, since the signature of the ANS precedes language and exact symbolic mathematics in infants, it has been assumed that the symbolic numerical system must build on this primitive ANS and not vice versa (Cantlon, 2012).

Analogous to the non-symbolic comparison task used to measure the ANS, the symbolic number comparison task is frequently used as a measure of symbolic number representation. In this task, the participant chooses the larger of two presented symbolic numbers (e.g., Arabic digits). Similarly to the non-symbolic version, the symbolic comparison task yields both distance and ratio effects; wherein trials with numbers that are further apart (large distance, small ratio) are performed faster and more accurately than trials with numbers that are closer together (small distance, large ratio; Moyer & Landauer, 1967). Since this behavioural pattern of a distance/ratio effect is considered a key signature of the ANS, it has been proposed that the symbolic number system is mapped onto the ANS (Dehaene, 1992; Feigenson, Dehaene, & Spelke, 2004). The ANS therefore, is often considered to be the evolutionary precursor to symbolic number representation.

1.3 Critiques of the evolutionary account of symbolic number

Although this ability to manipulate symbolic numerical information is key to daily functioning, little is known about how the human brain comes to assign meaning to arbitrary symbols (Coolidge & Overmann, 2012). This evolutionary account of number representation – that humans share with animals an innate number system that was evolutionarily set-up to allow us to represent numerical information symbolically – rests on research that is problematic in several ways:

1. *In the large majority of numerical cognition studies with animals, extensive training is required* (Núñez, 2017). Although there are examples of spontaneous magnitude discrimination, (see Hauser, Carey, & Hauser, 2000; rhesus monkeys naturally chose the larger amount of food reward, being successful at various ratios), these studies are in the minority. Cantlon and Brannon (2007) demonstrated that monkeys can solve simple non-symbolic arithmetic problems (albeit approximately) similarly to adult humans. However, unlike humans, the monkeys did not improve even after three years of practice, whereas humans show great gains in arithmetic with repeated practice. Typically, only the cases where animals succeed in training are published, and hence it is impossible to know how many failed to use number reliably. Ecologically, these studies are highly unnatural, and raise the question of whether we are measuring a "natural" ability of these animals.
2. *Animals do not form exact symbolic representations of number.* Animals may demonstrate some competencies with non-symbolic tasks, however, it is clear that these abilities are limited in their preciseness, consistent with an ANS. Differences between human and animal number abilities become readily apparent when exact

representation is required. For example, Mechner (1958) trained rats to press Lever A for a certain number of times before pressing Lever B in order to receive a reward. To maximize the amount of food received, the rat needed to press A exactly the right number of times, every trial. However, this was not the case; rats would press A approximately the correct number of times (i.e., on average, the number of presses would be correct). They were unable to demonstrate an exact representation of number, and instead their responses could be described by recourse to the ANS. Furthermore, there are very few non-human animal studies that demonstrate the use of symbols, and none that have demonstrated spontaneous development of symbolic representations of numerical magnitude in non-human species. From the few available studies in which the authors are able to train animals to work with symbols, it can be concluded that any ability of animals to associate magnitudes with arbitrary symbols requires a lifetime of highly extensive training (Dehaene, 1997). This is in stark contrast to the abilities of even very young children, who rapidly become proficient with symbol use in mathematics.

3. *Non-numerical cues are likely used for non-symbolic numerical tasks.* There are numerous critiques of the non-symbolic stimuli (e.g., arrays of dots) used in the tasks to measure supposed numerical processing in animals and infants (e.g., Leibovich, Katzin, Harel, & Henik, 2017). More specifically, many continuous properties, such as surface area and density, are correlated with numerosity, making it difficult to determine if the participant is using one or a combination of these visual cues to perform the task, as opposed to number. For example, if in a number comparison task two arrays of dots of are composed of dots of equivalent sizes, the arrays will differ not only in number but also in surface area; i.e., the array with the larger number of dots will also have a larger cumulative surface area. Furthermore, even if one alters the size of the dots so that surface area and number are no longer correlated, it is not possible to control for all continuous properties that show a correlation with number (Leibovich et al., 2017). Therefore, research with animals and infants using these non-symbolic tasks may not actually be demonstrating a capacity for number abilities per se.

4. *The direction of causation between non-symbolic and symbolic numerical representation has not been empirically demonstrated.* Although the assumption is that non-symbolic numerical representation must provide the foundation for symbolic numerical representation, evidence for this view is severely lacking. When studies are designed specifically to evaluate this claim, the majority of the evidence points to a relation that operates in the reverse direction; that symbolic numerical representation may actually refine non-symbolic numerical representation (Goffin & Ansari, in press).
5. *Symbolic and non-symbolic performance is not related.* Several studies have failed to find a relation between symbolic and non-symbolic distance/ratio effects (Krajcsi, 2017; Lyons, Nuerk, & Ansari, 2015). If the ANS gives rise to distance effects in both the symbolic and non-symbolic comparison tasks, it would follow that these effects should be associated. Although the ANS theory may appear to fit with the behavioural patterns observed with number comparison tasks, other theories have been suggested to have more explanatory power for symbolic numerical processing. For example, Krajcsi, Lengyel and Kojouharova (2018) rigorously tested whether the ANS account fit the data generated by both a symbolic number comparison and non-symbolic number comparison task equally well. Predictions from the ANS model fit the non-symbolic data, in terms of error rate, reaction time and diffusion model drift (a measure of evidence accumulation that takes into account both error rate and reaction time). However, for the symbolic number condition, the ANS predictions did not accurately predict the error rate, reaction time or drift rate patterns observed. This suggests that the ANS account is not sufficient to explain data from the symbolic numerical task.
6. *Symbolic and non-symbolic representation differ at the neural level.* In a quantitative meta-analysis examining functional magnetic resonance imaging of symbolic and non-symbolic number, Sokolowski, Fias, Mousa and Ansari (2016) found that although there were overlapping networks that were recruited for symbolic and non-symbolic tasks, symbolic tasks were more likely to recruit left-lateralized parietal regions, while non-symbolic were more likely to recruit right-lateralized parietal regions. Furthermore, Lyons, Ansari, and Beilock (2015) found that although an

analog model for representation fit non-symbolic number representation at the neural level, symbolic number representation, by contrast, was better fit by a discrete model, as opposed to one with overlapping representations. Additionally, there was no evidence of an association between the neural patterns across symbolic and non-symbolic numbers. In agreement with Lyons et al. (2015), others have demonstrated dissociable neural activity for symbolic and non-symbolic magnitudes (Bulthé, De Smedt, & Op de Beeck, 2014; Damarla & Just, 2013)

In summary, the ability of animals and infants to perform non-symbolic comparison and addition has been taken as evidence that the ANS is an evolutionarily ancient system. In view of this, it has been argued that the more recent invention of numerical symbols is linked to this ancient system for numerical magnitude representation. The shared behavioural signatures of the symbolic and non-symbolic comparison task – the distance and ratio effect – are taken as further evidence to support these claims. However, as voiced by Núñez (2017), this assumption is problematic: "Training a dog to snowboard…may provide valuable data for particular purposes, but not for supporting the conclusion that canines have an evolved capacity for snowboarding." (p. 417). Just because animals seem to have the capability to demonstrate numerical abilities does not mean these abilities were necessarily evolved for this function. Research with animals may not be providing evidence for their innate numerical abilities. Furthermore, the theory that symbolic number is a consequence of the ANS is not empirically supported and does not take into account evidence that symbolic and non-symbolic representations seem to diverge at both the behavioural and neural level. This begs the question: if the ANS theory does not provide a satisfactory explanation, what are the mechanisms underlying symbolic number representation?

1.4 Neural correlates of symbolic number

Given the relatively recent invention of number symbols, it is highly unlikely that the human brain was expressly adapted over the course of evolution to represent symbolic numbers. More specifically, representing number symbolically occurs with enculturation, and consequently does not occur without learning (Núñez, 2017). Symbolic numbers need to become processed and represented in the brain over developmental time.

Studying this process of enculturation and what underpins it may allow for insight into how human neurobiology adapts to culturally-derived symbolic representations. Therefore, how the human brain comes to represent symbolic numbers over the course of learning and development is a key question for the field of numerical cognition, but also speaks to the learning of symbol abstraction more generally.

Neuroimaging tools such as functional magnetic resonance imaging (fMRI) have been used to address this question. fMRI has relatively high spatial resolution compared to other non-invasive neuroimaging methods (e.g., electroencephalogram; EEG) and allows researchers to probe the neural mechanisms underlying constructs of interest. Investigating the neural correlates of number representation can offer a level of inference that complements and adds to that offered by behavioural measures (Matejko & Ansari, 2018). Therefore, the use of fMRI has added significantly to our understanding of number processing. A large body of evidence using fMRI implicates certain brain regions in the representation of numerical symbols. Regions within the parietal lobes, such as the IPS are consistently activated when participants compare the numerical magnitude of two symbolic numbers (e.g., which of 3 and 5 is numerically larger?; e.g., Bugden, Price, McLean, & Ansari, 2012; Cohen Kadosh et al., 2005; Göbel, Johansen-Berg, Behrens, & Rushworth, 2004). Similarly, activation along the left parietal cortex has been observed when participants are asked to solve arithmetic problems presented in a symbolic format (e.g. 1+3; Arsalidou & Taylor, 2011; e.g., Grabner et al., 2009; Venkatraman, Ansari, & Chee, 2005). Additionally, studies of patients with left parietal lesions find numerical skills are negatively impacted (Ashkenazi, Henik, Ifergane, & Shelef, 2008; Cipolotti, Butterworth, & Denes, 1991; Lemer, Dehaene, Spelke, & Cohen, 2003). In a quantitative meta-analysis of fMRI studies, Sokolowski, Fias, Mousa, and Ansari (2016) found that overall, a distributed fronto-parietal network was recruited for symbolic number processing (Sokolowski et al., 2016). However, activity in the left superior parietal lobule (SPL) was found to be consistently correlated with symbolic (i.e., Arabic digit) numerical processing. In summary, regions in the parietal lobe, particularly the left parietal cortex have been demonstrated to be important for symbolic number processing.

1.5 Refining the study of symbolic number representation using fMRI-adaptation

A limitation of many fMRI studies is that tasks requiring participants to compare two numbers (e.g., Holloway, Price, & Ansari, 2010) or perform calculations (e.g., Rivera, Reiss, Eckert, & Menon, 2005) necessitate a response selection on the part of the participant. Thus, rather than attributing parietal activation to numerical representation, it could be argued that the activation observed in these studies is the result of overt response selection that is part of the decisional process invoked by the task at-hand (Göbel et al., 2004). A passive design that does not place response selection demands on the participant is one method that can be used to mitigate these confounds.

fMRI-Adaptation (fMRI-A) makes use of a passive design in order to investigate neural correlates of interest without introducing response selection demands. The passive nature of fMRI-A is not only useful for removing response selection confounds from imaging data but is also, in general, a cleaner way of studying number representations. Behavioural paradigms such the number comparison task have been argued to tap into mechanisms that are not number-specific. More specifically, as opposed to number-specific mechanisms, evidence has suggested the distance effects observed in number comparison tasks may be related to a variety of domain-general constructs, such as inhibitory control (Gilmore et al., 2013), visual-spatial working memory (Bugden & Ansari, 2015) or response selection (Van Opstal, Gevers, De Moor, & Verguts, 2008). This makes drawing inferences about the mechanisms underlying number representation using tasks such as number comparison extremely difficult.

In fMRI-A, as opposed to active tasks, participants are simply asked to watch the stimuli on the computer screen. fMRI-A uses repeated presentation of a stimulus in an “adaptation phase”. Brain regions that are recruited for the representation of the repeated stimulus demonstrate decreased activation during this phase. Following the adaptation phase, a new stimulus – the deviant – is presented. The deviant stimulus is different from the adaptation stimulus in a characteristic of interest. With the presentation of the deviant, neural regions involved in the representation of this deviant stimulus characteristic tend to demonstrate rebound in activation in response to the change from the adaptation phase.

Therefore, the regions that demonstrate a rebound in activation are assumed to be recruited for the stimulus of interest.

The fMRI-A method has been used in fields such as object and face processing (Grill-Spector, Henson, & Martin, 2006). Importantly, fMRI-A has been used in previous research to investigate the neural correlates of symbolic number representation (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Holloway et al., 2013; Notebaert, Nelis, & Reynvoet, 2010; Notebaert, Pesenti, & Reynvoet, 2010; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Vogel, Goffin, & Ansari, 2015, Vogel et al., 2017). In research investigating symbolic number using fMRI-A, the adaptation phase involves the repeated presentation of the same number symbol. During the adaptation phase, regions responsive to number tend to show a decrease in activation. A deviant number is then presented after this adaptation phase. The presentation of the deviant number leads to a rebound in the activation of regions that are involved in symbolic number representation. Interestingly, this rebound in activation tends to be related to the numerical ratio between the adaptation number and the deviant number within the left IPS (Holloway et al., 2013; Notebaert, Pesenti, & Reynvoet, 2010; Vogel et al., 2015). Put differently, previous research has found that the amount of rebound in activation within the IPS is greater when the ratio between adaptation and deviant number is smaller (e.g., an adaptation value 6 and a deviant of 3 have a ratio of 0.5) relative to when the ratio between the adaptation and deviant number is larger (e.g., an adaptation value of 6 and a deviant of 4 have a ratio of 0.67). This pattern in the rebound of neural activity is suggestive of a number-specific signature, as opposed to an effect that may not be stimulus specific. For example, given the passive nature of the paradigm, the ratio-dependent modulation of the rebound effect may reflect semantic processing of magnitude as opposed to response selection. The ratio-dependent modulation of the rebound effect is key to establishing this effect as a signature of number, because if the rebound in activation was the same across all presented deviants, this effect could be attributed to attentional mechanisms. This ratio-dependent pattern in the rebound of activation is often called a parametric effect.

What evidence is there that this parametric effect exhibited in numerical fMRI-A reflects semantic processing of number? Holloway et al. (2013) extended previous fMRI-A work by including two groups: a bilingual group (could read Chinese and Arabic numerals) and a non-Chinese literate group (could read Arabic numerals but not Chinese numerals). Additionally, two conditions were used in the adaptation task: a Chinese numeral condition and an Arabic digit condition. Holloway et al. (2013) demonstrated a ratio-dependent recovery effect in the neural activation of the left IPS for Arabic numerals in both groups. In the Chinese numeral condition, the ratio-dependent signal recovery effect was observed only in the right IPS of the bilingual group. The authors attribute this lateralized result to differential levels of experience with the two numeral formats (Holloway et al., 2013). In the Arabic condition, the bilingual group showed a ratio-dependent signal recovery effect in the left IPS because of their high familiarity with the Arabic numerals. However, the bilingual group was less familiar with the Chinese symbols, resulting in a ratio-dependent effect in the right IPS. Importantly, the rebound effect appeared to be driven by semantic processing of numerical information, since it was only present in the IPS for the conditions in which participants understood the meaning of the stimuli presented. That is, the rebound effect occurred in response to only Arabic digits in the case of the non-Chinese literate group, whereas it occurred in response to Arabic *and* Chinese digits in the case of the bilingual group. This study provided support for the proposal that the above-described, parametric ratio effect observed in the IPS in adaptation studies reflects a level of semantic processing of the number stimuli, as this effect is not obtained when participants do not understand the meaning of the symbols.

This finding of a ratio-dependent rebound effect in the parietal cortex in response to numerical symbols has been demonstrated across multiple studies (Holloway et al., 2013; Notebaert, Nelis, et al., 2010; Vogel et al., 2015; Vogel et al., 2017). What mechanisms underlie this ratio-dependent rebound effect? The ANS is a commonly cited explanation. As described above, the noise, or the distribution around the real location of the number, results in an analog representation of number magnitudes (Notebaert, Pesenti, et al., 2010). Specifically, larger ratios between the adaptation and deviant numbers are hypothesized to correspond to greater representational overlap/similarity. In other words, the more the deviant stimulus differs from the adapted stimulus in the variable of interest (in this case numerical magnitude) the greater the expected rebound brain response.

However, the mechanisms underlying the representation of symbolic number are disputed (Leibovich & Ansari, 2016; Lyons, Ansari, et al., 2015; Núñez, 2017). This theory of the symbolic number system being mapped directly onto the ANS is a point of conflict within the numerical cognition field and requires further empirical testing.

1.6 Overview of the current thesis

fMRI-A is a useful tool for empirically investigating mechanisms underlying symbolic number representation. Assessing the effect that different ratios between the deviant number and adaptation number have on brain activity can identify neural areas that respond to the semantic processing of number (e.g., Holloway et al., 2013). In contrast, brain regions that show similar rebound in activation for all number deviants may be responding to attributes of number symbols that do not reflect semantic processing of the number symbols (e.g., visual characteristics). Furthermore, when fMRI-A is used to investigate different hypotheses surrounding number representation, differences in task difficulty in various conditions is not a confounding issue. The use of a passive paradigm means we can isolate the effects of the variables of interest to representation of number in the brain more precisely than what is possible with the use of active tasks. Therefore, investigating the parametric effect allows us to ask questions about the mechanisms underlying numerical representation.

Given the questions surrounding the ANS account of symbolic number representation, my PhD research empirically tested different mechanisms underlying the neural representation of symbolic number. More specifically, using fMRI-A I investigated whether number symbols are represented similarly to other ordered symbols (i.e., letters) at both the neural and behavioural level (Chapter 2), how symbolic number representation changes across development of the brain (Chapter 3) and whether sensorimotor functions may be associated with neural symbolic number representation (Chapter 4).

1.6.1 Chapter 2, Experiment 1

The aim of Chapter 2 was to explore the mechanisms of the distance/ratio-dependent recovery effect observed in numerical fMRI-A research. To date, the nature of the ratio-dependent rebound effect in the IPS has not been tested empirically in the literature. Is the parametric effect observed in parietal regions actually related to changes in numerical magnitude? It is unclear whether the parametric effect observed in the IPS in response to varying symbolic numerical stimuli is reflective of a direct mapping of symbolic number onto the ANS, or whether some other numerical attribute could explain this pattern, for example ordinality. Ordinality refers to the positional information in a series of ordered objects. As previously mentioned, the theory that symbolic numbers are directly mapped onto the ANS is a disputed concept within the numerical cognition field (Lyons, Ansari & Beilock, 2012). Experiment 1 of Chapter 2 addressed the question of whether the IPS will demonstrate a parametric rebound effect when symbols are processed that have ordinal relationships, but lack magnitude associations.

More specifically, twenty-four adults completed two runs of a symbol adaptation task. The task stimuli consisted of English letters and Arabic numerals. Seven different single digit numbers were used, and the corresponding letters were used for the letter condition (e.g., B corresponds to 2). Similar to Notebaert et al. (2010), Holloway et al. (2013), Vogel et al. (2015) and Vogel et al. (2017), parametric predictors were created to identify any brain regions that demonstrated a distance-dependent rebound effect for numbers or letters. Results from Chapter 2 speak to an alternate hypothesis surrounding symbolic number representation: whether or not general ordinal relationships between symbols may account for the neural parametric effect observed in adaptation tasks.

1.6.2 Chapter 2, Experiment 2.

Like symbolic numbers, letters have an ordinal sequence (Jou & Aldridge, 1999). Unlike symbolic numbers however, letters do not represent magnitudes. In a study that calls into question the assumption that a non-symbolic numerical magnitude system underlies ratio/distance effects, Van Opstal, Gevers, De Moor and Verguts (2008) demonstrated that the comparison of letters generates a distance effect. If the ANS theory of symbolic number representation could account for the distance/ratio effects observed in behavioural data of numerical tasks, symbols that do not have this hypothesized connection with the ANS should not generate distance effects. In Experiment 1 we used letter stimuli to examine an ordinal hypothesis for the neural parametric effect. In

Experiment 2, we examined whether the stimuli used in Experiment 1 give rise to a distance effect in an active behavioural task.

Two groups of participants were collected for this study: a letter training group (n = 90) and a number training group (n = 94). Participants completed ordinality tasks with the letter and number stimuli used in Experiment 1. In the ordinality tasks, participants were presented with a number or a letter in the centre of the computer screen and asked to judge whether the presented number comes before or after 5, or whether the presented letter comes before or after E. Results from Experiment 2 are discussed in relation to the findings from Experiment 1. Methods from Experiment 2 of Chapter 2 were preregistered (https://osf.io/s6e7u/). Together, findings from Experiment 1 and 2 of Chapter 2 speak to our understanding of both neural and behavioural distance effects, and the implication of these effects for understanding symbolic number representation.

1.6.3 Chapter 3.

Few studies have used fMRI-A to examine the development of symbolic number (e.g., Arabic digit) representation in school-aged children. To better understand the development of symbolic number processing, Vogel et al. (2015) had a cross-sectional sample of 19 children ages 6-14 years passively view Arabic digits in an fMRI-A paradigm. Results showed a parametric rebound effect in the right IPS that was significant across the whole age group (Figure 1.2a). Interestingly, there was a significant positive correlation between age and the ratio-dependent neural rebound effect in the left IPS, whereby older children showed increased ratio-dependent activation within the left IPS (Figure 1.2b). Chapter 3 sought to replicate Vogel et al. (2015) with a larger sample of children, and extend the study by examining links between functional activation in the IPS and behavioural measures of numerical processing and arithmetic. We expected to replicate the results of Vogel at el., (2015) and find a significant correlation between increased age and the parametric recovery effect in the left IPS when passively viewing digits.

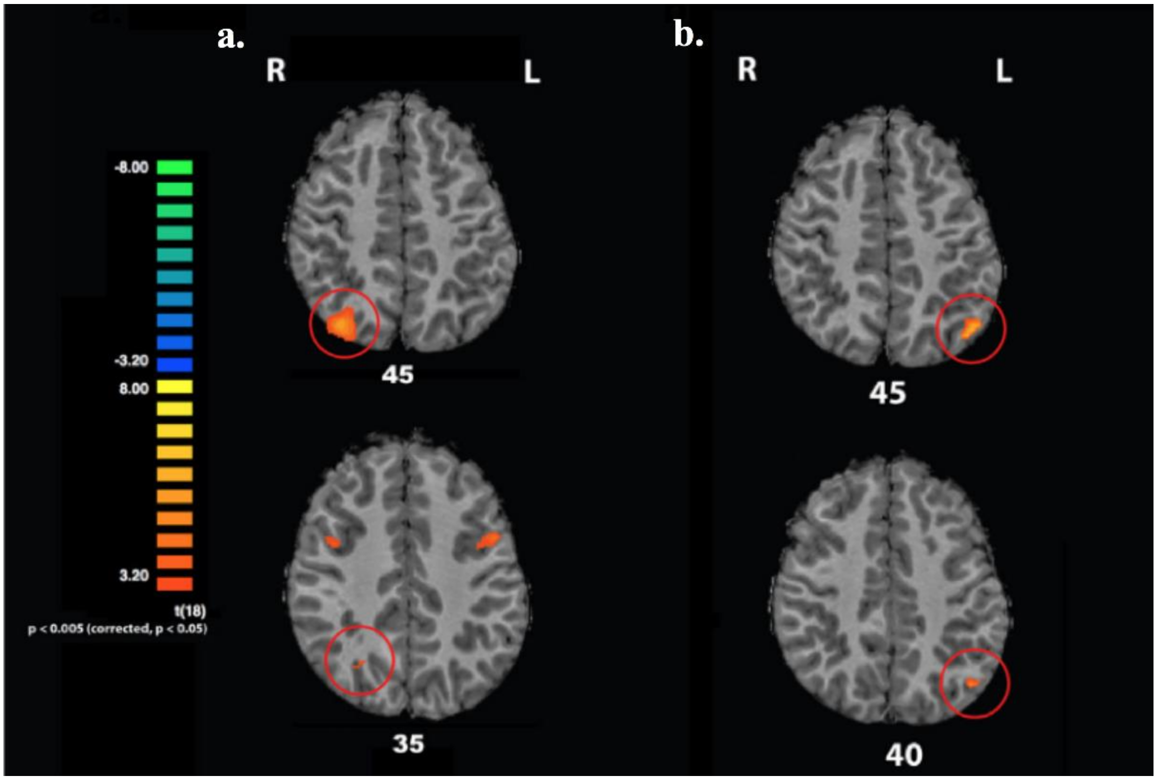

Figure 1.2: Figure adapted from Vogel et al. (2015), Neuroimage, Elsevier, p. 67 and 68. a. Age-invariant parametric effect observed in the right IPS. b. Age correlation for the parametric effect in the left IPS.

A sample of forty-five 6-14-year olds was collected. The number adaptation task was the same adaptation task used in Vogel et al., 2015 and Vogel et al., 2017 experiment 1. Participants were adapted to the number '6'. The repeated presentation of the number 6 was randomly interspersed with deviant trials. The ratio between the adaptation and deviant number was varied. This task allowed us to examine the ratio-dependent rebound effect in a developmental sample.

There are still many questions surrounding the developmental trajectory of symbolic numerical representation. Chapter 3 sought to replicate a key finding in the field: that the left IPS shows a correlation between age and the ratio-dependent rebound effect. The replication of research findings is key to the progression of science (Zwaan, Etz, Lucas, & Donnellan, 2018). Psychology as a field has been experiencing a replication crisis: originally reported findings in many cases do not replicate (Baker, 2016; Pashler & Wagenmakers, 2012). This could in part be due to the small sample sizes and inflated effect sizes reported in published data (Szűcs & Myers, 2017), as well as the tendency for null results to go unpublished (Pashler & Wagenmakers, 2012). Therefore, the results from Chapter 3 are discussed with respects to the critical need for more replication studies; as "A finding is arguably not scientifically meaningful until it can be replicated with the same procedures that produced it in the first place." (Zwaan et al., 2018, p. 13). The methods, hypotheses and planned analyses for Chapter 3 were preregistered https://osf.io/zsfbk/.

1.6.4 Chapter 4.

The left parietal lobe has been repeatedly linked to the processing of symbolic number (Sokolowski et al., 2016). Although the left-laterality of symbolic number has been repeatedly demonstrated, to date the mechanisms underlying this laterality are unclear. Why is the left parietal cortex more likely to be involved in symbolic number representation than the right? Chapter 4 sought to examine a hypothesis for the left laterality of symbolic number: that handwriting handedness may play a role in the laterality of symbolic number representation.

Participants recruited for neuroimaging are largely right-handed, which could create a bias in the pattern of results generated from these studies. Interestingly, when left-handed participants are included in neuroimaging research, it has been demonstrated that handedness is associated with the laterality of word processing, language, visuospatial attention and even letter processing (Cai, Van der Haegen, & Brysbaert, 2013; Longcamp, Anton, Roth, & Velay, 2005; Willems, Hagoort, & Casasanto, 2010; Willems, Van der Haegen, Fisher, & Francks, 2014). These associations between handedness and neural laterality led to the hypothesis in Chapter 4 that handedness may affect the laterality of number representation as well. More specifically, because learning number symbols involves sensorimotor processes (e.g., practicing tracing, copying and writing number symbols), we predicted that handedness for handwriting would be associated with the laterality of symbolic number representation.

Chapter 4 included two groups: a left-handed group (n = 25) and a right-handed group (n = 25). Participants completed four runs of the number adaptation task used in Vogel et al., (2015), Vogel et al., (2017) as well as Chapter 3. We predicted that we would replicate the left-lateralized ratio-dependent rebound effect in the group of right-handers, while the left-handers would show a tendency towards right-lateralization of this parametric effect.

Chapter 4 has been accepted for publication as a Registered Report in the journal *Cortex* (Goffin, Sokolowski, Slipenkyj & Ansari, in press, https://doi.org/10.1016/j.cortex.2019.07.017). In the registered report format, the introduction, methods and proposed analyses are submitted for peer review prior to the start of data collection. If successful, the study is granted in-principle acceptance; which comes with the understanding that if the authors follow the agreed upon methods, the journal will publish the outcome (even if null results are obtained). Data collection and data analysis then proceed as planned, and the completed manuscript is submitted for a second round of peer review. Here, the manuscript is evaluated on adherence to the stated methods, the suitability of any post hoc analyses and conclusions drawn from the results. The registered report format was designed to improve the transparency, replicability and reproducibility of research. More specifically, this design helps to address many of the issues that have led to the current reproducibility crisis: p-hacking, publication bias, lack of data sharing, hypothesizing after results are known (HARKing) and low statistical power (Figure 1.3).

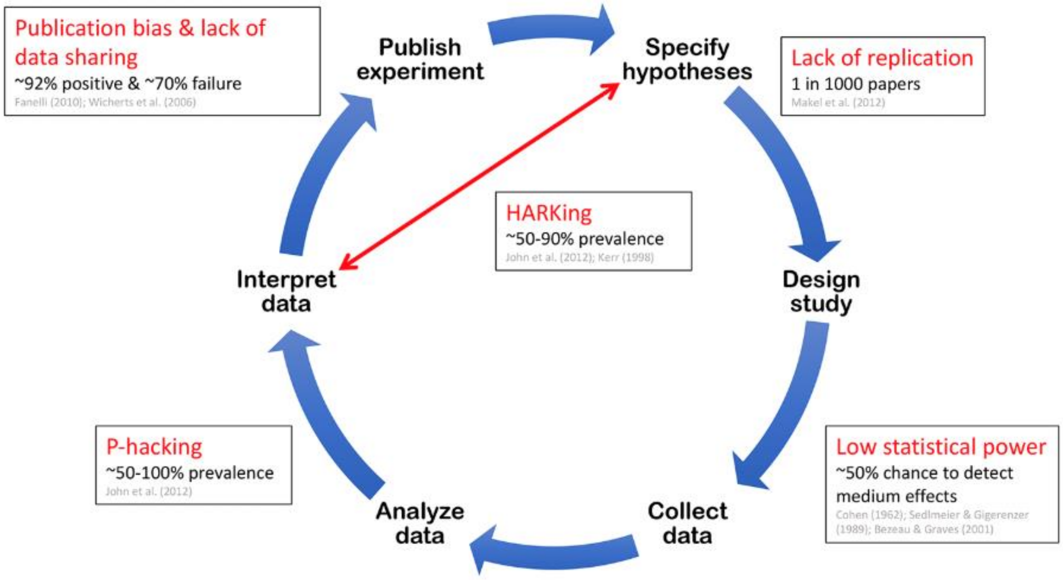

Figure 1.3: From https://cos.io/rr/. A model of how the research process can be influenced by poor research practices (in red font). P-hacking: refers to either collecting data until you have the result you want, or only reporting the analyses that work out. HARKing: Hypothesizing After Results are Known: looking at the results and then framing the paper as if that is what was expected from the beginning. Publication bias: tendency for journals to reject null findings.

1.6.5 Summary

Chapters 2, 3 and 4 speak to the representation of symbolic number in the human brain. More specifically, the empirical chapters of this dissertation address important outstanding questions surrounding symbolic number representation using fMRI-A:

- Chapter 2: Can general ordinal relationships provide a mechanism by which numbers may be represented symbolically? Specifically, can ordinal relations between symbols account for the parametric effect observed in number adaptation studies? Is the ANS theory necessary to explain this effect?
- Chapter 3: What does symbolic number representation look like developmentally at the neural level? Are there replicable age-related effects on the parametric effect observed in the IPS?
- Chapter 4: Are sensorimotor processes – i.e., handwriting handedness – related to symbolic number representation? Is handedness associated with the laterality of symbolic number representation, thereby providing a possible mechanism through which this laterality may occur? Is there a relation between handedness and the laterality of the parametric effect?

Through an empirical investigation of the neural rebound effect in response to symbolic number, the data presented in this dissertation explore the nature of symbolic number representation. Using both behavioural and neuroimaging methods, in adults and in children, we add to the field's understanding of how the human brain comes to create representations for arbitrary symbols.

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Chapter 2

2 A comes before B, like 1 comes before 2. Is the parietal cortex sensitive to ordinal relationships in both numbers and letters? An fMRI-Adaptation study

2.1 Introduction

Number symbols (e.g., Arabic numerals) are a relatively recent human invention, therefore, it is unlikely that evolution has adapted the human brain to process and represent numbers symbolically (R. E. Núñez, 2017). This prompts an important question: how does the brain come to represent numerical symbols?

To date, the precise mechanisms that enable the human brain, over the course of learning and development, to represent and manipulate numerical symbols remain poorly understood (Coolidge & Overmann, 2012). In the present functional neuroimaging study and behavioural study we investigate whether numerical symbols and letters are represented in similar or different ways.

2.1.1 Involvement of the Parietal Lobe in Number Representation

Adult fMRI research has repeatedly shown that the activity in the parietal cortex is correlated with tasks that involve the processing of numerical symbols (e.g., number comparison). In particular, the intraparietal sulcus (IPS) has been highlighted as a key region for symbolic number representation (e.g., Dehaene, Piazza, Pinel, & Cohen, 2003; Holloway, Battista, Vogel, & Ansari, 2013; Notebaert, Nelis, & Reynvoet, 2010; see Ansari, 2008 for a review). Additionally, studies of patients with parietal lesions as well as studies involving transmagnetic stimulation (TMS) of the parietal area find numerical skills are negatively impacted when the activity in parietal neural regions is interfered with (Cohen Kadosh et al., 2007; Dehaene & Cohen, 1997). In a recent meta-analysis of fMRI studies, Sokolowski, Fias, Mousa, and Ansari (2016) found that the left superior parietal lobule (SPL) is consistently activated for symbolic (i.e., Arabic digit) numerical processing. To date, the research has converged upon areas in the parietal lobe such as the IPS and SPL as key neural regions for the processing of numerical stimuli.

A limitation of many fMRI studies is that the tasks employed to elicit neuronal activation in response to numerical symbols require that participants compare two numbers (e.g., Holloway, Price, & Ansari, 2010) or perform calculations (e.g., Rivera, Reiss, Eckert, & Menon, 2005). Such active tasks are potentially problematic because it becomes challenging to separate activation related to response selection from that attributable to the processing of numerical symbols. Put differently, rather than attributing parietal activation to numerical representation, it could be argued that the activation observed in these studies is the result of participants being required to select between two or more response options. It is well established that the parietal cortex plays a critical role in motor control and response selection. In view of this it is perhaps not surprising that Göbel, Johansen-Berg, Behrens, & Rushworth (2004) found that neural activity during number comparison was difficult to distinguish from control tasks that did not involve processing of numerical symbols, but did require response selection. In other words, the parietal regions often associated with number representation are recruited for response selection processes that do not involve symbolic number processing. Such findings cast legitimate doubt on the notion that the parietal cortex is critical for the representation and processing of numerical symbols. One method that can be used to mitigate such a confound and to investigate the neural correlates of symbolic number in the absence of response selection is to use a passive task design that requires no overt decisional processes.

2.1.2 Functional Magnetic Resonance Imaging Adaptation and Symbolic Numerical Representation

The central assumption behind functional magnetic resonance imaging adaptation (fMRI-A) designs is that the repeated presentation of a certain stimulus attribute (e.g., colour) will result in the reduction of activation in the neural regions that are critical for processing a given attribute/stimulus characteristic (Kalanit Grill-Spector et al., 2006). A rebound effect can then be observed when another stimulus that differs from the adaptation-phase stimulus in the attribute of interest - a so-called “deviant” stimulus - is presented. Upon presentation of the deviant stimulus, the previously reduced activation in the adapted brain region rebounds (i.e., increases).

Using an fMRI-A event-related design, Notebaert and colleagues (2010) examined brain activation in response to symbolic number presentation. Participants' brain responses were adapted to either the Arabic digit "6" (small number condition) or the digit "32" (large number condition). Numbers that deviated from the adaptation number were presented randomly throughout the run after the adaptation periods. The left IPS showed a significant ratio-dependent neural rebound effect for both the small and large number conditions. More specifically, greater activation in the left IPS was revealed for deviants whose ratio with the adapted number was relatively small compared to deviants whose ratio with the adapted number was comparatively large (Notebaert et al., 2010). This ratio-dependent rebound effect has been replicated by multiple studies (e.g., Holloway et al., 2013; Vogel et al., 2015; Vogel et al., 2017).

fMRI-A research using numerical stimuli has for the most part converged on the finding that the IPS shows a signal recovery effect that is dependent on numerical ratio (Notebaert et al., 2010; Holloway et al., 2013; Piazza et al., 2007; Vogel et al., 2015; Vogel et al., 2017). This ratio-dependent neural rebound effect has been suggested to result from the mapping of the symbolic numerical system onto a noisy, analog system of magnitude representation, called the Approximate Number System (ANS; Dehaene, 1997). In this ANS account of number representation, number magnitudes are represented on a mental number line in an analog fashion, and symbolic numbers are mapped onto this noisy magnitude system (Dehaene, 1997). Each numerical quantity on this number line is hypothesized to be associated with a distribution of representational uncertainty (e.g., the representation of 4 also includes that of 3 and 2) around the precise location of the number quantity, resulting in an analog representation of numerical magnitude (Dehaene, 1997). When people are asked to compare two numbers, this analog system of representing number results in a characteristic behavioural signature: the numerical distance effect (NDE; Moyer & Landauer, 1967). The NDE is measured as an increase in reaction time and decrease in accuracy when presented numerical stimuli are numerically closer together, as compared to farther apart. It has been hypothesized that numbers that are numerically closer have more overlap in their distributions (share more of their representational uncertainty) on the mental number line. Increased overlap between these distributions results in the increased reaction time and decreased accuracy observed in the behavioural NDE (Moyer & Landauer, 1967). In a similar vein, overlap in these representations has been proposed to explain the ratio-dependent rebound effect observed in symbolic number adaptation studies.

However, this theory that symbolic numbers are directly mapped onto the ANS has been challenged within the numerical cognition field (e.g., Lyons, Ansari & Beilock, 2012). For example, research has called into question the presence of a strong link between symbolic and non-symbolic numerical systems. Lyons et al. (2012) found a processing "cost" when participants were asked to complete a task involving both symbolic and non-symbolic stimuli compared to conditions with a single format, suggesting that these formats are not interchangeable without extra processing. Moreover, Lyons, Nuerk and Ansari (2015) found that measures of acuity for symbolic and non-symbolic numerical representation were not significantly associated with one another in a sample of elementary school aged children. These findings suggest that number symbols are not necessarily inextricably tied to non-symbolic quantities, questioning the notion of a direct link from non-symbolic to symbolic numerical representation. Furthermore, symbolic and non-symbolic systems may show divergent patterns of representation at the neural level. While non-symbolic numerical representation can be modelled using a tuning curve function, symbolic numerical representation does not follow this pattern, and instead fits a more precise, non-analog model (Lyons, Ansari, et al., 2015). A lack of a direct link between non-symbolic and symbolic behavioural measures and qualitatively different representations at the neural level challenge the ANS theory of symbolic number representation.

What factors, other than overlap in the representations of analog numerical magnitudes, could explain the ratio-dependent rebound effects frequently observed for symbolic number? It could be plausibly hypothesized that instead of being involved in the representation of numerical magnitude, the IPS is engaged by the ordinal associations between numerical stimuli. Numbers can be arranged ordinally; early on children learn that two follows one and three follows two (Brian Butterworth, 2005). Thus, is it possible that the ordinal associations between number stimuli create a recovery effect that mimics what we would see with an analog number representation system? But how can this be examined? In the aforementioned fMRI-A studies it is impossible to distinguish whether adaptation effects are driven by ordinal or ratio-dependent representations, since the existing data is equally plausible under both accounts (e.g. 2 and 3 have both a larger ratio and have greater ordinal proximity than 2 and 6).

Critically, the use of letters as stimuli provide the opportunity to test whether general ordinal associations underpin the representation of symbolic number in the IPS. Letters can be ordered (i.e., the alphabet) and, as is the case for numbers, children learn this ordinal sequence (e.g., they practice that B follows A and C follows B; Justice, Pence, Bowles, & Wiggins, 2006). As adults we use an alphabet ordering system for various tasks, such as filing and organizing references. Although letters have ordinal associations, unlike numbers they do not have magnitude associations. The presence of an order system and the absence of a magnitude system make letters ideal stimuli in order to disambiguate between the aforementioned ratio-dependent and ordinal associations accounts of adaptation of symbolic number in the IPS. More specifically, if there are similarities in the rebound effects for letters and numbers in the IPS, then an ordinal account is more likely. If, however, only numbers exhibit such an effect, then great confidence can be associated with the ratio-dependent explanation of the rebound from adaptation of the IPS signal to symbolic number.

In view of the above, the aim of the current study was to explore the mechanisms of the distance/ratio-dependent recovery effect observed in numerical fMRI-A research. Presently, it is unknown whether the parietal recovery effect is specifically modulated by changes in numerical magnitude. Put differently, it is unclear whether the recovery effect observed in the IPS can be unambiguously attributed to the direct mapping of symbolic numbers onto an analog system of magnitude representation, or whether it may be reflective of some other numerical attribute, such as ordinality. The ordinal associations between numbers could generate an effect that is indistinguishable from that which would be generated by overlapping representations of numerical magnitude, thereby resulting in the mistaken attribution of the neural parametric effect to an ANS system of number representation.

With this gap in the literature in mind, the current study will address the following question: Will the IPS show a recovery effect if presented with non-numerical, ordered stimuli with no magnitude associations? To address this question, we presented adults with symbolic stimuli that have strong ordinal associations: digits and letters. Letters have been shown in previous research to have strong ordinal associations (Jou & Aldridge, 1999), but unlike symbolic numbers, letters do not have a magnitude associated with them.

If direct mapping from symbolic digits to non-symbolic magnitudes can explain the ratio/distance modulated recovery in signal observed in the IPS, symbolic stimuli with no inherent magnitude association should not elicit a parametric effect (Figure 2.1).

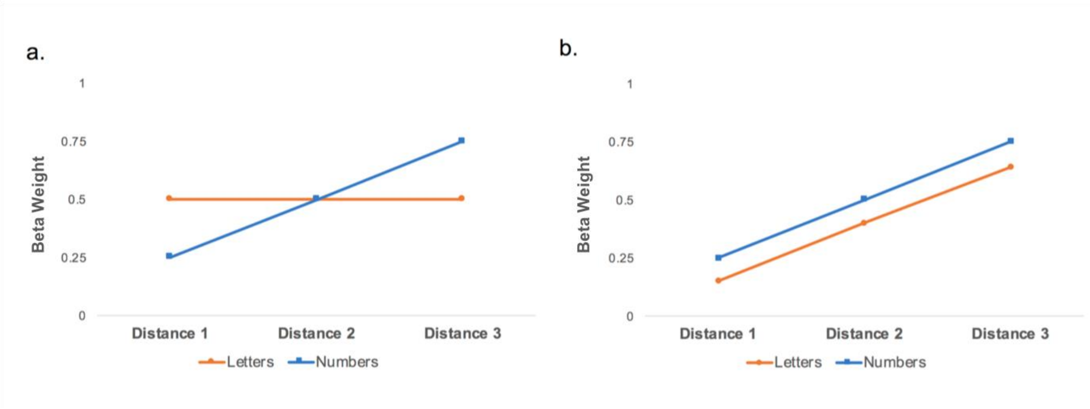

Figure 2.1: Predictions for parietal activation during the adaptation task for the number (blue) and letter (orange) conditions. Distance represents numerical distance between the adapted value and deviant. [a] Only numbers demonstrate a distance-dependent rebound effect. This would not support the hypothesis of ordinal mechanisms as underlying the parametric effect, and would suggest this effect is more number-specific. [b] Both numbers and letters result in a parametric modulation of brain activity. This would suggest that ordinal relationships between symbols could account for the parametric effect.

There already exists some data to suggest that there may be similarities in the way in which letters and number are processed in the brain. Specifically, Attout, Fias, Salmon and Majerus (2014) and Fias, Lammertyn, Caessens and Orban (2007) found activation in the horizontal section of the IPS in response to both letter and number stimuli, which suggests that the IPS activation observed for numerical stimuli could be at least partially reflective of general ordinal relationships among symbols.

In Experiment 1, we build on the existing evidence and probe whether letters and numbers lead to similar patterns of rebound from adaptation in the IPS. Using letters allows us to disentangle two different mechanisms that could result in similar patterns of activation; representational overlap as predicted by the ANS, and symbol-symbol ordinal associations. Moreover, using a passive design allows us to mitigate the response selection confound that was present in previous studies.

2.2 Experiment 1

2.2.1 Materials and Methods

2.2.1.1 Participants.

Participants were recruited from the University of Western Ontario campus in London, Canada. Twenty-seven healthy, right-handed adults with normal or corrected to normal vision participated in this study. In order to be included for analysis, participants had to pass the motion and accuracy criteria for at least one of the two functional adaptation runs. Motion could not exceed 3mm of drift across the entire run or greater than 1.5mm jump between successive volumes (Vogel, Goffin, & Ansari, 2015). Runs that did not meet these motion criteria were not included in analysis. Accuracy on the adaptation task catch trials had to be at least 5/7 catch trials.

Three participants were not included in the analysis for the following reasons: one participant experienced claustrophobia and pressed the emergency call button, ending the scanning session before completion, and two participants did not fulfill the accuracy criteria for the adaptation runs, therefore we cannot assume that they were awake for the duration of the run. This left 24 participants ages 19.17 – 28.08 years (M_{age} = 22.78 years; 14 males) for analysis. Informed consent was obtained, participants were compensated monetarily for their time, and were sent a picture of their brain.

2.2.1.2 Adaptation Task.

The design of the adaptation task was based on Vogel et al. (2017). The task stimuli consisted of black (R-G-B values 0, 0, 0) English letters and Arabic numerals displayed on a grey background (R-G-B values 192, 192, 192). The catch trials were presented in red (R-G-B value 255, 0, 0). The numbers used were: 2, 3, 4, 5, 6, 7, 8. The letters corresponding to these numbers were used: B, C, D, E, F, G, H. In order to minimize adaptation to the visual characteristics of the symbols, two font sizes (size 40pt and size 50 pt) and four font types (Times New Roman, Courier New, Calibri and Arial) were used. Additionally, the location of the symbol varied randomly across six locations, all 2 degrees from the display centre (x,y position from the centre = 435, 300; 365, 300; 375, 325; 425,325; 375,275; 425,275). Eprime 2.0 software was used to project the stimuli onto a screen in the MRI.

An event-related design was used. Each symbol appeared on the screen for 200ms and was followed by a blank screen for 1200ms (see Figure 2.2). Half of each run of the adaptation task was made up of only numbers, and the other half only letters. In other words, both the number and letter conditions were presented within each run, separated by a short break (14 000ms) The order of presentation of the number and letter conditions was counterbalanced across participants. For the number condition the digit 5 was used to habituate brain response, and the corresponding letter E was used for the letter condition. In the adaptation period, the number 5 for the number condition, or the letter E for the letter condition, was repeated between five and nine times, with an average of seven repetitions across the run. The adaptation period was followed by the pseudorandom presentation of one of 48 deviant trials (8 for each numerical/letter deviant), one of 7 catch trials, one of 8 null trials or one of 7 scrambled trials per condition. A pseudorandom order was used in order to ensure that catch trials would appear throughout duration of the run. Deviant trials differed from the habituation value 5 or E by a distance of 1, 2 or 3 (see Table 2.1). Catch trials consisted of each of the stimuli used presented in red font and were included to help ensure participants were attending to the stimuli on the screen. Participants were asked to press a button as soon as they saw a red symbol. Null trials consisted of another presentation of the habituation value (i.e., 5 or E). As the null trials were indistinguishable from the adaptation period, these trials were modelled in the baseline for the neural rebound effect. The baseline was used in all contrasts in the whole-brain analyses to identify regions that demonstrated activation above baseline (the specific contrasts are described in the Data Analysis section). The scrambled stimuli consisted of a Fourier-transformed version of each of the number and letter stimuli used. These nonsense stimuli were included so as to further control for regions that may show a rebound effect simply for change in visual features. To our knowledge, this is the first number adaptation study to use nonsense symbols as a control for lower-level perceptual changes. As these scrambled stimuli were not recognizable as a number or a letter, they did not have a semantic meaning. See Figure 2.3 for an example of each of the stimuli types.

Table 2.1: Stimuli used in the number and letter conditions in the adaptation task

Distance	Numbers		Letters	
0	5		E	
1	4	6	D	F
2	3	7	C	G
3	2	8	B	H

Stimuli are sorted by distance from the adaptation symbol (i.e., 5/E).

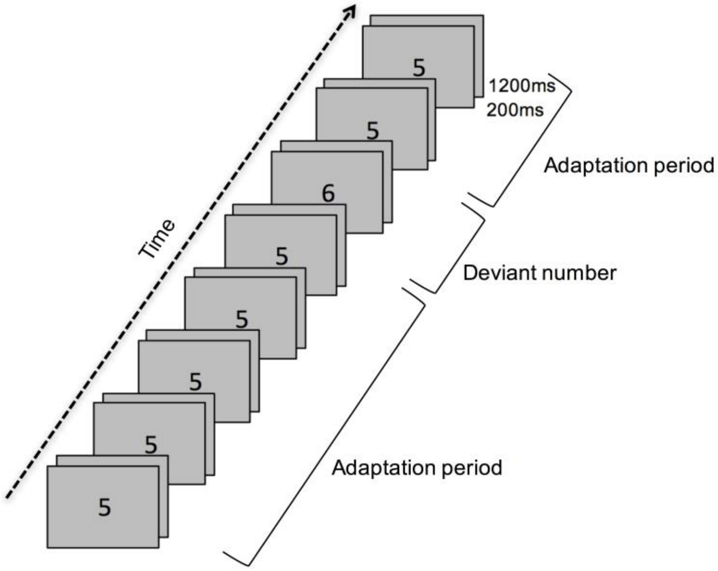

Figure 2.2: Example of the number condition in the adaptation task. The adaptation period (repeated presentation of 5) is sometimes followed by a deviant number (in this case 6).

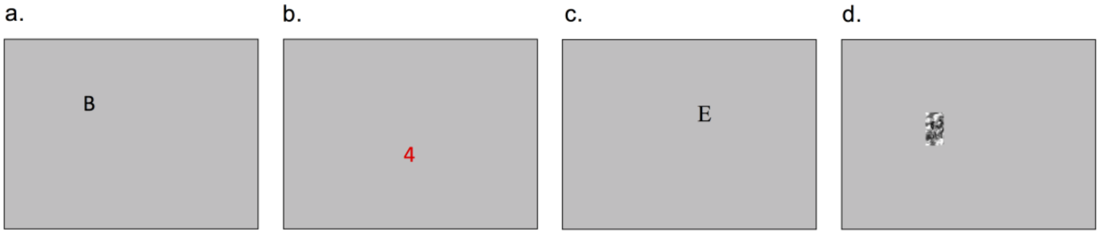

Figure 2.3: Trial types that followed the adaptation periods. a. Deviant trial, b. catch trial, c. null trial, d. scrambled trial.

2.2.1.3 Procedure.

Participants were screened for MRI safety and the task instructions were explained. They were given ear plugs to reduce the noise of the scanner and foam cushions were used around the head to reduce head movement. Participants viewed the tasks through a mirror system attached to the head coil of the scanner. For the adaptation task, participants were told that they would see numbers and letters appear on the screen, and to keep their eyes on the screen for the duration of the task. They were shown the button response and told to press the button with their right index finger whenever they saw a red symbol. Participants also completed an arithmetic verification task and a phonology task, however, for the purposes of this paper these tasks are not included in the analysis. Participants completed two runs of the adaptation task, and one run each of the arithmetic and phonology tasks. The order of the tasks was counterbalanced across participants, however to reduce fatigue effects the two adaptation runs never directly followed one another. An anatomical scan was collected last. The participants were in the scanner for approximately 1.5 hours. After the scanning session, participants completed a Math Fluency task from the Woodcock Johnson III Tests of Achievement as well as a phonology verification task, however these tasks were not analyzed for the purposes of the current paper. The entire testing session took no more than two hours.

2.2.1.4 fMRI Data Acquisition.

Functional and anatomical data were collected with a 3T Siemens Magnetom Prisma scanner at the Robarts Research Institute in London, Canada using a Siemens 32-channel head coil. fMRI-A data were collected with a BOLD-sensitive T2* weighted echo planar (EPI SE) sequence. Thirty-five slices per volume were acquired covering the whole brain using an ascending-interleaved method (3mm thickness, 70 x 70 matrix; field of view = 210 x 210mm; TR = 2000ms; echo time = 57ms; flip angle = 78 degrees). For the adaptation task, 860 volumes per functional run were acquired. Each run was 28 minutes and 40 seconds long.

High-resolution T1-weighted MRI data were collected at the end of the functional runs in the sagittal plane (voxel size of 1mm x 1mm x 1mm; 192 slices; TR = 2300ms).

2.2.1.5 fMRI Analysis.

Functional data were preprocessed using Brainvoyager 20.6 software (Brain innovation, Maastricht, The Netherlands). Functional data were corrected for head motion, low frequency noise and differences in slice scan-time acquisition and spatially smoothed with a 6mm FWHM Gaussian smoothing kernel.

Functional imaging data were aligned with the anatomical data. The anatomical data and functional runs were transformed into MNI-152 space for analysis at the group level. The hemodynamic response was modeled using a 2-gamma function. A whole-brain, random effects general linear model (GLM) was then used. An uncorrected threshold of $p < .005$ was used to find neural regions active for each analysis. Cluster correction was then used to correct for multiple comparisons (Forman et al., 1995; Rainer Goebel, Esposito, & Formisano, 2006) at the whole-brain level. A mask of the whole brain was used to restrict the cluster calculation to voxels inside the brain. A Monte-Carlo algorithm with one thousand iterations was used to determine the minimum size of a cluster that would result in a false positive rate of 5% (Rainer Goebel et al., 2006). The cluster correction was then carried out at a whole-brain level and clusters that remained at a threshold of $p < .05$ (cluster-corrected) were identified as significant.

2.2.1.6 Data Analysis.

As a first step, accuracy on the adaptation task catch trials was examined, resulting in any run scoring below 71.4% (5/7 catch trials) being removed from further analysis. This number was chosen to match as closely as possible to the accuracy cut-off used in previous studies (e.g., Vogel et al. 2015: cut-off = 6/8 catch trials, or 75%).

To examine the presence of a neural distance-dependent rebound effect for letters or numbers, parametric predictors were created for each participant. Using the deviant stimuli, predictors were weighted for distances 1 (4 and 6; D and F), 2 (3 and 7; C and G) and 3 (2 and 8; B and H) in relation to the adaptation symbol (5/E). The parametric predictors were created for the number condition (i.e., distance effect for number) and the letter condition (i.e., distance effect for letter). The weighted deviant trials were entered as parametric regressors into a GLM (Holloway et al., 2013). The parametric predictors allowed us to identify regions with a distance-dependent recovery effect. More specifically, this model predicts an increase in signal recovery with an increase in distance from the adaptation symbol. This analysis is similar to analyses used by Holloway et al. (2013), Vogel et al. (2015) and Vogel et al. (2017). A predictor for catch trials was also created. This predictor was entered into the GLM as a predictor of no interest to account for additional variance in the model (Vogel et al., 2015). The baseline was modeled on the adaptation and null stimuli. The recovery effect was evaluated by looking at the signal change from baseline with the presentation of a deviant.

Using the parametric predictors described above, whole-brain multisubject GLMs were run. We looked for regions that exhibited distance-dependent recovery of activation for the letter and number deviants. To identify these regions, the following contrasts were run: parametric effect of $\text{deviant}_{\text{Letter}}$ > baseline and parametric effect of $\text{deviant}_{\text{Number}}$ > baseline. This analysis will identify regions that show a distance-dependent recovery in activation (parametric distance effect). Based on previous number adaptation literature, we expect to find a parametric recovery effect in the left IPS for both the letter and number stimuli. Next, we examined any differences between the letter and number conditions: parametric effect of parametric effect of $\text{deviant}_{\text{Number}}$ > parametric effect of $\text{deviant}_{\text{Letter}}$. Within FSLview, the MNI standard map (avg152T1_brain.nii.gz) was loaded and peak coordinates and centre of gravity coordinates were entered in MNI space. Brain regions were then identified using the Jülich Histological Atlas (Eickhoff et al., 2005) and Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476) within the FSLview software (Smith et al., 2004).

Main effects for the letter and number deviants were modelled in order to identify brain regions that show any recovery effect due to a change in stimulus. For this purpose the following contrasts were used: main effect of $\text{deviant}_{\text{Number}}$ > baseline, main effect of $\text{deviant}_{\text{Letter}}$ > baseline. For these contrasts we expected to see IPS activation as well as visual and frontal regions involved in attention and change detection.

A main effect predictor was also calculated for the scrambled stimuli. We used the scrambled symbol events to investigate whether regions identified in the deviant number and letter main effect were responding to the meaning of the symbols, or rather a change in visual properties. In other words, if the main effect for the meaningful symbols (i.e., letters and numbers) identifies regions that show activation over and above that shown for the scrambled stimuli, that would suggest that regions demonstrating a main effect may be involved in representation of the symbols. However, if there are no regions that demonstrate greater activation for the main effect vs. the scrambled main effect, this would suggest the symbol main effect is reflective of some sort of change detection mechanism. Therefore, to look for regions that demonstrate a recovery effect specific to meaningful symbols (rather than simply deviants in visual properties) the following contrasts were calculated: main effect of $\text{deviant}_{\text{Number}}$ > main effect of number scrambled $\text{symbols}_{\text{Number}}$, main effect of $\text{deviant}_{\text{Letter}}$ > main effect of letter scrambled $\text{symbols}_{\text{Letter}}$. Activation in the IPS and frontal regions was predicted for both of these contrasts.

2.2.2 Results

2.2.2.1 Behavioural Results.

To be included in the analyses, participants had to catch at least 5 of 7 catch trials in each condition of each run. Each participant completed 2 runs of the adaptation task. Of the 24 participants that had at least one run of the adaptation task that fulfilled the motion and accuracy criteria, five runs were not included because they exceeded the motion cut off, and four runs were not included because they did not fulfill the accuracy cut off. This left 39 runs in total for the analysis. Accuracy on these runs had a mean of 0.97, *SD* = .06.

2.2.2.2 Imaging Results.

To identify regions of the brain that respond to any deviation in the number or letter stimuli, the main effect of the deviants for each condition was contrasted against the baseline activation. This analysis models all deviant symbols as the same; in other words the deviants are not modelled according to their distance from the adapted symbol. At the whole-brain level, 2 clusters in the visual cortex were significant after cluster correction for the contrast main effect for numbers > baseline (Table 2.2). For the contrast main effect for letters > baseline, 5 clusters reached significance (Table 2.3).

Next, the whole brain was examined for a distance-dependent parametric recovery effect for each of the number and letter conditions. For the contrast parametric regressor for numbers > baseline, 4 significant clusters were identified (see Table 2.4). Most notably, clusters in the right anterior IPS and left anterior IPS were found to show the expected distance-dependent activation pattern (see Figure 2.4). No significant regions were found to show a parametric effect for the parametric regressor for letters > baseline contrast. Moreover, even at an increased threshold of .01 uncorrected, no regions demonstrated a parametric effect for letters.

Table 2.2: Location of significant clusters identified at the whole-brain level for the main effect of number deviants.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Visual cortex V3V	Right	31.05	-87.78	-2.76	6.97	3.91	5.44	848	Visual cortex V4	39	-86	-8	4.360484	0.000229
Visual Cortex V3V	Left	-23.91	-90.67	-6.7	6.09	4.91	5.31	2621	Visual cortex V2 BA18	-24	-97	-8	4.070763	0.000472

Coordinates are in MNI space. Cluster size is given in number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005).

Table 2.3: Location of significant clusters identified at the whole-brain level for the main effect of letter deviants.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Visual cortex V1 BA17	Right	0.05	-74.71	0.51	30.31	15.15	15.87	80661	Visual cortex V4	45	-67	-14	8.716191	<.000001
Anterior IPS hIP1	Left	-25.39	-65.7	40.91	3.42	7.3	9.12	6263	Superior parietal lobule 7A	-27	-70	34	5.443437	0.000016
Frontal orbital cortex*	Left	-30.01	29.01	1.17	3.48	4.66	3.47	1200	Insular cortex*	-30	29	4	4.254945	0.000298
Broca's area BA44	Left	-41.19	22.94	17.52	4.65	2.55	5.71	1090	Broca's area BA45	-39	26	13	4.353102	0.000234
Broca's area BA44	Left	-45.01	4.83	33.86	6.29	5.12	2.85	3058	Corticospinal tract	-39	-1	34	5.528336	0.000013

Coordinates are in MNI space. Cluster size is given in number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005) unless no region was found in this atlas for the specified coordinates. These regions (marked with *) were identified using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

Table 2.4: Location of significant clusters identified at the whole-brain level for the parametric effect of number deviants.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Anterior IPS hIP1	Right	33.28	-65.29	37.8	4.07	3.1	2.63	1313	Anterior IPS hIP1	33	-67	37	4.261469	0.000293
Anterior IPS hIP2	Right	33.13	-37.25	32.86	3.15	7.6	2.54	1365	Anterior IPS hIP3	33	-40	34	4.063882	0.00048
Premotor cortex BA6	Right	28.39	1.39	48.96	3.05	4.58	3.52	1262	Premotor cortex BA6	33	-4	49	4.385268	0.000216
Optic radiation	Left	-38.71	-45.68	20.15	5.29	2.06	5.65	945	Anterior IPS HIP1	-39	-46	22	4.472119	0.000174

Coordinates are in MNI space. Cluster size is given in number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005).

Table 2.5: Location of significant clusters identified at the whole-brain level for the parametric effect of number deviants > parametric effect of letter deviants.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Inferior parietal lobule PGp	Left	-35.49	-70.91	26.36	2.9	2.24	8.94	1210	Optic radiation	-33	-70	25	4.031529	0.00052
Middle temporal gyrus, temporooccipital part*	Left	-48.11	-50.64	13.88	5.17	4.2	2.37	1491	Angular gyrus*	-45	-52	16	4.440388	0.000188

Coordinates are in MNI space. Cluster size is given in number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005) unless no region was found in this atlas for the specified coordinates. These regions (marked with *) were identified using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

Table 2.6: Location of peak voxels for significant clusters identified at the whole-brain level for the main effect of number deviants > main effect of scrambled numbers.

Region - Center of Gravity	**Hemisphere**	**mean x**	**mean y**	**mean z**	**stdev x**	**stdev y**	**stdev z**	**Cluster size**	**Region - Peak Voxel**	**x**	**y**	**z**	**t**	**p**
Visual cortex V4	Right	39.57	-63.58	-10.72	6.98	13.9	7.11	15153	Temporal occipital fusiform cortex*	42	-58	-11	-7.259053	<.000001
Broca's area BA44	Right	41.79	9.21	31.31	3.96	3.7	3.83	2132	Broca's area BA44	42	8	31	-5.239583	0.000026
Interior occipito-frontal fascicle	Right	31.64	23.91	-0.92	3.4	4.64	3.08	945	Inferior occipito-frontal fascicle	27	26	1	-3.896417	0.000727
Anterior IPS hIP3	Right	34.37	-58.55	44.78	2.16	4.39	2.75	962	Anterior IPS hIP3	33	-61	46	-4.022963	0.000531
Occipital fusiform gyrus*	Left	-40.26	-65.22	-11.4	6.49	11.87	5.88	14527	Lateral occipital cortex, inferior division*	-45	-67	-11	-7.163185	<.000001

Coordinates are in MNI space. Cluster size is given in number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005) unless no region was found in this atlas for the specified coordinates. These regions (marked with *) were identified using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

Table 2.7: Location of peak voxels for significant clusters identified at the whole-brain level for the main effect of letter deviants > main effect of scrambled letters.

Region - Center of Gravity	**Hemisphere**	**mean x**	**mean y**	**mean z**	**stdev x**	**stdev y**	**stdev z**	**Cluster size**	**Region - Peak Voxel**	**x**	**y**	**z**	**t**	**p**
Visual cortex V5	Right	41.4	-60.2	-8.33	10	15.04	9.64	17237	Temporal occipital fusiform cortex*	39	-55	-20	-8.193955	<.000001
Broca's area BA44	Right	43.7	16.9	24.59	6.57	12.48	12.39	14148	Broca's area BA44	48	11	28	-7.776074	<.000001
Anterior IPS hIP1	Right	31.95	-64.6	39.38	3.21	7.04	8.25	3077	Superior parietal lobule 7P/Anterior IPS hIP1	30	-67	40	-4.511512	0.000157
Premotor cortex BA6	Right	7.1	16.75	47.86	2.06	5.57	3.42	992	Premotor cortex BA6	9	23	43	-4.259583	0.000295
Visual cortex V4	Left	-37.06	-61.83	-13.74	6.14	12.64	5.02	9535	Temporal fusiform cortex, posterior division*	-36	-40	-24	-7.38112	<.000001

Coordinates are in MNI space. Cluster size is given in number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005) unless no region was found in this atlas for the specified coordinates. These regions (marked with *) were identified using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

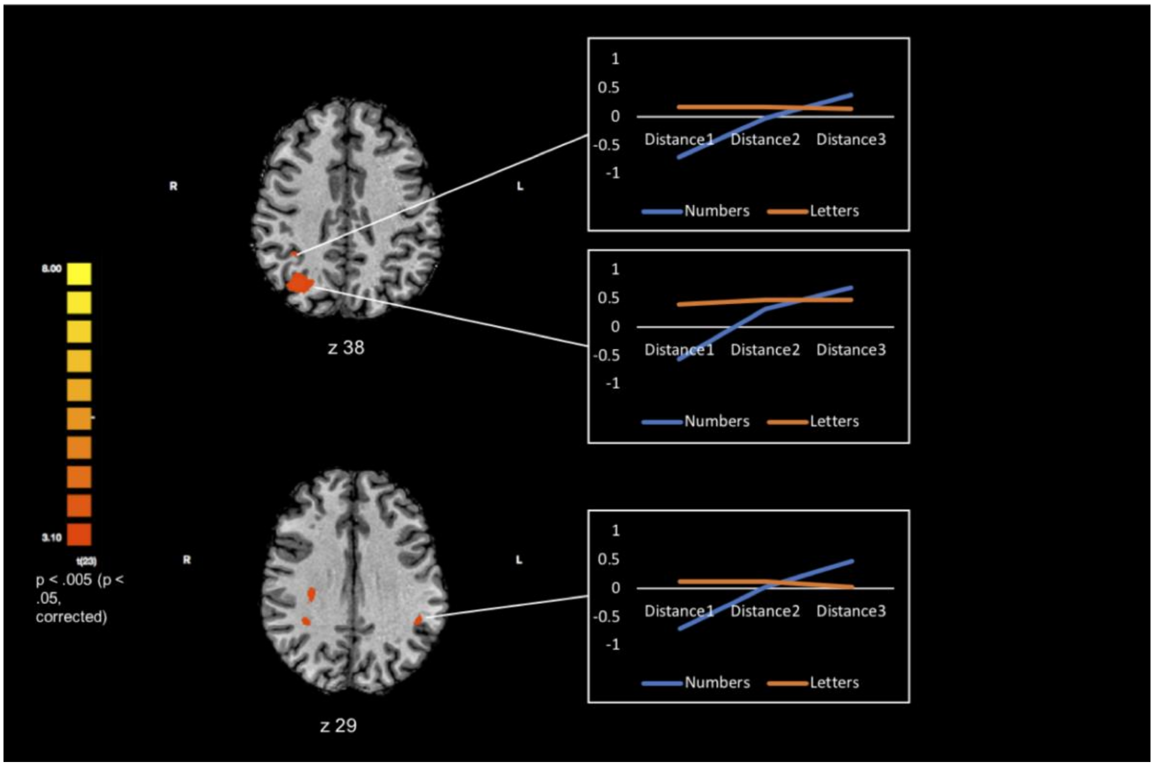

Figure 2.4: Right anterior IPS clusters and left anterior IPS are activated for the number parametric effect. Coordinates are in MNI space. The line graphs represent the distance-dependent modulation for numbers (blue) and letters (orange) in the right anterior IPS clusters (top) and left anterior IPS. These points were derived by extracting the beta weights from the parietal regions that exhibited a significant parametric effect for numbers. Numbers demonstrate the predicted distance-dependent parametric increase of rebound of activation, whereas letters do not demonstrate this pattern.

To further investigate the specificity of the parametric effect for numbers, the following contrast was carried out at the whole-brain level: parametric effect for numbers > parametric effect for letters. Two significant clusters were found including the left inferior parietal lobule (see Table 2.5 and Figure 2.5).

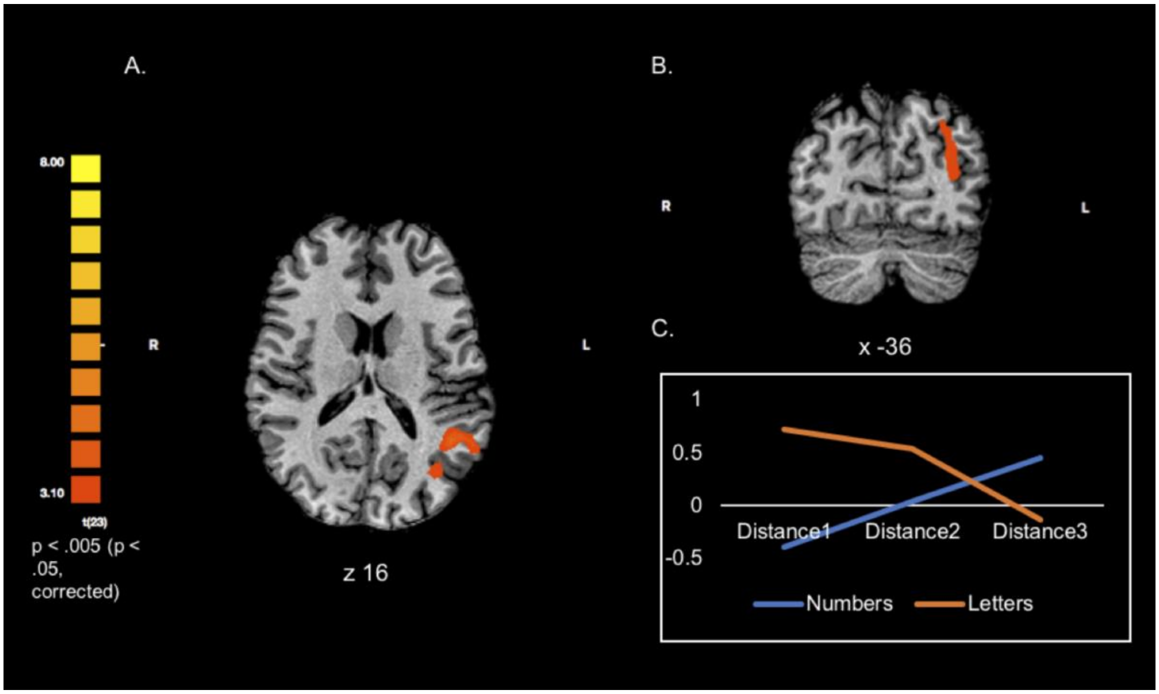

Figure 2.5: Significant parietal cluster for the contrast number deviant parametric effect > letter deviant parametric effect. A. Transverse view of statistically significant parietal cluster. B. Coronal view of statistically significant parietal cluster. C. The line graph represents the distance-dependent modulation for numbers (blue) and letters (orange) in the left inferior parietal lobule. These points were derived by extracting the beta weights from the parietal regions that exhibited a significant parametric effect for numbers. Numbers demonstrate the predicted distance-dependent parametric increase of rebound of activation, whereas letters do not demonstrate this pattern.

Contrasts with the scrambled symbolic stimuli were also examined at the whole-brain level in order to better understand the main effect findings. In particular, because the scrambled stimuli have no meaning, if the number and letter main effects are contrasted with the scrambled stimuli we can examine whether the main effects are related to a change detection mechanism, as opposed to processes related to symbol processing. More specifically, if the main effect for numbers and letters reflect any stimulus specific processing, then these main effects should show greater activation for either letters or number relative to the scrambled conditions. If however, the main effects are mostly reflective of general processes such as change detection and a change in attentional state, then there should be no regions that show a greater main effect for letters or numbers compared to the scrambled symbols. Indeed, this is what we found. For the contrast of main effect of numbers > main effect of scrambled numbers, there were 5 regions that were greater for the scrambled stimuli (i.e., showed greater activation for scrambled numbers compared to numbers; Table 2.6). Similarly for the letter main effect > main effect of scrambled letters, 5 clusters demonstrated negative activation (Table 2.7). These findings are convergent with a change detection explanation of the main effects observed, rather than processing of symbol-specific information. If the main effects were specifically associated with symbolic processing, we might expect to see activation for the numbers and letters that is greater than the activation for the scrambled stimuli. Instead, there is evidence for more robust activation in response to the scrambled symbols which carry no semantic meaning but greater novelty. Whatever may explain the greater activation for scrambled symbols, the evidence does not point to the main effects being reflective of stimulus-specific activation patterns.

Contrary to our predictions, letters did not exhibit a distance related parametric effect in any brain region, even at very liberal statistical thresholds (i.e., .01). However, an absence of evidence does not imply evidence for absence. In view of this, in order to further constrain our understanding of the null results obtained for the parametric effect of letters, we quantified the evidence for the null hypothesis (no parametric distance effect for letters) using Bayesian statistics. Specifically, an ROI analysis was conducted using the parietal clusters identified for the number parametric effect > baseline analysis. Average beta weights for the letter parametric effect were extracted from the right anterior IPS HIP1 (M = 0.04, SD = 0.75), right anterior IPS HIP2 (M = -0.02, SD = 0.80) and left anterior IPS (M = -0.05, SD = 0.66). Using JASP, a Bayesian one-sample t-test was then run to determine the strength of the evidence, or Bayes Factor, for the null hypothesis (BF_{01}); i.e., that there was not a significant parametric effect for letters (JASP Team, 2019). The parametric effect for letters was not found to be significant for the right anterior IPS HIP1, t(23) = 0.27, p = .792, BF_{01} = 4.51, right anterior IPS HIP2, t(23) = -0.12, p = .903, BF_{01} = 4.63, or left anterior IPS, t(23) = -0.41, p = .688, BF_{01} = 4.32. Overall, the Bayesian t-tests indicated substantial support in favor of the null hypothesis (Jeffreys, 1961).

2.2.3 Discussion

Which mechanisms underlie the parametric effect observed in numerical adaptation studies? Experiment 1 used fMRI-A to test whether this effect is driven by an analog system of magnitude representation or whether it can, at least in part, be explained by general processing of ordinal relationships. This was tested by examining the neural adaptation to letters and numbers, which are both ordinal sequences, but numbers, unlike letters, carry information about numerical magnitude as well as numerical order. Bilateral regions in the IPS were shown to be modulated by numerical distance when participants were presented with number symbols. Contrary to the account that posits that the processing of general ordinal associations (e.g., the fact that 1 come before 2 like A comes before B) can account for the adaptation of the IPS to numerical symbols, letters were not found to be associated with a parametric effect anywhere in the brain. Put differently, following adaptation, the ordinal distance between the adapted and deviant letters was not found to modulate brain activation. Finally, when compared to letters, the left inferior parietal lobule was found to be more strongly correlated with the parametric processing of numerical deviants.

Against the background of the findings from Experiment 1, we did not find support for the hypothesis that the parametric effect in the IPS in response to symbolic number can be explained by the processing of ordinal relationships that exist for both letters and numbers. Such an account would have been supported if the parametric response to letters and number was similar. However, presenting participants with letters - symbols that have ordinal associations but no magnitude associations – did not result in a parametric effect. If symbol-symbol ordinal relationships could explain the neural parametric effect observed in the parietal lobe in numerical adaptation studies, presenting participants with letters in an analogous task should have generated a pattern similar to that revealed for number symbols. However, results from Experiment 1 do not provide evidence in support of this hypothesis. Of course, it is also possible that there are differences in the relative degree to which the ordinal associations get activated when participants view a number vs. a letter. Perhaps there are different levels to the automaticity with which we access internal representation of such ordinal relationships; with ordinal associations being activated more automatically for numbers, and less automatically for letters. This could also explain the lack of a parametric effect observed for letters.

It is important to highlight that these findings therefore do not refute the ANS theory of symbolic number representation. However, it should be noted that these results also do not provide direct support for the ANS theory either. The current study was not designed to explicitly test the theory of an analog number system as underlying symbolic numerical representation; only to test whether a general representation of order (for both letters and numbers) could account for the data observed. Although ordinality could not explain the parametric effect, it remains to be seen whether a different mechanism can explain the parametric effect for number symbols. For example, perhaps ordinal associations underlie this effect, but the ordinal associations between these symbols must be processed fluently and automatically in order to generate the parametric effect in a passive task (Vogel et al., 2019). Further research that empirically tests alternative mechanisms is necessary to rule out other possible accounts.

In contrast to the present findings, previous research using a letter ordinality task demonstrated bilateral activation in the IPS (Fulbright, Manson, Skudlarski, Lacadie, & Gore, 2003). Specifically, Fulbright et al. (2003) found a network of regions including bilateral IPS to be more activated for letter ordering than identification. While the present results also revealed activation of the left IPS when contrasting the presentation of letter deviants against rest (i.e., the main effect for letters), the interpretation of such an effect is not straightforward. This is because the main effect analysis treats all deviants as the same (i.e., the deviants are not parametrically weighted), thereby making it difficult to distinguish between brain activation due to processing of ordinal position of the letters or something such as change detection. To further demonstrate the lack of specificity of the main effect, when the main effect for letter stimuli was contrasted with the scrambled letter condition, there were no regions that showed greater activation for letters than for the nonsense scrambled condition. Because the scrambled condition stimuli were not identifiable as letters, this supports the interpretation that the letter main effect that was observed can likely be attributed to the detection of a change in visual stimulus, as opposed to ordinal processing of the letter stimuli or indeed anything specific to the processing of letters. This converges with findings demonstrating a key role for the IPS in visuo-spatial attention and suggests that the parietal activation observed in the main effect contrasts likely reflects domain-general visuo-spatial attention (e.g., Materna, Dicke, &

Thier, 2008; Silk, Bellgrove, Wrafter, Mattingley, & Cunnington, 2010). Examining the brain for regions that show a parametric increase in rebound of activation is therefore a more precise measure of any processing of ordinality rather than the main effect, which most likely reflects activation that is not stimulus specific, such as change detection, or a change in attentional state for example.

2.3 Experiment 2

2.3.1 Introduction

Experiment 1 tested the hypothesis that the processing of ordinal mechanisms drives the neural parametric effect that has been repeatedly observed in numerical adaptation tasks. Although the parametric effect for numbers was replicated, letters did not exhibit a similar pattern; a finding that does not support such an account. Even though a parametric effect for letters was not obtained at the neural level with a passive task, based on previous research we would still expect letters to generate a behavioural distance effect (Van Opstal et al., 2008). In a behavioural study, Van Opstal et al. (2008) used letters to challenge the theory that representational overlap underlies the NDE. When participants were asked to complete a comparison task, an NDE was obtained for both the number and letter condition. The NDE was thus attributed to processes related to response selection, as opposed to a specific numerical process (Van Opstal et al., 2008).

In view of this, the first goal of Experiment 2 was to test whether a distance effect can be obtained with the specific letter stimuli used in Experiment 1. In the absence of such data it is plausible to posit that the lack of a neural parametric effect may reflect an inability to process the ordinal association between letters. More specifically, if a behavioural distance effect is not obtained with these letter stimuli, perhaps the letters included do not elicit the processing of sequential order. However, if a behavioural distance effect is obtained with the letter stimuli, this would support the notion that there exists a dissociation between the neural parametric effect and the behavioural NDE. To this end, a between-groups design was used in which participants were randomly assigned to complete an ordinality comparison task in either the number condition or the letter condition. Based on previous research, demonstrating distance effects with letter stimuli, we expected to find distance effects for both the number and letter conditions (Van Opstal et al., 2008).

The second goal of Experiment 2 was to probe whether participants used a numerical magnitude strategy to complete the letter ordinality task. Importantly, if a distance effect is generated with a task using letter stimuli, it could be argued that participants were using a numerical magnitude strategy, in which they assigned a numerical value to each letter in order to complete the letter task (e.g., B = 2). To test this, a letter arithmetic task was used, in which participants were explicitly instructed to assign numerical values to letters to solve a letter arithmetic problem. To test whether completion of the letter condition in the ordinality task involved the use of a numerical magnitude strategy, performance on a letter arithmetic task was compared between two groups: a number and a letter group. If participants are using a numerical assignment strategy to complete the letter behavioural task (e.g., B=2), one might expect better performance on the letter arithmetic task in the group that practiced the letter ordinality task (i.e., the letter group) when compared to a group that did not practice letter ordinality (i.e., the number group). This is because the letter arithmetic task explicitly asks participants to use a numerical assignment strategy. However, if performance on the letter arithmetic task is not enhanced in the letter group, it is more likely participants are completing the letter behavioural task using the ordinal associations between letters, as opposed to assigning numerical quantities to the letters.

The methods of Experiment 2 were pre-registered on the Open Science Framework (OSF). Additional preregistered analyses with these data not relevant to the current manuscript are also available on the OSF page (https://osf.io/s6e7u/).

2.3.2 Materials and Methods

2.3.2.1Participants.

Data from two groups of participants were collected for this study: a letter training group and a number training group. Two participants were excluded because of incomplete data collection. This left a total of 184 participants for analysis: 90 in the letter training group (64 females; M_{age} = 22.97 years; SD_{age} = 3.99) and 94 in the number training group (60 females; M_{age} = 22.63 years; SD_{age} = 3.34). The sample size was calculated using a Bayesian stopping point described below in the results section (Marsman & Wagenmakers, 2017).

2.3.2.2 Procedure.

Participants completed the following tasks in this order:

1. Four runs of ordinality training with a comparison to standard task (either letters or numbers depending on training group).
2. Letter arithmetic task
3. Number arithmetic task
4. Ordinality task of not-trained format (either numbers or letters depending on training group).

For the purposes of the current paper, the number arithmetic task (task 3) and ordinality task of not-trained format (task 4) were not analyzed, as the focus of the current study was whether or not distance effects could be obtained with the letter stimuli (task 1 for the letter group), and in turn how each trained condition (letters or numbers) influenced performance on the letter arithmetic task. A fixed order of the tasks was used so that the letter arithmetic task always followed the four runs of training with the ordinality task.

In the ordinality training tasks (task 1), participants were presented with a number or a letter in the centre of the computer screen (5000ms or until response, followed by a fixation point, 1000ms). They were asked to judge as quickly and as accurately as possible whether the randomly presented number comes before or after 5, or whether the randomly presented letter comes before or after E. Stimuli with distances 1, 2, and 3 from 5/E were used (see Table 2.1). A total of 192 trials were used per run. In the letter arithmetic task, participants saw an addition (12 problems) or subtraction problem (12 problems) with a solution on the screen (30 000ms or until response), using the letter stimuli listed in Table 2.1. Participants indicated as quickly and as accurately as possible whether the solution was correct or incorrect. Participants were instructed to treat the letters as if they represent their corresponding numerical value (e.g., B = 2).

2.3.3 Results.

Analyses were carried out using SPSS software for the frequentist statistics and JASP (JASP Team, 2018) for the Bayesian statistics. First, trials for which reaction time was greater/less-than three standard deviations from the participant's mean reaction time were removed from analysis, as were all trials with reaction time less than 100ms (Goffin & Ansari, 2016). This outlier analysis was conducted so as to reduce the inclusion of trials in which participants likely responded without processing the stimuli (unusually low response time), or were not attending to the task (unusually high response time). Next, accuracy for each task was examined (collapsed across groups) and participants who scored below three standard deviations from the mean accuracy on that task were not included in analyses involving that task. This resulted in the following participants being removed: two participants from run 1 of the ordinality task, three participants from run 2, four participants from run 3, four participants from run 4 and five participants from the letter arithmetic task.

Accuracy was near ceiling for both the letter and number ordinality training task (Table 2.8). Therefore, reaction time data analyses included only correct trials. To examine the effect of distance on the reaction time data, distance effects were calculated using the numerical distance between the presented symbol and the standard symbol (5 or E depending on number or letter condition) for each participant. For this purpose, we used a regression analysis with distance (1, 2 and 3) as a predictor to estimate an individual distance effect for every subject (De Smedt, Verschaffel, & Ghesquière, 2009; Sasanguie, De Smedt, Defever, & Reynvoet, 2012; Vanbinst, Ghesquiere, & De Smedt, 2012).The regression slope is an indicator of the size of the distance effect; the larger the regression slope value, the greater the size of the distance effect (Table 2.9). These standardized regression slopes were then tested against 0 with a one-sample t-test to determine whether a significant distance effect was present. Participants in both the number and letter groups demonstrated a negative slope; indicative of decreased reaction time as a function of increasing numerical distance between the presented symbol and the standard in all four runs, in the letter, $t_{\text{Run1}}(89) = -11.50$, $p < .001$.; $t_{\text{Run2}}(89) = -9.44$, $p < .001$; $t_{\text{Run3}}(87) = -8.00$, $p < .001$; $t_{\text{Run4}}(87) = -7.83$, $p < .001$ and number group, $t_{\text{Run1}}(91) =$ -

16.93, $p < .001$.; $t_{\text{Run2}}(90) = -15.82$, $p < .001$; $t_{\text{Run3}}(91) = -13.66$, $p < .001$; $t_{\text{Run4}}(91) = -15.90$, $p < .001$. This decrease in reaction time for larger numerical distances can be visualized in the average reaction time across the three distances (Figure 2.6).

Table 2.8: Average accuracy for correct trials for ordinality tasks for the number and letter groups.

	Run 1	**Run 2**	**Run 3**	**Run 4**
Letter group	0.96 (0.04)	0.96 (0.04)	0.97 (0.03)	0.96 (0.03)
Number group	0.97 (0.02)	0.97 (0.02)	0.97 (0.03)	0.96 (0.03)

Values represent mean accuracy (standard deviation).

Table 2.9: Average of the standardized regression coefficients for each group across the four training runs.

	Run 1	**Run 2**	**Run 3**	**Run 4**
Letter group	-0.11 (0.09)	-0.09 (0.09)	-0.07 (0.08)	-0.08 (0.09)
Number group	-0.14 (0.08)	-0.14 (0.09)	-0.14 (0.10)	-0.13 (0.08)

Values represent mean distance effect (standard deviation).

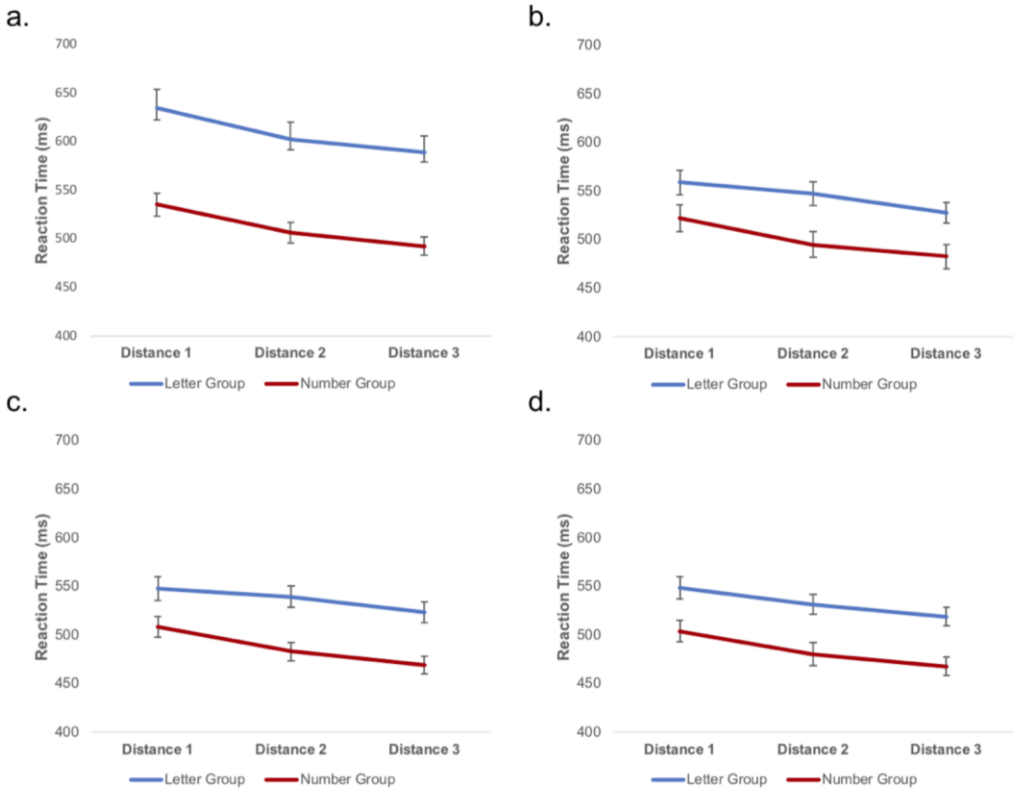

Figure 2.6: Mean reaction time (ms) for correct trials for distances 1, 2 and 3 on run 1 (a), run 2 (b) run 3 (c) and run 4 (d) of the ordinality training task for the letter (blue) and number (red) groups. Bars indicate standard error of the mean. Both groups demonstrated decreased reaction time with increased distance for all four runs.

We were also interested in how the letter and number groups compared on the ordinality training tasks (i.e., how the ordinality comparison tasks differed between the groups). Put differently, we wanted to determine whether the number group and letter group differed significantly in their performance on their respective ordinality tasks. More specifically we used independent t-tests to compare reaction time (for correct trials only) and distance effects between the groups. For this purpose, independent t-tests were used to compare run 1 between the letter and number groups, as well as run 4 between the letter and number groups on mean reaction time and distance effects. For mean reaction time, the letter group completed the letter ordinality task significantly more slowly (*M* = 608.08ms, *SD* = 169.43) than the number group performed the number ordinality task (*M* = 511.07ms, *SD* = 101.91) for run 1, *t*(145.34) = 4.67, *p* < .001. Levene's Test indicated unequal variances (*F* = 6.32, *p* = .013), therefore degrees of freedom were adjusted from 180 to 145.34. On run 4, the letter group also performed the letter ordinality task significantly more slowly (*M* = 532.81ms, *SD* = 93.20) than the number group performed the number ordinality task (*M* = 483.59ms, *SD* = 100.56), *t*(178) = 3.40, *p* = .001. For the distance effects, the groups demonstrated a significant difference in run 1, with the letter group showing a significantly smaller distance effect than the number group, *t*(180) = 2.70, *p* = .008. In run 4, the letter group also showed a significantly smaller distance effect than the number group, equal variances not assumed (*F* = 4.04, *p* = .046), *t*(170.42) = 4.09, *p* < .001. Therefore, the letter ordinality task seemed to be more difficult for participants, as indicated by the higher reaction time.

The letter ordinality task was performed more slowly than the number ordinality. One explanation for this finding could be that in order to complete the letter ordinality task, participants were mapping the letter stimuli onto their respective numerical counterparts (e.g., assigning B to a magnitude of 2), as this would involve an extra step of processing in comparison to the number ordinality task. To ensure that participants were not just using a number magnitude strategy in the letter ordinality task, we compared performance on the letter arithmetic task between the letter and number groups. For the letter arithmetic task, we calculated the average accuracy, reaction time for correct trials and performance for each group (see Table 2.10). The performance measure was calculated using a formula to combine reaction time and error rate: Performance = Reaction Time(1 + 2(Error rate)), where reaction time referred to average response time of both correct and incorrect trials (Goffin & Ansari, 2016; Lyons, Price, Vaessen, Blomert, & Ansari, 2014). We carried out an independent samples t-test as well as an independent samples Bayesian t-test for reaction time, accuracy and performance on the letter arithmetic task. For these analyses, we predicted that the letter and number groups would perform similarly on the letter arithmetic task. Better performance on the letter arithmetic task in the letter training group would imply that participants are using a strategy involving assigning numerical magnitudes to letters (e.g., C = 3) during the ordinality training. This would indicate a use of a numerical cardinality strategy, as opposed to a symbolic ordinality strategy. Similar behavioural performance on the letter arithmetic task in the letter and number groups however, could indicate that the letter group performed the letter ordinality by activating their representations of the ordinal relationships between letters. In other words, we expected to find support for the null hypothesis, and continued data collection until a BF in support of the null indicated strong evidence for no difference between-groups (BF $H_{01} = 6$). The use of a BF stopping rule allows the researcher to continue collecting data until a cut-off BF is achieved that signifies the evidence in favour of an alternative or null hypothesis is strong (Marsman & Wagenmakers, 2017). This means that excess data will not be collected, and the strength of the confidence in favour of the hypothesis can be quantified. In the current study, data collection continued until the data were six times more likely under the null hypothesis (no significant difference between the letter and number groups on the letter arithmetic task) than the alternative. This stopping rule was pre-registered on the Open Science Framework (https://osf.io/s6e7u/). Results from the independent t-tests indicated that the number and letter groups did not differ significantly in reaction time, accuracy or performance on the letter arithmetic task, $t(177) = 0.11$, $p = .92$, $BF_{01} = 6.14$; $t(177) = -0.17$, $p = .86$, $BF_{01} = 6.09$; $t(177) = 0.31$, $p = .756$, $BF_{01} = 5.90$, respectively. From the results of the Bayesian t-tests we can surmise that there is substantial evidence for the null hypothesis that the letter and number groups did not differ on the letter arithmetic task (Jeffreys, 1961). More specifically, finding support for the null hypothesis suggests that participants did not assign numerical values to letters in the letter ordinality task, and instead, likely relied on their representations of the ordinal relationships between the letter stimuli to complete the task.

Table 2.10: Mean reaction time (ms), accuracy and performance on the letter arithmetic task for the letter and number groups.

	Reaction Time (ms)	**Accuracy**	**Performance**
Letter group	6530.92 (2262.14)	0.93 (0.07)	7528.12 (2868.63)
Number group	6496.71 (2034.68)	0.93 (0.07)	7404.68 (2431.11)

Standard deviation is given in brackets.

2.3.4 Discussion

The first goal of Experiment 2 was to determine if the stimuli from the adaptation task in Experiment 1 generated behavioural distance effects when participants were asked to process the ordinal relationships between the symbols. When presented in a passive task, the letter stimuli did not demonstrate a neural parametric effect in Experiment 1. Therefore, it was important that we verified that the letter stimuli used in Experiment 1 generate a behavioural distance effect, and that results from Experiment 1 - the lack of a parametric effect for letters - did not occur due to an issue with the stimuli chosen. In Experiment 2, participants in both the number and letter training groups demonstrated distance effects. The symbols chosen were the same as used in the adaptation task in Experiment 1, thereby confirming that at the behavioural level, these letter stimuli generate distance effects. Therefore, even though the letter stimuli did not generate a parametric effect at the whole-brain level in Experiment 1, the same letter stimuli do generate a distance effect in an explicit task. However, it should be noted that the distance effects obtained from the letter ordinality task were significantly smaller than the number ordinality task, which could indicate that performance on the letter task was not as strongly affected by the ordinal relationships between letters as performance on the number task. Support for the proposal that the ordinal relationships are not as fluent in letters in comparison to numbers also comes from the finding that the letter ordinality task was performed more slowly than the number ordinality task, which fits with previous research (Van Opstal et al., 2008;Vogel, Haigh, et al., 2017).

Although the letter and number groups showed quantitative differences in the magnitude of the distance effects obtained, the finding that both sets of stimuli elicited distance effects in the same pattern – increased response time with decreased distance – provides support for a qualitative similarity between the sets of symbols at the behavioural level.

The second goal of Experiment 2 was to investigate whether the distance effect in the letter ordinality task could have been an artefact of a numerical magnitude assignment strategy. However, there was substantial evidence that the different training groups did not differ on the letter arithmetic task. If the letter group -- the group that practiced the letter ordinality task -- outperformed the number group, it could be argued that the letter group performed the letter ordinality task using a numeric strategy. More specifically, practice over the four runs of the ordinality task in which they assigned numeric values to letters to complete the task could have led to this group outperforming the number group when asked explicitly to apply a numeric strategy to the letter arithmetic task. However, the two groups scored very similarly on the letter arithmetic task, which suggests that the letter ordinality task was not carried out using a numerical magnitude strategy. Participants seem to instead be performing the letter task by accessing the ordinal relationships between these symbols. However, it should be noted that this interpretation rests on the assumption that there would be transfer in training on the letter ordinality training task to the letter arithmetic task. In other words, the assumption is that if the participants were using a numerical assignment strategy in the letter ordinality task, that this would enhance their performance on the subsequent letter arithmetic task. Therefore, there still remains a possibility that participants used a numerical strategy for the letter ordinality task, however, this practice did not result in an advantage on the letter arithmetic task. Further research is needed to disentangle these explanations.

It is unclear what mechanisms underlie the behavioural distance effects observed in both letter and number tasks. Distance effects generated from symbolic numerical tasks are often explained through the ANS theory of number representation; number symbols are mapped onto an analogue magnitude system with overlapping representations. However, the theory of the ANS underlying symbolic distance effects is a subject of significant debate. As previously discussed, Van Opstal and colleagues (2008) demonstrated that a distance effect could be obtained with letter stimuli, a finding that was replicated by the current study. Given that letters are not referents for a quantity system, these behavioural findings of distance effects that are common to both numbers and letters call into question the theory that the ANS theory is necessary or sufficient to explain the distance effects observed with number stimuli.

Alternative mechanisms have been suggested to explain distance effects due to symbolic numerical stimuli. For example, Krajcsi (2017) suggested instead of the ANS, a discrete semantic system (DSS) underlies symbolic number representation. Here, symbolic numbers exist as nodes that are connected through semantic associations. In this account, the NDE is a result of these connections between the number nodes, as opposed to the representational overlap posited by the ANS theory. In support of the DSS view of representation, recent behavioural evidence suggests that the ANS is not sufficient to explain the pattern of responses observed in symbolic numerical comparison tasks (Krajcsi et al., 2018). Instead, the DSS, in which numbers are represented discretely with semantically associated nodes, seems to better fit symbolic numerical comparison behavioural data, and thus may reflect a more suitable explanation for the NDE in symbolic numerical tasks than the ANS. Fitting with this hypothesis that different mechanisms underlie symbolic and nonsymbolic numerical representation, both Krajcsi (2017) and Lyons, Nuerk and Ansari (2015) did not find a significant association between measures from symbolic and nonsymbolic comparison tasks within-participants. If these tasks are tapping into representations that have a shared underlying mechanism (i.e., the ANS), one would expect an association between the nonsymbolic and symbolic measures.

In summary, the precise mechanisms underlying distance effects are contested. Although letters and numbers seem to share a similar behavioural signature, in Experiment 1 we found that the response to these same stimuli was quite dissimilar. However, Experiment 2 demonstrated that the lack of a finding of a neural distance effect for letters in Experiment 1 is not because the stimuli list of Experiment 1 cannot generate distance effects, given the finding of a behavioural distance effect for letters in Experiment 2. Instead, it could be hypothesized that different mechanisms underlie behavioural distance effects in forced response tasks, and the neural distance effect in numerical adaptation tasks. Perhaps a response selection mechanism underlies the behavioural distance effects, while a more number-specific mechanism better fits the neural distance effect (at least in the passive fMRI-A design).

2.4 General Discussion

What mechanisms underlie the distance-dependent parametric rebound effect that has been reproduced across different studies following adaptation to numerical symbols?

What can this effect tell us about symbolic number representation? It is often hypothesized that the symbolic number system is mapped onto an approximate nonsymbolic magnitude system, and that the parametric effect is a signature of this analog system. The current experiments tested an alternate hypothesis: whether ordinal relationships between symbols can explain the parametric rebound effect. Contrary to our predictions we found that, in Experiment 1, letters, in contrast to numbers, do not exhibit this neural parametric effect anywhere in the brain during an fMRI adaptation task. However, in Experiment 2, we found that the letters we included in Experiment 1, do elicit a behavioural distance effect. What do these results suggest about symbolic number representation? Several explanations could be offered for the findings from Experiment 1 and 2 – behavioural distance effects for both numbers and letters; a neural distance effect only for numbers – including but not limited to:

1. Different mechanisms underlie behavioural distance effects and neural distance effects:
    a. Response selection mechanisms lead to behavioural distance effects, and representational overlap leads to the neural parametric effect observed for numbers.
    b. Response selection mechanisms lead to behavioural distance effects, and *highly salient* ordinal relationships lead to the neural parametric effect for numbers.
    c. Response selection mechanisms lead to behavioural distance effects, and another number-specific property generates the neural parametric effect for numbers.
2. Different mechanisms underlie number and letter distance effects. A number-specific mechanism (e.g., representational overlap, salient ordinal relationships, etc.) underlies the number distance effects at both the behavioural and neural level. Differences in the demands on response selection elicit the letter distance effect.
3. Different mechanisms underlie all three effects (i.e., behavioural number distance effects, behavioural letter distance effects, neural number parametric effects).

Further research that empirically investigates the mechanisms underlying neural and behavioural distance effects is necessary to help distinguish between these options. In general, it seems that a level of semantic processing of a symbol is required to generate a neural distance effect; whether or not this is indicative of mapping onto the ANS or some other property of number, remains to be seen. More specifically, the processing of a symbol with an ordered sequence, alone is not sufficient to generate a neural parametric effect. This suggests that the system for symbolic number representation may automatically activate more number-specific properties when presented with a number symbol, as opposed to other more general (in that they also exist for letters) numerical symbol set properties, such as order.

2.4.1 A different response for letters vs. numbers at the neural level

A key question is why did the neural response for numbers and letters differ? Vogel et al., (2019) suggested that the ordinal relationships between numbers may be processed automatically. It could be that ordinal relationships are not as fluent in letters as they are in numbers. In other words, although letters can be arranged as an ordinal sequence (i.e., the alphabet), perhaps this sequence is not activated as automatically as it is for letters. Put differently, when we are presented with a single letter, it could be the case that the letter's place in the ordinal sequence is not activated as automatically as it may be for numbers. Therefore, accessing the ordinal relationships between letters could be a more effortful process that requires an active task. This hypothesis is supported by the finding in Experiment 2 that demonstrates the letter ordinality task was associated with significantly higher reaction times than the number ordinality task. Previous studies have also found longer reaction times in letter processing tasks compared to number processing tasks (Fulbright et al., 2003; Van Opstal et al., 2008; Vogel, Haigh, et al., 2017; Vos, Sasanguie, Gevers, & Reynvoet, 2017)**.**

It is also possible that the parametric distance effect observed in the IPS is not solely related to ordinal relationships between symbols. The present data do suggest that the parametric effect is reflective of some semantic processing of number symbols. However, perhaps symbol-symbol ordinal relationships are not a good model for the mechanisms underlying the parametric distance effect, and another property of number will provide a better explanation. It may also be possible that the left IPS is more specialized for ordinal relationships in numbers, as opposed to ordinal relationships more generally (e.g., between letters). Further research is needed to address this question.

Another possibility for the lack of parametric effect for letters is that our study was underpowered. However, the number of participants included in the current study was based on previous symbolic numerical adaptation studies that have demonstrated the ratio-dependent rebound effect. Holloway et al. (2013) included 26 participants (13 participants per group) and found an effect in the left IPS region significant at the whole brain level when using a cluster-level correction for multiple comparisons set to $p < .05$. Using the same threshold, Vogel et al. (2017) demonstrated parametric left IPS activation using 20 participants. Notebaert and colleagues (2010) had a sample size of 13. The current study used an adaptation task based closely on these previous studies, and therefore collected a sufficient number of participants to replicate the number parametric effect found in previous research. The fact that we successfully identified parietal regions that demonstrated the expected numerical parametric effect means that our study was sufficiently powered to pick up on this effect, although it is still possible that the effect is present in letters but is much weaker and thus more participants are required to reveal the effect. In support of this prediction, in Experiment 2 we show that letters generate a behavioural distance effect that is significantly smaller than the distance effect for numbers. However, it should also be noted that even at a very liberal, uncorrected threshold, we still did not find a neural parametric effect for letter. Furthermore, Bayesian statistics determined that there was substantial evidence for the absence of the parametric effect for letters within three clusters in the IPS. If the lack of a parametric effect for letters could be attributed to a lack of power to pick up the effect, the Bayesian t-test would have indicated weak or anecdotal evidence for the null. Although it is difficult to draw conclusions from the absence of an effect, the lack of this effect even at an uncorrected, lenient threshold and the presence of substantial evidence for the null hypothesis supports the notion that there is not a significant neural distance effect for letters in the current study.

Although both numbers and letters have elicited behavioural distance effects, at the neural level the processing of these symbols diverges. In the current study we did not find a parametric distance effect with letters, but observed this effect for numbers. This finding is somewhat inconsistent with Fulbright et al. (2003). When participants were asked to judge whether letters were in order or not in order, trials that had a smaller numerical distance elicited more activation in several areas including bilateral inferior and middle frontal gyrus and right IPS, compared to trials with a larger numerical distance. The differences between studies in the letter tasks could explain why the current study did not yield distance effect for letters, while Fulbright et al. (2003) did observe some regions demonstrating sensitivity to distance in letters. Fulbright et al. (2003) used an active task requiring participants to select a response, whereas the current study used a passive design. Therefore, differences may arise when participants are asked to explicitly judge the order of a sequence of letters as opposed to viewing letters passively. Since the purpose of our study was to examine symbol representation in the absence of other cognitive processes such as decision making, response selection and working memory, it is not surprising that our results diverge from an explicit letter ordering task. Differences in active vs. passive tasks may similarly explain why Attout et al., (2014) found a neural distance effect for a letter ordering task in bilateral regions of the IPS.

2.4.2 Hemispheric differences for the number parametric effect

The finding of a left-lateralized parametric effect in the parietal lobe is consistent with previous number symbol adaptation research (Holloway et al., 2013; Notebaert, Nelis, & Reynvoet, 2011; Vogel et al., 2015; Vogel et al., 2017). In a quantitative meta-analysis of adaptation studies presenting subjects with symbolic numbers, Sokolowski et al. (2016) found that the left superior parietal lobule showed a parametric effect for number. In agreement with these results, the current study also found a left-lateralized parietal cluster for the numerical parametric effect, however two right-lateralized parietal clusters were also identified. Right IPS has been found in previous numerical adaptation research (Holloway et al., 2013; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Vogel et al., 2015). For example, Holloway et al. (2013) found a parametric recovery effect using Chinese numerals in a group of Chinese-speaking participants. This effect was attributed to a lower familiarity with the Chinese notation when compared to the highly familiar Arabic digit notation (for which this group showed the expected left-lateralized parametric effect). Vogel et al. (2015) also found parametric modulation of the right IPS with a number symbol adaptation task. A group of children age 6-14 showed a right-lateralized parametric effect in response to number. The right IPS demonstrated this parametric effect across all ages, while the left IPS parametric effect was positively correlated with age. As children also have comparatively less experience with number symbols than adults, the involvement of the right IPS may reflect a lower level of fluency with number symbols.

The right IPS may also show parametric modulation when non-symbolic stimuli are used in an adaptation task or when cross-format adaptation (number symbols and dot arrays) is used (Piazza et al., 2004, 2007). More specifically, Piazza et al. (2007) presented participants with four conditions (adaptation format-deviant number format): dots-dots, Arabic-Arabic, dots-Arabic and Arabic-dots. Brain regions that showed neural recovery that was greater for deviants that were further away from the adapted value compared to closer were identified. Overall, a distance-dependent recovery effect was observed in parietal regions bilaterally. However, the right parietal cortex showed more distance-dependent recovery during cross-notation adaptation. The authors suggested that the right parietal cortex may represent number magnitude symbolically and non-symbolically in an approximate manner, while the left parietal cortex is refined by number symbol acquisition and offers a more exact representation of magnitudes.

The current study supports the notion of left parietal regions, relative to right parietal areas, as being more strongly involved in fluent, exact symbolic processing, as evidenced by the left parietal clusters identified in the parametric effect contrasts, and specifically in the contrast between the number parametric effect and the letter parametric effect. It is unclear why right IPS clusters were also identified in the contrast $\text{parametric}_{\text{Number}}$ > baseline, however the finding that the left parietal region seems to be more specified for number processing (the result of the number > letter contrast) is consistent with previous research. The contributions of the left vs. right IPS to symbolic numerical processing is still a topic of investigation in the literature.

2.4.3 Conclusions

To date, it has been unclear whether the correlation between symbolic number processing and the IPS reflects the processing of numerical magnitude, ordinal information or a combination of the two. The findings reported above do not provide evidence in support of the notion that the representation of general (across stimulus categories) ordinal relationships explain the neural parametric distance effect observed for numerical symbols. Consistent with previous literature, several parietal clusters were found to be modulated by numerical distance when participants were shown symbolic numbers. Specifically, the left inferior parietal lobule seems to show specificity for the number parametric effect. However, no regions exhibited such a parametric distance effect for letters. These results therefore do not provide support for the alternative to the most common hypothesis that symbolic number is mapped onto a noisy non-symbolic magnitude system, which generates the parametric distance effects. However, it could be the case that symbol-symbol relationships are not as fluent in letters as they are in numbers and therefore are not activated during passive adaptation to letters. Further research is needed to investigate the nature of neural number representation.

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Chapter 3

3 Investigating age-related changes in symbolic number processing in the brain: A replication study

3.1 Introduction

3.1.1 Neural Correlates of Symbolic Number

How does the human brain develop the capacity to represent number symbols (e.g., Arabic digits)? In terms of evolutionary time, the use of symbols to represent magnitudes is a recent invention and one that is uniquely human (Everett, 2017). Symbolic representations of number are the product of human cultural history. Thus, it is unlikely that any brain circuits have been adapted by evolution to subserve symbolic number processing. Every individual living in a culture that uses numerical symbols must learn symbol abstraction (e.g., learning that the number word ‘three’ represents all sets of 3 items). However, the precise mechanisms underlying the development of symbolic number representation remain poorly understood.

When it comes to cognitive neuroscience research, it has been demonstrated, primarily using functional Magnetic Resonance Imaging (fMRI), that the activity of regions in the parietal cortex is consistently correlated with symbolic number processing. More specifically, various tasks involving active number symbol processing, such as number comparison (e.g., choosing the numerically larger of two presented values) and arithmetic (e.g., determining whether 3+4=8 is correct or not), have been found to be associated with activity in and around the intraparietal sulcus (IPS; e.g., Arsalidou & Taylor, 2011; Cohen Kadosh et al., 2005; Dehaene, Piazza, Pinel, & Cohen, 2003). Furthermore, quantitative meta-analytic findings have indicated that the left parietal cortex seems to be of particular importance for symbolic number processing (Sokolowski et al., 2016). This has led to the conclusion that the areas in and around the IPS, in particular in the left hemisphere, may play a critical role in the developmental construction of symbolic number representations in the brain.

3.1.2 The Developing Brain and Symbolic Number Representation

The association between left-lateralized parietal regions and symbolic number processing has been repeatedly demonstrated in studies with adult participants in the literature using both active (e.g., number comparison) and passive tasks (e.g., fMRI adaptation; for recent meta-analyses see: Sokolowski et al., 2016, 2017). Despite the multitude of studies demonstrating the correlation between the processing of Arabic numerals and activation of the left parietal cortex in adults, relatively little is known about the developmental trajectory of this left-lateralized parietal effect.

From the sparse body of available developmental data, we know that research using active symbolic numerical tasks has also suggested involvement of the left IPS for symbolic numerical tasks. For example, in an fMRI study, Bugden, Price, McLean and Ansari (2012) presented third- and fourth-graders with a symbolic number comparison task in which they were asked to indicate the larger of two presented Arabic numerals. The left IPS demonstrated a neural ratio effect, whereby there was more activation for trials with larger ratios between the presented number compared to trials with smaller ratios. This ratio effect was positively correlated with arithmetic scores, and negatively correlated with behavioural ratio effects. Therefore, a larger ratio effect in the left IPS was associated with better arithmetic performance and smaller behavioural ratio effects. The right IPS, however, did not exhibit a significant neural ratio effect (Bugden et al., 2012). This finding of a neural ratio effect that was present in the left IPS and absent in the right IPS suggests different roles in numerical representation for the left and right hemispheres of the IPS, and is convergent with findings from adults demonstrating a tendency for symbolic numerical representation to be left lateralized.

In another study examining the role of the left vs. right IPS in the development of numerical skills, Emerson and Cantlon (2014) had children aged 4-9 years complete a number matching task in the MRI, and again 1-2 years later. Children indicated whether a presented symbolic number and dot array matched (i.e., the number of dots on the screen was equal to the symbolic number). Activity in the right IPS was correlated across the time points, whereas the activity in the left IPS at time 1 was not predictive of activity in the left IPS at time 2. Time 2 left IPS activity was instead related to change in the acuity of numerical processing. These findings suggest that, early on, the right IPS is associated with the representation of cardinality (i.e., the fact that each number symbol refers to a specific number of items in a set – “four” is a representation of all possible sets of four items) that follows a predictable trajectory of development, while cardinality representation in the left IPS is more malleable and is shaped by experience and expertise with symbolic number.

Other developmental research on symbolic number processing has been indicative of a fronto-parietal shift for symbolic numerical processing; whereby a network of frontal regions is recruited in children for symbolic numerical processing, and the IPS becomes more involved later in development. For example, Ansari, Garcia, Lucas, Hamon and Dhital (2005) had a group of children (mean age = 10.4 years) and adults complete a symbolic number comparison task in an MRI scanner. A whole-brain analysis was conducted for both groups separately to identify brain regions that showed a neural distance effect; i.e., more activation for number pairs with a smaller numerical distance compared to a larger numerical distance. Children generally demonstrated a neural distance effect in a network of frontal regions, including the right inferior and medial frontal gyri and bilateral precentral gyrus, however they also exhibited this pattern in the right superior parietal lobule (SPL). These results conflict with results from Bugden et al. (2012) who found a distance effect in the left IPS, but not the right in a group of slightly younger children. Adults, on the other hand, tended to recruit parietal areas as opposed to more frontal regions, providing support for a reliance on parietal regions for number representation by adulthood.

In another, related, study Mussolin, Noël, Pesenti, Grandin and De Volder (2013) also examined neural activity during a symbolic number comparison task. The data from a group of children ages 8-14 years were characterized by a negative correlation between age and the neural distance effect (contrasted with a colour discrimination task) in several frontal regions as well as the left IPS. In other words, a network of frontal regions and the left IPS showed less of a distance effect in the older children than in the younger children. The right IPS and right SPL on the other hand, demonstrated a positive correlation with the behavioural distance effect that was consistent across the age range.

Put differently, in these regions, children with a greater neural distance effect also demonstrated a greater behavioural distance effect. Mussolin et al. (2013) suggested that the decrease with age in the recruitment of the frontal regions and left IPS likely reflected greater automaticity in symbolic number processing in the older children. The association of the right parietal regions with the distance effect, regardless of age might be taken to suggest these regions are involved in the semantic representation of numerical magnitudes and subserve the increasing fluency of utilizing such representations. This finding of a smaller distance effect within the left IPS in older children could reflect greater fluency in symbolic number representation. Therefore, although there is some evidence for a fronto-parietal shift across development in active symbolic numerical processing tasks, currently the involvement of the left vs. the right IPS in the development of symbolic number representation is unclear.

In summary, we do not yet have a solid understanding of the neural underpinnings of the development of symbolic number representation. However, across multiple studies investigating the neural correlates of the development of number processing, it has been suggested that children undergo a fronto-parietal shift (e.g., Houdé, Rossi, Lubin, & Joliot, 2010). As children gain experience with numerical information, frontal regions tend to become recruited less and parietal regions, such as the IPS, are recruited more robustly. Yet, there is conflicting evidence for the role of the left vs. the right IPS in the developmental trajectory of symbolic number processing. In some cases, only the left IPS has demonstrated a neural distance effect (Bugden et al., 2012), while other studies have shown the left IPS becomes recruited later in development for symbolic number processing (e.g., Ansari et al., 2005), while others show a decrease in distance effect within the left IPS with age (e.g., Mussolin et al., 2013). Furthermore, Bugden et al. (2012) found a negative correlation between the left IPS neural distance effect and the behavioural distance effect, while Mussolin et al. (2013) exhibited a positive correlation between right IPS activity and behavioural distance effects. Moreover, there is some evidence that the right IPS is recruited early on for symbolic number processing (e.g., Mussolin et al., 2013), although others have not found this to be the case (e.g., Bugden et al., 2012).

It is important to note that the evidence discussed thus far is based on paradigms with active task designs (participants are asked to make a decision, such as which of two Arabic numerals is numerically larger, by pressing a corresponding button). It has been demonstrated that non-numerical tasks that require response selection (e.g., choosing between two different stimuli) show correlated neural activation in regions that are often recruited for number comparison (Göbel et al., 2004). Additionally, response selection and reaction time differences are particularly problematic in developmental samples that include a wide age range (Church, Peterson, & Schlagger, 2010; Dehaene, Dehaene-Lambertz, & Cohen, 1998). More specifically, young children are typically slower at responding than older children and adults, therefore any brain activation differences revealed between children vs. adults or younger children vs. older children from an active paradigm, may reflect age-related changes in brain activation or differences in reaction times between the groups. The demands of a task for children of different ages may vary in unpredictable ways that are difficult to account for (Church et al., 2010). For example, in fMRI research it is possible that younger children may find a task much more difficult than older children, which can create a confound in any observed differences between younger and older children (Church et al., 2010). As well, a task that was intended to be a control measure could be much more difficult for younger children, which is problematic when the control task is used to subtract processes that are not of interest from the task of interest (Church et al., 2010; Logothetis, 2008). Therefore, passive tasks, that unconfound response selection and age, are useful in furthering our understanding of the development of numerical representation.

To better understand the representation of symbolic number in the brain, in the absence of other cognitive processes and task demands, researchers have been utilizing a method referred to as fMRI adaptation (fMRI-A). fMRI-A studies use a passive design (i.e., the participant is not asked to make a decision related to the numerical stimuli presented) to allow for further investigation of the neural correlates of symbolic number representation. This design mitigates issues due to response selection and difficulty level that have been shown to confound active numerical processing tasks (Church et al., 2010; Göbel et al., 2004). In the numerical adaptation paradigm, the same number (e.g., the Arabic numeral '6') is presented repeatedly during an adaptation phase, resulting in a diminished response in number-related neural regions. This adaptation phase is followed by the presentation of a new number (called the deviant, e.g. ‘8’), which differs from the adaptation value by a specific ratio (calculated here as smaller number/larger number). Across a growing body of studies it has been demonstrated that the presentation of the deviant is associated with a rebound of activation in number-related regions. Put differently, while the repeated presentation of a particular Arabic numeral (e.g. ‘6’) is associated with decreases in activation, the intermittent presentation of other numerals (e.g., ‘8’) results in an increase in activation relative to the repeated numeral (‘6’). Results from symbolic number adaptation studies in adults have demonstrated that left-lateralized parietal clusters, specifically the IPS and SPL, are related to the passive viewing of number symbols (Holloway, Battista, Vogel, & Ansari, 2013; Notebaert, Nelis, & Reynvoet, 2010; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004; Vogel et al., 2017; for a meta-analysis see Sokolowski, Fias, Ononye, & Ansari, 2017). More specifically, the left parietal regions have been found to demonstrate a parametric rebound effect, wherein the amount of rebound of neural activation is related to the numerical ratio between the deviant and adaptation value. For example, with the adaptation value ‘6’, more rebound in activation would be observed within the left IPS with the presentation of the deviant ‘9’ (ratio = 0.67) than with the deviant ‘8’ (ratio = 0.75). In the literature, this numerical adaptation task has been used to disentangle the neural correlates of semantic symbolic number representation from task-related demands. Because the parametric rebound effect is modulated by the ratio between the adaptation value and presented deviants, this effect is thought to reflect semantic processing of numerical symbols. In other words, the parametric effect allows for inferences about the mechanisms underlying symbolic number representation, as this effect seems to reflect processing of numerical information, as opposed to responses to change in the visual characteristics of the stimuli. Expanding on this, identifying brain regions that demonstrate a parametric rebound effect goes beyond identifying regions of the brain that may be recruited for attentional shifts and change detection when the symbol changes: regions of the brain that show a parametric recovery effect are more likely to be processing some aspect of semantic numerical information.

The most frequent explanation given for this ratio-dependent neural pattern is that the symbolic number system of representation is mapped on an analog system of magnitude representation: the approximate number system (ANS; Dehaene, 1997). Here, magnitudes are represented on a number line, with each number having a distribution of noise surrounding its placement on the number line. The overlap in these distributions of noise is what is claimed to result in the ratio-dependent effect described above (Dehaene et al., 1998). In other words, numbers that have a smaller ratio (e.g., ‘6’ and ‘9’) have less overlap in their distributions, making them easier to distinguish when compared to two numbers that have a larger ratio (e.g., ‘6’ and ‘8’). Therefore, a deviant with a smaller ratio from the adaptation value triggers a larger recovery effect than a deviant with a larger ratio from the adaptation value. The ANS is said to be evolutionarily derived, allowing a wide range of species to represent quantity information (Dehaene, Dehaene-Lambertz, & Cohen, 1998). However, it is a subject of debate whether the symbolic system is mapped onto the ANS (Chapter 2; Leibovich & Ansari, 2016; Lyons, Ansari, & Beilock, 2015; Núñez, 2017). Therefore, this theory of overlapping representations for explaining the parametric effect requires further inquiry.

To date, there only exists one study that utilized a passive symbolic numerical adaptation task to investigate symbolic number representation in cross-sectional sample of 6-14 year-olds (Vogel et al., 2015). More specifically, Vogel and colleagues used an fMRI adaptation design based on Holloway et al. (2013) to adapt children to the Arabic numeral 6. Deviant numbers that differed systematically in ratio from the number 6 were interspersed randomly into a stream of repeated 6’s. The findings of this study revealed that at the whole-brain level, activation in the right IPS was characterized by a parametric ratio-dependent recovery effect. More specifically, the right IPS exhibited a ratio-dependent rebound in activation, wherein greater recovery in activation was observed for number deviants further away from 6. Importantly, this effect in the right IPS was not dependent on age – that is, there was no correlation between the ratio-dependent adaptation effect in the right IPS and children’s chronological age. In contrast, in the left IPS there was a significant correlation between age and the ratio-dependent recovery effect. Put differently, older children were found to show a greater correlation between activation of the left IPS and numerical ratio (the ratio between the adaptation number 6 and the interspersed deviants).

Taken together, using an adaptation paradigm, Vogel et al. (2015) were able to demonstrate that children show the ratio-dependent rebound effect in response to symbolic number – an effect that had previously only been demonstrated with adults. Perhaps most critically, results from Vogel et al. (2015) suggested that the left IPS may become increasingly recruited for symbolic number representation as children gain greater automaticity in processing the semantic meaning of number symbols. On the other hand, the findings by Vogel et al. conflict with those reported in prior fMRI studies that required response selection and found no ratio effect within the right IPS. Results from Vogel and colleagues suggest instead that the right IPS is engaged similarly by children across the included age range tested, similar to results from Mussolin et al. (2013). These results help to inform our understanding of the development of the neural underpinnings of symbolic number representation, and suggest that the left IPS may undergo a process of age-related specialization for the representation and processing of numerical symbols. Vogel et al. (2015) were the first to provide evidence of an age-related change in the involvement of the left IPS in symbolic number representation using a passive task and thereby suggested that this brain region may be particularly important in subserving children's increasing fluency and expertise with numerical symbols over the course of learning and development.

3.1.3 The Importance of Replication

The results of Vogel et al. (2015) hold promise for advancing our understanding development of symbolic number representation in the brain. However, it is imperative that these findings be replicated. Replicability is a cornerstone of the scientific method; in order for findings to make a contribution to theory it must be demonstrated that they can be reproduced using the same methods (Zwaan et al., 2018). It has been argued that verifying findings through replication should be "mainstream" in psychology research (Zwaan et al., 2018).

In recent years, the replicability of scientific findings has been seriously questioned. Some have even declared a “crisis of confidence” for results from psychological research (Pashler & Wagenmakers, 2012). In a large initiative to assess the level of replicability of 100 psychology studies, the Open Science Collaboration reported that only 36% of the replications produced significant results, whereas 97% of the original studies had significant results (Open Science Collaboration, 2015). Additionally, the effect sizes found in the replications were halved in size compared to the original studies. A recent survey reported that of the 1576 researchers polled, 90% agreed there was some level of a replicability crisis (Baker, 2016). Furthermore, Szucs and Ioannidis (2017) examined effects sizes and power for 3801 psychological and cognitive neuroscience articles. They concluded that it is likely that more than 50% of reported findings are actually false positives. According to their findings, cognitive neuroscience research was particularly likely to have high false positive rates, due to factors such as small sample sizes (Szucs & Ioannidis, 2017).

In this context of high false positive rates and failed replications, it is imperative that we replicate the original Vogel et al. (2015) findings. Vogel et al. (2015) had a sample size of 19 children. Importantly, Szucs and Ioannidis (2017) found that studies published in the cognitive neuroscience field were particularly prone to false positives given the high incidence of low sample sizes in this field of research. Therefore, the current study sought to replicate the Vogel et al. (2015) study, using a sample size of n = 45, six to fourteen-year-olds, more than doubling the sample size of the original study. To replicate the 2015 study, we expected to find a ratio-dependent rebound effect that is not dependent on age in the right IPS. We also predicted a positive correlation between age and the ratio-dependent rebound effect in the left IPS.

Furthermore, we extended the 2015 study by assessing the relationship between the neural parametric effect and behavioural measures of basic number processing and math achievement. Assessing such relationships could contribute to our understanding of the mechanisms underlying the parametric rebound effect. Although previous research has demonstrated an association between the neural distance effect and arithmetic as well as the behavioural distance effect, it is unclear what the nature of this association is. More specifically, it is unclear if the relationship between IPS activity during numerical tasks and behavioural measures of numerical processing reflects shared mechanisms related to numerical processing, or some other more domain-general mechanism such as response selection. An association between the neural rebound effect in the IPS during a passive task and behavioural measures of number processing and math would lend support to the proposal of shared mechanisms underlying these constructs. In other words, investigating the association between the parametric effect and behavioural math measures can help to shed more light on previous findings that demonstrated an association between IPS activity and math, but whose designs confounded number-related activity with activation associated with a response. The current study was preregistered on the Open Science Framework (OSF; https://osf.io/zsfbk/).

3.2 Methods

3.2.1 Participants

Our goal was to collect 45 useable datasets; five children for each of the age points from 6-14. As per the original Vogel et al. (2015), only healthy, right-handed, fluent English-speaking children who fulfilled the following, preregistered criteria (https://osf.io/amuc5/) were included in the analyses: 1. Motion of no greater than 3mm over the course of the run and no greater than 1.5 mm between frames. 2. Accuracy of at least 6/8 on the catch trials (described in more detail below). 3. At least two runs that fulfill these first two criteria. Data collection continued until we had a sample size of 45 that met these criteria. In total, 65 children were consented to participate in the study. Two children were found to be ineligible for the study (one because they were left-handed, one reported learning disabilities), five children participated in the behavioural session but did not return for the MRI session. Two refused to complete more than one run of the adaptation task. Ten children were excluded because they had fewer than two runs that fulfilled the above motion and accuracy criteria: six because of failure to meet our preregistered head-motion criteria, one because of accuracy on the catch trials, and three because of a failure to meet both the motion and accuracy criteria. One participant was not included due to an incidental finding in the anatomical data. For two children, five runs that fulfilled all the above criteria were collected. To follow the preregistered maximum number of runs included in analysis for each participant, we took the four best runs for each of these two participants (based on accuracy and motion). This left a sample size of 45 children for analysis (18 females, M_{age} = 125.44 months, SD_{age} = 31.46 months), five children at each of the ages 6-14 and a total of 161 runs of the adaptation task for analysis. Children received $25 gift cards to a bookstore for participating in each of the two sessions, and pictures of their brain after the MRI session. Written informed consent was obtained from the parent of each child and written assent was obtained from the children. This study was approved by the Research Ethics Board at Western University in Canada.

3.2.2 Procedure

Participation involved two sessions on separate days: session one involved a mock scanner procedure and collection of behavioural data, session two was the MRI session. In session one, children and their parent(s) were acclimated to the MRI procedure. The researchers first explained the MRI procedure including important safety information using a child-friendly picture book. Next, children completed training with the mock scanner, which mimics the sights, sounds and experiences of the real MRI. Children practiced lying still on the scanner bed while noises from a real MRI scanner were played. Next, children practiced the adaptation task for approximately two minutes. After the first 41 children, the mock scanner was upgraded to a new model, however the same procedures involving acclimation to the MRI environment and task practice were followed for all children. Finally, we collected a battery of measures to index symbolic number processing, math achievement and IQ. The order of administration of these behavioural measures was counterbalanced across participants. The entire length of the session was approximately 1.5 hours. Children who were comfortable with the mock scanning procedure and wished to continue to the real MRI scan returned for session two.

Session two took place at Robarts Research Institute at Western University. Children and their parent(s) accompanied researchers to the 3T scanner, where the researchers went through the MRI picture book for a second time and reminded the families of the procedure and safety information. Children then practiced the adaptation task and an MRI safety screening form was completed. The scanning procedure involved collection of four adaptation runs, an anatomical scan and a diffusion tensor imaging (DTI) scan. A fifth run of the adaptation task was also collected if, at the time of the scan, the online motion criteria looked as though it would not meet the motion cut-off, and if the child agreed to do another run. The DTI scan was not analyzed for the purposes of the current manuscript. The researcher that the child met in session one remained in the MRI room with the child for the entirety of the scanning procedure. Session two took no longer than 1.5 hours. Imaging data for the study are available on OpenNeuro (https://openneuro.org/datasets/ds002116). Behavioural data are available on the Open Science Framework (https://osf.io/38xu4/).

3.2.3 Measures

3.2.3.1 Behavioural Measures

3.2.3.1.1 Math achievement.

Math achievement was measured using two standardized tasks: the Math Fluency subtest from the Woodcock Johnson III Tests of Achievement (Woodcock, McGrew, & Mather, 2007) and the Numeration subtest from the KeyMath 3 Diagnostic Assessment: Canadian Edition (Connolly, 2008). In the Math Fluency subtest, participants completed as many simple arithmetic problems as possible in three minutes. The Math Fluency has a mean standard score of 100 and a standard deviation of 15. The Numeration subtest adheres to the Canadian math curriculum and is an untimed measure of numerical understanding (e.g., counting, rounding numbers, fractions). Numeration has a scale score mean of 10 with a standard deviation of 3.

3.2.3.1.2 Numerical Processing.

To measure basic numerical processing, children completed three subtests of the Numeracy Screener 2.0 (https://osf.io/pvda6/): symbolic comparison, mixed comparison and symbolic ordering. These paper and pencil tasks require children to complete as many problems as possible in one minute. For the purposes of the current study, only the symbolic comparison task was used. For the symbolic comparison task, children cross out the numerically larger of two single digit Arabic numbers.

3.2.3.1.3 IQ.

IQ was measured using the Kaufman Brief Intelligence Test-II (KBIT-II; Kaufman & Kaufman, 2004). The K-BIT involves three subtests: Verbal Knowledge, Matrices and Riddles. Verbal Knowledge and Riddles provide an assessment of verbal IQ, while Matrices assesses nonverbal IQ. The KBIT-II provides an overall IQ score with a standardized mean of 100, SD = 15.

3.2.3.2 Adaptation Task

Participants completed four runs of the symbolic numerical adaptation task used in Vogel et al. (2015) while fMRI data was collected (https://osf.io/zsfbk/). This was an exact replication with regards to the paradigm used. All stimuli were presented using Eprime 2 software, using black font on a grey background. During the adaptation period, the digit ‘6’ was repeated between 5-9 times, with a mean of 7 repetitions over the run, creating a jitter in the presentation intervals that allowed oversampling of the haemodynamic response. After the adaptation period, a deviant number (18 trials), catch trial (8 trials) or null trial (4 trials) was pseudo-randomly presented (see Figure 3.1 for an example of each of the stimuli types). Deviant numbers differed from the adaptation value of ‘6’ by specific ratios (see Table 3.1). Catch trials consisted of a number presented with a “smurf” character. Children were instructed to press a button with their right index finger whenever a smurf appeared. Catch trials were included so as to ensure children were attending to the stimuli on the screen at all times and were modelled out in the analyses. Null trials consisted of a further presentation of the digit ‘6’ and therefore were not distinguishable by the participant from the adaptation period. The null trials were included so as to model the baseline of the adaptation effect. Two strategies were used to reduce the likelihood of lower-level visual-spatial adaptation effects: 1. Two font types were used (Times New Roman and Courier New). 2. Stimuli were presented in six different locations around the centre of the screen (x,y coordinates: 435/300, 365/300, 375/325, 425/325, 375/275 and 425/275). The task was 6 minutes and 26 seconds long.

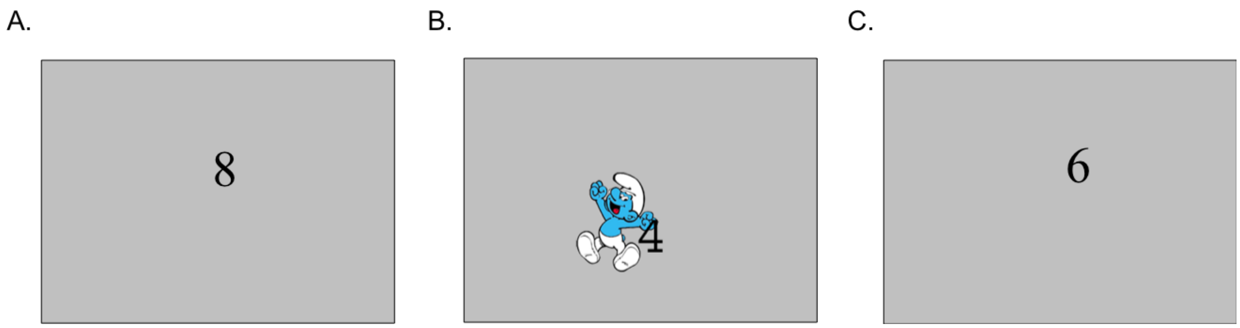


Figure 3.1: Examples of each type of stimuli used. A. Deviant trial: differs from the adaptation value ‘6’ by specific ratios. B. Catch trial: consisted of a number deviant with a smurf character. C. Null trial: consisted of an additional presentation of ‘6’.

Table 3.1: Numerical stimuli used in the adaptation task.

Number Stimuli	Ratio	Ratio Bin
3, 12	.5	Small
4, 9	.67	Medium
5, 8	.79	Large
6	1	Null

Stimuli are arranged by ratio from the adaptation value ‘6’, and binned into large, medium and small ratio categories based on their ratio from ‘6’.

3.2.4 MRI Data Acquisition

Anatomical and functional MRI data were collected with a 3T Siemens Magnetom Prisma scanner using a Siemens 32-channel head coil. To collect fMRI data, a BOLD-sensitive T2* weighted echo planar sequence was used. Each volume included 48 slices that covered the entire brain (voxel size = 2.5mm x 2.5mm x 2.5mm, 2.5mm thickness, TR = 1000ms, TE = 30ms, multiband factor = 4, FOV = 208x208mm, matrix size = 84 x 84, flip angle = 40°. The slices were collected in an ascending-interleaved method. A total of 386 volumes were collected for each run of the adaptation task. The anatomical data was collected using high-resolution T1-weighted images in the sagittal plane (voxel size = 1mm x 1mm x 1mm, TR = 2300ms, TE = 2.98ms, TI = 900ms, flip angle = 9°, in-plane resolution = 256mm x 256mm). A total of 192 slices covering the whole brain were collected.

3.2.5 Imaging Preprocessing

Imaging data were preprocessed in Brainvoyager QX version 20.6 software (Brain Innovation, Maastricht, the Netherlands). Cubic-spline interpolation was used to correct for slice scan-time acquisition. To remove low-frequency noise, a 2-cycle cut-off high-pass filter (GLM-Fourier) was used. To correct for motion, trilinear/sinc interpolation was used. A 6mm FWHM Gaussian smoothing kernel was used to smooth the data spatially. To analyze the data at the group level, individual data was transformed into MNI space.

In all analyses, catch trials were modelled as predictors of no interest. GLM events were convolved with a 2-gamma hemodynamic response function in order to predict BOLD response with RFX analysis (Friston et al., 1998a).

In the original Vogel et al. (2015) article, an initial uncorrected threshold of .005 was used to identify active brain regions. However, it has since been noted that .001 may be a more suitable threshold (Eklund, Nichols, & Knutsson, 2016; Goebel, 2017). Therefore, to identify active brain regions, an initial uncorrected threshold of $p < .001$ was used. Multiple comparisons were corrected for using cluster correction (Forman et al., 1995; Goebel, Esposito, & Formisano, 2006). A Monte-Carlo simulation with 1000 iterations determined the cluster size needed for a false positive rate of 5%. Therefore, only clusters that survive this $p < .05$ threshold at the whole-brain level were considered significant. Significant clusters were labelled using the Jülich Histological Atlas (Eickhoff et al., 2005) and Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476) within the FSLview software (Smith et al., 2004).

3.2.6 Planned Analyses

The main analyses used in the current study followed those used in the original Vogel et al. (2015) study. Accordingly, the deviant numbers were placed into four ratio bins (Table 3.1). These bins were then entered as a parametric regressor in the GLM and contrasted against the baseline (parametric effect > baseline), to identify regions at the whole-brain level that showed a parametric increase in recovery with ratio. To investigate age differences in the parametric effect, we conducted a whole-brain correlation analysis looking for regions that show an association between chronological age and the ratio-dependent recovery effect. Age was calculated as exact age in months at the date of the MRI.

We also wanted to model the main effect. For this analysis, all deviants are weighted equally. The main effect identifies any regions of the brain that respond to a change in number (main effect > baseline), regardless of the ratio between the deviant and adaptation value. We also looked at the correlation between age and the main effect of number deviants at the whole-brain level.

Finally, across the entire group we examined the conjunction between the parametric effect and the main effect (parametric effect $\cap$ main effect > baseline). This contrast provides a more stringent test of the parametric effect, as only regions that demonstrate a parametric modulation of neural activity as well as a main effect in neural activity will be significant. Put differently, by running this contrast we avoid potentially finding regions that exhibit a parametric effect but are not actually activated for all deviant stimuli.

Our secondary analyses investigated associations between the behavioural measures obtained from the children (see above) and parametric effect in the IPS. To this end, beta weights were extracted for each participant for the ratio-dependent parametric recovery effect. We then ran a correlation analyses in JASP Version 0.8.5.1 between these beta weights and the measures of math achievement and symbolic number processing (Jasp Team, 2019).

3.3 Results

3.3.1 Behavioural Results

Measures of average performance on the math achievement, numerical processing and IQ measures for each age bracket are reported in Table 3.2. Overall Math Fluency, Numeration and IQ scores were within the normal range across the entire sample. For the included runs of the adaptation task (at least 6/8 accuracy), average accuracy was M = 7.77, SD = 0.52.

Table 3.2: Performance on behavioural measures

Age	Math Fluency	Numeration	Symbolic Comparison	IQ
6	101 (10.15)	11.2 (2.17)	25 (4.47)	110.6 (11.01)
7	91.4 (15.22)	10.8 (1.48)	29 (7.00)	107.6 (15.47)
8	90.4 (12.10)	10.8 (1.92)	33.4 (3.21)	108.8 (9.12)
9	88 (14.20)	12.2 (2.49)	40 (3.54)	116.8 (13.68)
10	97.4 (14.36)	12.4 (3.36)	43.2 (9.36)	113.8 (6.30)
11	95.2 (8.70)	12.2 (2.68)	54.2 (13.50)	108.8 (14.10)
12	90.8 (9.78)	12.2 (1.79)	50 (12.25)	113.6 (6.69)
13	97.2 (13.99)	10.8 (3.35)	62 (8.03)	106.8 (11.78)
14	105.6 (22.23)	12.4 (2.41)	66.6 (10.48)	113.6 (11.35)
Total	95.22 (13.73)	11.67 (2.35)	44.82 (15.93)	111.16 (10.87)

Mean performance on the included behavioural measures, separated by age bracket (rows). Standard deviation is in brackets. Standardized scores are given for math fluency and IQ, scaled scores for Numeration. Average of the total number of correct items is given for Symbolic Comparison.

3.3.2 Imaging Results

3.3.2.1 Primary analyses

First, we examined the whole-brain for regions that demonstrated a parametric recovery effect: parametric effect > baseline. This analysis identified brain regions that show an increase in activation for smaller ratios from the adapted value, in comparison to larger ratios, across the entire age range. This contrast revealed eight significant clusters (see Figure 3.2, Table 3.3), notably left and right IPS. This finding is in partial agreement with results by Vogel et al. (2015), who found the right IPS but not the left IPS demonstrated a parametric effect across the age group. To visualize the parametric effect in the left and right IPS, beta weights for each ratio were extracted, averaged across participants and plotted (Figure 3.2C). The individual-level data for this visualization is presented in Figure 3.3. Next, we examined whether any neural regions demonstrated a correlation between the parametric effect and age in months. A whole-brain correlation between age and activation was run. This analysis did not return any significant clusters (see Figure

3.2D for a visualization of the beta weights for the parametric effect plotted for each participant). This result directly contrasts with previous findings by Vogel and colleagues (2015), who identified a whole-brain correlation between age and the parametric effect in the left IPS. Given that Vogel et al. (2015) used an initial threshold of .005 to detect significant activation, the same analysis examining the correlation between age and the parametric effect was run at this more lenient threshold. Again, no significant clusters were identified.

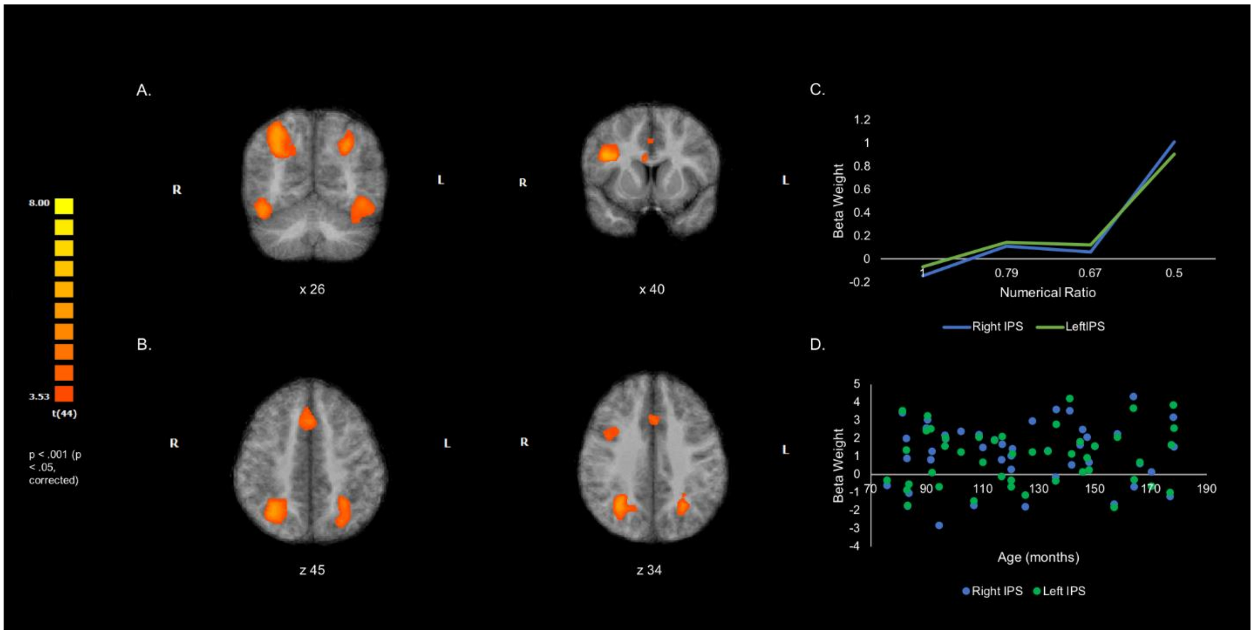


Figure 3.2: Significant clusters identified for the contrast parametric effect > baseline. A. Coronal view of significant clusters at two different slices. B. Transverse view of significant clusters at two different slices. C. A plot of the average beta weights extracted for each numerical ratio from the right (blue) and left (green) IPS clusters for the parametric effect. Beta weights were extracted from the right and left IPS clusters that were found to be significant for the parametric effect. The ratio of 1 represents the adaptation value '6' and was modelled using the null trials. D. Beta weights extracted from the right (green) and left (blue) IPS clusters, plotted by age in months for the parametric effect.

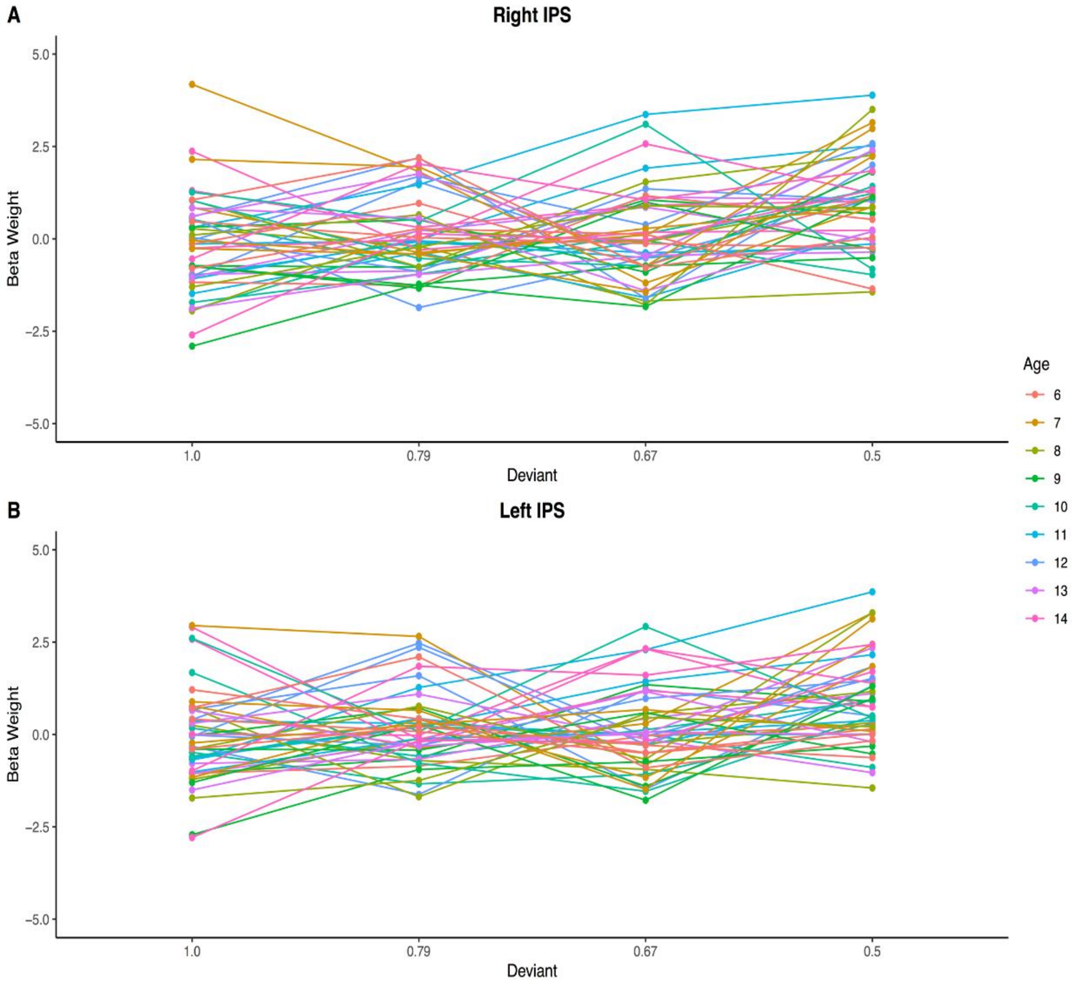


Figure 3.3: A plot of the individual beta weights extracted for each numerical ratio from the right (A) and left (B) IPS clusters for the parametric effect. Beta weights were extracted from the right and left IPS clusters that were found to be significant for the parametric effect. The ratio of 1 represents the adaptation value '6' and was modelled using the null trials. Each line represents an individual participant, colour-coded by age. Graphs were created with the ggplot2 package in R (Wickham, 2016).

The next whole-brain analysis examined the main effect across the entire age range: main effect > baseline. For this contrast, nine significant clusters were identified. However, one of these clusters spanned both hemispheres and all of the lobes of the brain (Figure 3.4). Therefore, in order to provide anatomical labels for this cluster, we split this cluster into 12 sub-clusters (Table 3.4). These sub-clusters were identified using a Matlab script (https://osf.io/3pujr/) that uses a k-means clustering algorithm (see Lyons & Beilock, 2018 for more information). Therefore, after splitting the large cluster, 20 clusters were identified (Table 3.5). We next ran a whole-brain correlation between the main effect and age. No significant regions were identified.

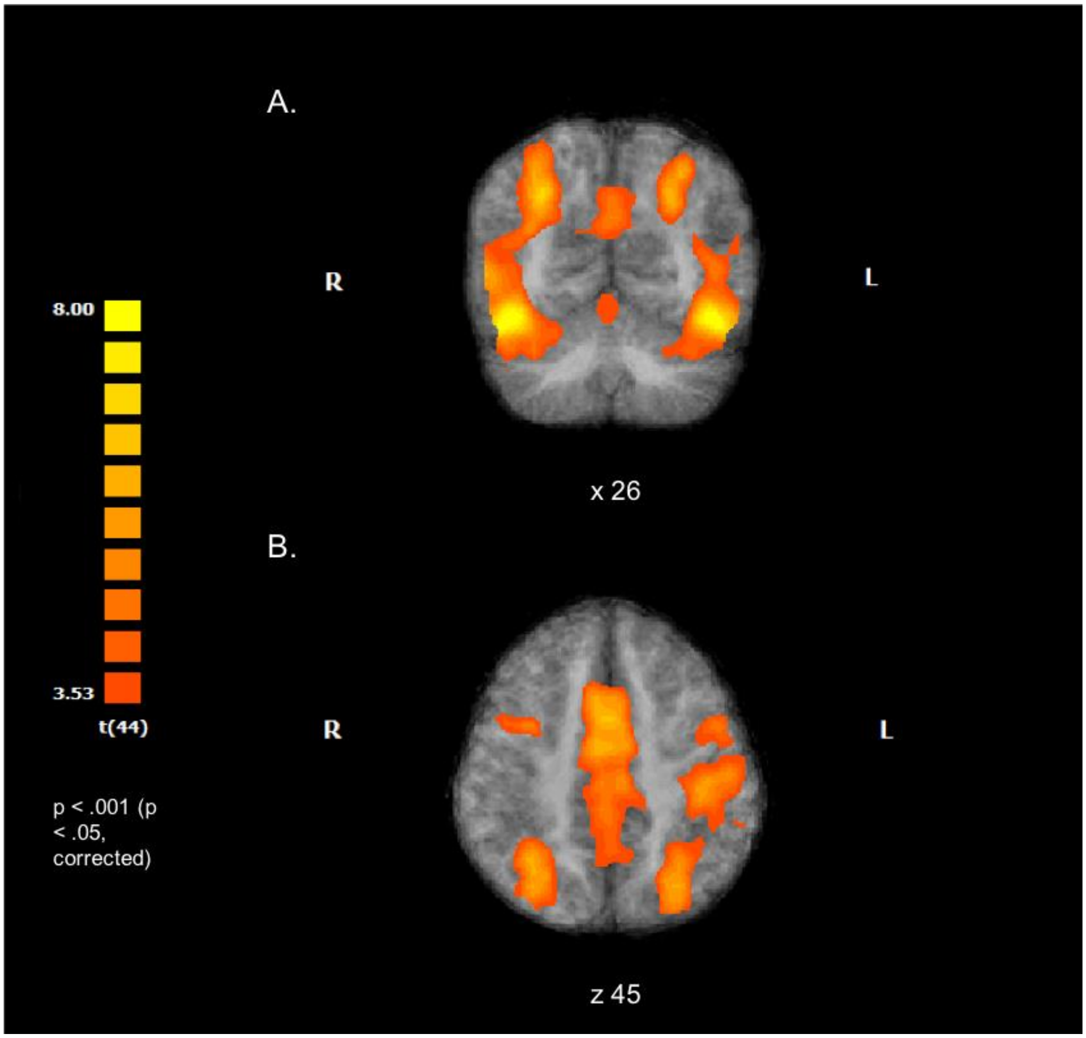


Figure 3.4: Significant clusters identified for the main effect contrast. A. Coronal view. B. Transverse view.

Finally, the conjunction between the main and parametric effect was examined: (parametric effect ∩ main effect > baseline). Here, six significant clusters were identified (see Figure 3.5, Table 3.5), including bilateral IPS.

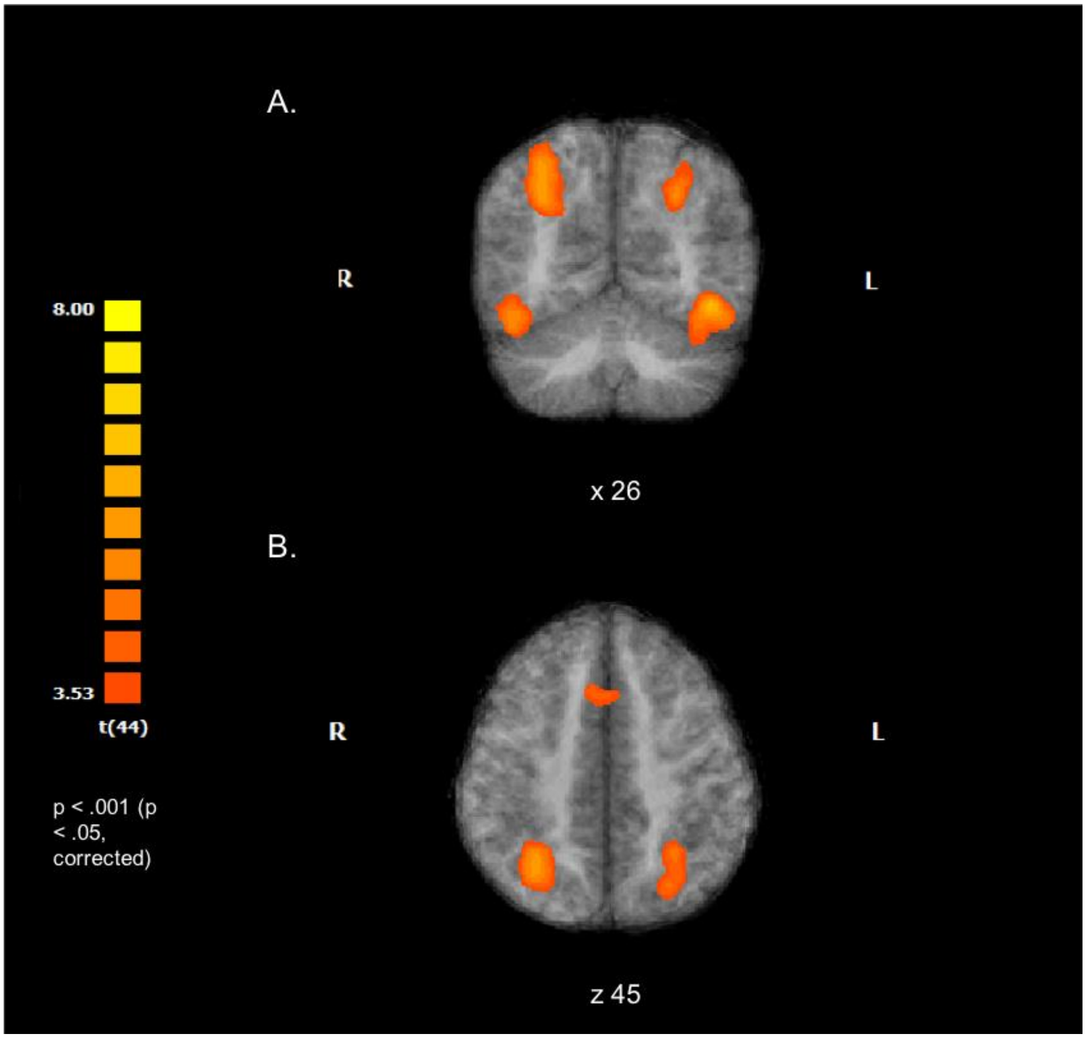


Figure 3.5: Significant clusters identified for the conjunction of the main and parametric effect. A. Coronal view of bilateral anterior IPS activation. B. Transverse view of the bilateral anterior IPS clusters.

Table 3.3: Significant clusters for the contrast parametric effect > baseline for the whole age group.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Temporal occipital fusiform cortex*	Right	43.55	-57.53	-14.97	7.72	12.4	6.28	9490	Temporal occipital fusiform cortex*	45	-55	-17	6.883256	<.000001
Broca's area BA44	Right	41.21	17.59	25.07	4.84	11.71	4.72	5228	Broca's area BA44	42	8	25	6.694193	<.000001
Anterior IPS hIP3	Right	29.97	-59.83	42.23	5.07	5.68	7.67	8857	Anterior IPS hIP1	33	-61	37	6.111075	<.000001
Callosal body	Right	5.91	-7.26	25.64	3.66	10.12	2.7	2433	Callosal body	6	2	25	5.932506	<.000001
Premotor cortex BA6	Right	1.91	19.28	42.69	3.64	4.65	4.86	2947	Paracingulate gyrus*	0	17	43	4.843523	0.000016
Anterior IPS hIP3	Left	-28.01	-60.1	41.88	3.27	6.97	5.32	4546	Anterior IPS hIP3	-30	-58	40	6.104719	<.000001
Visual cortex V3V	Left	-28.61	-92.38	-0.91	3.15	2.91	3.66	871	Visual cortex V3V	-33	-95	-5	4.176589	0.000138
Visual cortex V4	Left	-40.3	-62.09	-16.37	4.98	10.51	5.23	8429	Temporal occipital fusiform cortex*	-42	-61	-11	6.729499	<.000001

Coordinates given in MNI space. Cluster size is given in number of voxels. Cluster locations were labelled using the Jülich Histological Atlas (Eickhoff et al., 2005), unless no label was identified in this atlas for the specified coordinates. These regions (*) were labelled using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

Table 3.4: Significant clusters for the contrast main effect > baseline for the whole age group.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Middle temporal gyrus, anterior division*	Right	54.35	-2.72	-22.55	3.62	8.68	2.52	1193	Optic radiation	48	-13	-20	4.453786	0.000057
Inferior parietal lobule PGp	Right	46	-57.91	13.79	7.46	14.7	5.72	11503	Visual cortex V4	42	-83	2	6.982314	<.000001
Broca's area BA45	Right	44.98	19.43	27.13	6.34	11.66	8.79	13328	Broca's area BA44	42	8	28	7.740637	<.000001
Temporal occipital fusiform cortex*	Right	39.48	-52.97	-15.9	8.4	15.18	11.11	33559	Temporal occipital fusiform cortex*	45	-55	-17	11.815579	<.000001
Frontal orbital cortex*	Right	34.22	24.65	-2.92	4.4	4.43	6.06	3152	Insular cortex*	39	17	-11	5.544326	0.000002
Superior parietal lobule 7P	Right	31.47	-63.47	40.19	5.2	7.8	9.04	13059	Anterior IPS hIP1	30	-64	37	7.728463	<.000001
Primary motor cortex BA4p	Right	25.54	-28.96	65.44	5.9	3.16	3.29	1820	Primary motor cortex BA4a	24	-32	70	4.907578	0.000013
Occipital fusiform gyrus*	Right	7.91	-76.17	-24.3	13.92	7.26	10.2	12899	Visual cortex V4	36	-86	-8	7.906272	<.000001
Callosal body	Right	4.2	-31.1	7.5	12.38	11.23	11.78	29676	Fornix	-9	-22	13	7.006081	<.000001
----	Right	2.75	-49.75	-35.97	8.34	4.07	4.26	2655	Brain stem*	-9	-46	-42	5.705574	0.000001
Superior parietal lobule 7A	Right	0.2	-53.46	35.17	5.27	9.84	8.74	13779	Superior parietal lobule 7M	0	-67	28	5.585053	0.000001
Premotor cortex BA6	Left	-0.29	-8.31	49.27	6.34	13.63	10.38	26785	Premotor cortex BA6	-3	-7	49	7.00892	<.000001
Callosal body	Left	-0.46	17.21	18.96	8.52	17.29	11.38	23321	Lateral ventricle*	6	8	10	7.743277	<.000001
Corticospinal tract	Left	-6.37	-11.24	-15.85	6.02	4.04	3.53	1184	Corticospinal tract	-9	-10	-11	4.805412	0.000018
Anterior IPS hIP1	Left	-28.29	-64.99	40.19	4.4	7.23	8.58	9120	Inferior parietal lobule Pga	-30	-67	49	7.390533	<.000001
Inferior occipito-frontal fascicle	Left	-29.03	16.4	-4.05	5.27	8.26	7.57	5708	Frontal orbital cortex*	-33	29	1	6.100735	<.000001
Primary motor cortex BA4p	Left	-36.56	-23.72	55.08	9.95	11.18	8.07	22506	Primary motor cortex BA4p	-30	-28	58	7.967296	<.000001
Optic radiation	Left	-38.42	-32.23	2.81	11.46	11.64	14.59	14792	Hippocampus cornu ammonis	-24	-40	1	8.30289	<.000001
Visual cortex V5	Left	-41.61	-65.68	-6.21	7.6	12.29	14.84	28954	Temporal occipital fusiform cortex*	-42	-55	-17	9.409496	<.000001
Broca's area BA44	Left	-42.64	12.99	28.78	6.65	4.97	4.06	3854	Broca's area BA44	-36	8	28	5.85072	0.000001

Coordinates given in MNI space. Cluster size is given in number of voxels. Cluster locations were labelled using the Jülich Histological Atlas (Eickhoff et al., 2005), unless no label was identified in this atlas for the specified coordinates. These regions (*) were labelled using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

Table 3.5: Significant clusters for the contrast conjunction of main effect and parametric effect > baseline for the whole age group.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Temporal occipital fusiform cortex*	Right	42.5	-58.43	-15.72	6.61	12	5.86	8789	Temporal occipital fusiform cortex*	45	-55	-17	6.883256	<.000001
Broca's area BA44	Right	42.12	17.9	25.3	4.36	11.4	4.68	4397	Broca's area BA44	42	8	25	6.662276	<.000001
Superior parietal lobule 7A	Right	30.99	-60.4	43.12	3.98	5.6	7.43	7132	Anterior IPS hIP1	33	-61	37	6.111075	<.000001
Premotor cortex BA6	Right	1.78	16.5	41.45	3.78	3.16	4.71	1732	Premotor cortex BA6	3	14	40	4.674292	0.000028
Anterior IPS hIP3	Left	-27.9	-61.78	42.66	3.11	6.2	5.36	3704	Anterior IPS hIP3	-27	-58	37	5.937516	<.000001
Temporal occipital fusiform cortex*	Left	-40.77	-61.07	-16.44	4.82	9.95	5.3	7834	Temporal occipital fusiform cortex*	-42	-61	-11	6.729499	<.000001

Coordinates given in MNI space. Cluster size is given in number of voxels. Cluster locations were labelled using the Jülich Histological Atlas (Eickhoff et al., 2005), unless no label was identified in this atlas for the specified coordinates. These regions (*) were labelled using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

3.3.2.2 Secondary analyses.

To build on the original Vogel et al. (2015), we wanted to examine whether there was a relationship between the neural parametric recovery effect and the math and numerical processing measures. To this end, at the ROI level we ran correlation analyses in JASP (JASP Team, 2019) using the average parametric beta weights extracted from the left ($M = 0.97$, $SD = 1.58$) and right IPS ($M = 1.15$, $SD = 1.66$), IPS regions identified in the parametric effect > baseline contrast. Bayesian correlations were also run to determine the Bayes Factor (BF) that indicates the strength of the evidence in support of the alternate hypothesis (BF_{10}) if the correlation was found to be statistically significant, or the strength of the null hypothesis (BF_{01}) if the correlation was not found to be significant. The correlations between standardized Math Fluency scores and the right and left IPS parametric effect were not found to be significant, $r(43) = -.07$, $p = .665$, $BF_{01} = 4.92$; $r(43) = -.10$, $p = .531$, $BF_{01} = 4.45$, respectively. The correlations between the right and left IPS beta weights and the scaled Numeration scores were also not found to be significant, $r(43) = .16$, $p = .309$; $BF_{01} = 3.26$; $r(43) = .06$, $p = .678$; $BF_{01} = 4.95$, respectively. Finally, for the symbolic comparison task we used raw accuracy, as standardization norms were not available for this measure. Because JASP does not have a function to run partial correlations so that age could be controlled for, we used Bayesian regression to examine the relationship between symbolic comparison and IPS activation, while also including age in months in the model. This model was not found to be significant for the prediction of right IPS beta weights, $F(2,42) = 0.16$, $p = .855$, $R^2 = .007$. For the whole model, the $BF_{01} = 7.18$, and for the symbolic comparison as a predictor: $BF_{01} = 3.13$. Similarly, the model predicting left IPS beta weights for the parametric effect was not found to be significant, $F(2, 42) = 0.21$, $p = 0.809$, $R^2 = .01$, entire model $BF_{01} = 6.89$, symbolic comparison as a predictor $BF_{01} = 3.12$. In summary, none of the collected numerical measures demonstrated a significant association with the parametric effect within the IPS. Overall, the Bayesian analyses indicated anecdotal to substantial evidence in favor of the null hypothesis.

3.3.2.3 Exploratory analyses.

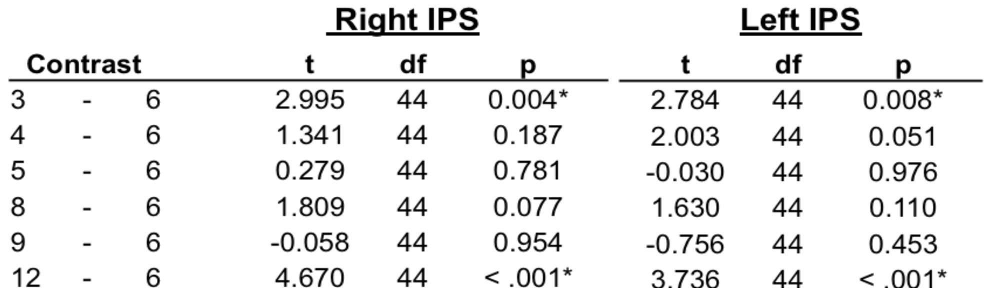
3.3.2.3.1 Comparing the left and right IPS parametric effect.

Although the following analyses were not preregistered, we wanted to determine if the hemispheres of the IPS differed in terms of magnitude of the parametric effect, given that Vogel et al. (2015) found a right-lateralized parametric effect. In this ROI analysis, average beta weights were extracted from the right and left IPS clusters that demonstrated a significant parametric effect. A Bayesian paired-samples t-test was run to determine whether the beta values in the right and left IPS for the parametric effect differed significantly. No significant difference was found between the parametric effect in the left and right IPS, $t(44) = 1.44$, $p = .156$, $BF_{01} = 2.36$. The BF indicated anecdotal evidence that the right IPS parametric effect does not differ from the left IPS parametric effect (Jeffreys, 1961).

3.3.2.3.2 Is 12 driving the parametric effect?

In the present paradigm, the deviant ‘12’ was the only two-digit number included. Therefore, considering plot C in Figure 3.2, it could be the case that the parametric effect was driven by the 12 within the 0.5 ratio. We examined this possibility by statistically comparing average beta weights for each deviant stimulus from the left and right IPS clusters defined by the parametric effect – i.e., the beta weights reported in Figure 3.2C. More specifically, paired t-tests were used to compare each deviant to the adaptation value ‘6’. For both the left and right IPS, the deviants with ratio 0.5 from ‘6’ (3 and 12) were both significantly different from ‘6’, suggesting that the parametric effect is not entirely drive by the deviant 12 (Table 3.6). This analysis allows us to investigate the patterns of the beta weights with respect to the amount of rebound for each deviant individually. Considering the magnitude of the t-statistics, overall, the deviants follow the pattern predicted by the parametric effect; larger deviation from 6 with decreasing ratio.

Table 3.6: Comparing the beta weights for each deviant to the adaptation value within the IPS.



	Right IPS			**Left IPS**		
Contrast	**t**	**df**	**p**	**t**	**df**	**p**
3 - 6	2.995	44	0.004*	2.784	44	0.008*
4 - 6	1.341	44	0.187	2.003	44	0.051
5 - 6	0.279	44	0.781	-0.030	44	0.976
8 - 6	1.809	44	0.077	1.630	44	0.110
9 - 6	-0.058	44	0.954	-0.756	44	0.453
12 - 6	4.670	44	< .001*	3.736	44	< .001*

* Denotes significance at a multiple comparisons-corrected threshold of .0083 (Bonferroni corrected).

3.3.2.3.3 Correlation between age and parametric effect at the ROI level.

As is evident from above, there were no regions that exhibited a correlation between age and the parametric ratio effect. To examine the strength of evidence for the null hypothesis, a Bayesian correlation analysis was run using the beta weights extracted above from the left and right IPS for the parametric effects and age in months. Substantial evidence was found for the null hypothesis with regards to the association between the right IPS and age, $BF_{01} = 4.62$, as well as the left IPS and age, $BF_{01} = 4.43$. At the ROI level there is substantial evidence that the parametric effect within the left and right IPS is not correlated with age in months (Jeffreys, 1961).

3.3.2.3.4 Considering spatial reproducibility of the parametric effect.

Both the current study and Vogel et al. (2015) obtained a parametric effect within the right IPS (although this effect was bilateral in the current study). It is important to establish whether the cluster identified in the current study could be considered close enough spatially to Vogel et al. (2015) to be considered a replication (Hong, Yoo, Wager, & Woo, 2019). Therefore, we calculated the Euclidean distance between the peak voxels reported in Vogel et al. (2015) and the current study (Table 3.3) for the parametric effect in the right IPS. First, the peak coordinates from Vogel et al. (2015) were translated from Talairach space to MNI space using http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html (peak voxel in MNI space (x, y, z) = 31, -76, 49). Next, following Vogel et al., (2017), Euclidean distance between peak voxels was calculated using the Scipy library within python 2.7, using the distance.euclidean function. The Euclidean distance between the peak voxels in the right IPS of the current study and Vogel et al. (2015) was 19.31mm. Because the current study obtained a bilateral parametric effect, the left IPS peak coordinates of the current study (Table 3.3) were compared to the left IPS coordinates in Vogel et al. (2015) that demonstrated the correlation between age and the parametric effect (peak voxel in MNI space (x, y, z) = -43, -69, 45. The Euclidean distance between the peak voxels in the left IPS of the current study and Vogel et al. (2015) was 17.75mm. Therefore, when examining the straight-line distance between the peak voxels of the parietal clusters that demonstrated a parametric effect in Vogel et al. (2015) and the current study, the clusters are relatively far apart (Figure 3.6).

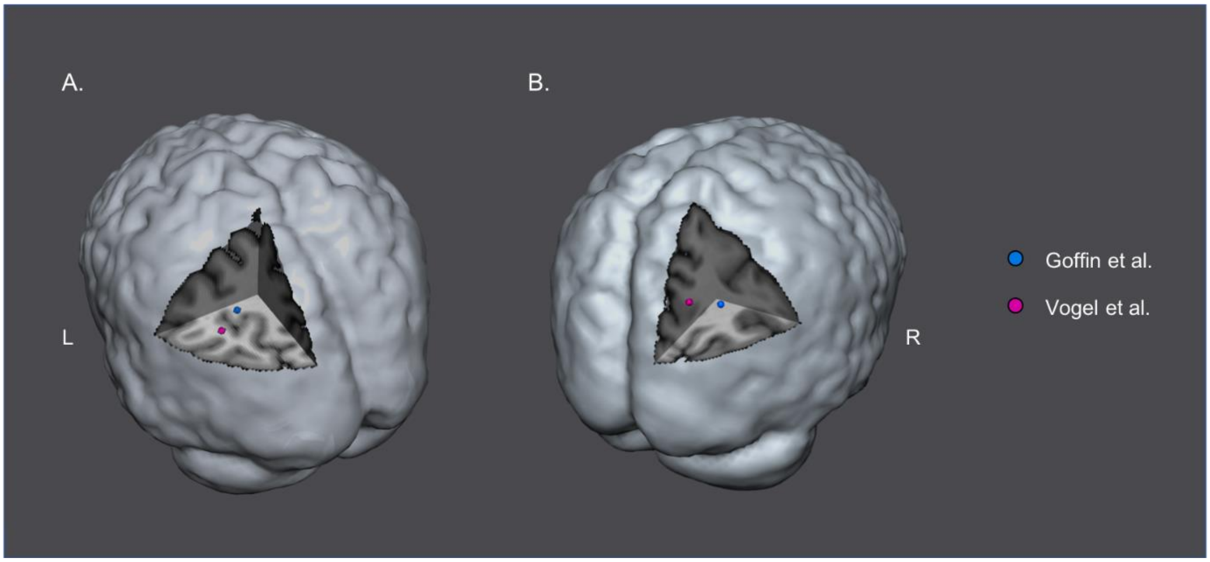


Figure 3.6: Peak voxels in MNI space from Vogel et al. (2015), purple, and the replication study (Goffin et al.), blue. Clusters were created using a 2mm sphere centered on peak voxel coordinates, mapped on a standard MNI Colins 27 mesh. Panel A: Peak voxel of the right IPS cluster for the parametric effect. Panel B: Peak voxel for the left IPS cluster demonstrating a parametric effect in Goffin et al. and a correlation between the age and parametric effect in Vogel et al. (2015)

3.4 Discussion

The central aim of the current study was to replicate Vogel et al. (2015) with a larger sample size. First, across the entire age group we found evidence of a strong parametric effect in response to symbolic number within bilateral IPS regions. This could be considered a partial replication of Vogel et al. (2015), as the original study found this effect constrained to the right IPS.

Second, the current study found no evidence to support a whole-brain correlation between the parametric effect and age. Conversely, Vogel et al. (2015) obtained a significant whole-brain correlation between the parametric effect and age in the left IPS. A follow-up ROI analysis in the current study examining the association between age and the beta weights extracted for the parametric effect from the left and right IPS also did not reach significance. Additionally, the Bayes Factors indicated substantial support for the null for this analysis. Thus, the present study failed to replicate the association between parametric ratio effect and chronological age in the left IPS or anywhere else in the brain.

Finally, the current study extended Vogel et al. (2015) by examining the relation between the parametric effect and numerical measures. Overall, neither math achievement or symbolic numerical processing were found to be significantly related to the parametric effect within the left or right IPS. Furthermore, Bayesian statistics indicated substantial support for no relationship between the parametric effect and math fluency. For the other numerical measures (numeration and symbolic comparison), the Bayes Factors were suggestive of anecdotal to substantial evidence for the null hypothesis, which could indicate that we did not have enough power for this analysis. It should be noted that the magnitude of the BF_{01} was not in the range of strong evidence for the null for any of these analyses. To be considered in the range for strong evidence, a Bayes Factor greater than ten would be needed (Jeffreys, 1961). It is therefore difficult to draw any conclusions regarding the relationship between these variables from the current data.

In summary, the current study did not replicate the main findings of Vogel et al. (2015). This lack of replication emphasizes the importance of replication studies as a process to verify the reliability of key findings that underpin theories regarding the development of symbolic number representation. We will now turn to a discussion of the implications of these results and some of the factors surrounding this lack of replicability.

3.4.1 The contribution of the left vs. right IPS for symbolic numerical processing

The current study found a bilateral parametric effect within the IPS, as opposed to the right-lateralized activation observed in Vogel et al. (2015). To date it is unclear from the numerical cognition literature what the role of the left vs. the right IPS is for symbolic number representation. From the adult literature, the left IPS seems to be more involved in symbolic numerical processing, while the right tends to be recruited more for non-symbolic numerical processing (Sokolowski et al., 2017). However, it is not unusual for studies to find bilateral activation within parietal regions for either symbolic or non-symbolic numerical processing. For example, in a quantitative meta-analysis examining numerical processing tasks in adults, Sokolowski et al. (2016) found bilateral parietal regions when examining the conjunction between symbolic and non-symbolic numerical tasks. More specifically, when Sokolowski et al. (2016) meta-analytically examined all published fMRI studies with numerical tasks, bilateral regions within the inferior parietal lobule (IPL) were found to be activated by symbolic as well as non-symbolic processing tasks. In addition, when the meta-analysis considered only passive tasks, the right IPL and several regions in the left SPL were active for both, passively presented, symbolic stimuli and non-symbolic stimuli. Therefore, although symbolic number representation tends to be more left-lateralized, the extent of this laterality is not necessarily clear-cut, even in adults.

Particularly unclear is the developmental trajectory of the involvement of the left and right IPS in symbolic number representation. As discussed above, there does not seem to be agreement within the literature as to the role of the left vs. the right IPS as children develop symbolic numerical understanding (e.g., Ansari et al., 2005; Bugden et al., 2012;

Houdé et al., 2010; Mussolin et al., 2013). In a quantitative meta-analysis, Kaufmann, Wood, Rubinsten and Henik (2011) examined 14 developmental fMRI studies that included a symbolic and/or non-symbolic numerical comparison task. For symbolic number processing, a large network of fronto-parietal regions was identified. In the results from the parietal lobe, Kaufmann et al. (2011) found that although the left parietal cortex seemed to be more specialized than the right for symbolic number, children also tended to recruit bilateral parietal regions, including the bilateral inferior parietal cortex. Unfortunately, Kaufmann et al. (2011) could not examine how parietal involvement may change across age; currently there is an insufficient number of developmental fMRI studies examining symbolic numerical processing to carry out a quantitative analysis examining the developmental trajectory of the involvement of the left vs. right IPS for symbolic number. As well, it is important to note that neural response to the symbolic comparison task -- the focus of the Kaufman et al. (2011) findings – is, as discussed above, confounded with response selection processes.

In one of the few studies to examine passive viewing of numerical stimuli in young children using fMRI, Cantlon, Brannon, Carter and Pelphrey (2006) presented a group of four-year-olds (n = 8) and a group of adults (n = 12) with arrays of shapes. The adaptation array of shapes consisted of 16 circles. The deviants presented varied in terms of the number of shapes presented (8 or 32), or the type of shape presented (squares or triangles). For the group of children, a network of regions was more activated for the change in number compared to the change in shapes, including the right IPS and SPL, as well as left IPL. Although this study examined non-symbolic as opposed to symbolic numerical processing using a passive task, bilateral activation in parietal regions was found for this small group of children. Clearly the left IPS is not only responsive to symbolic representations of numerical magnitude. Considering the available developmental literature, it seems that representation for number may recruit a large network of regions, including largely bilateral parietal regions. The current study supports this hypothesis of a contribution of bilateral parietal regions by demonstrating a similar pattern for symbolic number.

Although there is some evidence that symbolic number representation may recruit bilateral parietal regions, or largely left-lateralized parietal regions, in Vogel et al. (2015) the right IPS was recruited. Currently it is unclear why this may be the case. In other domains of symbolic processing, such as reading, a progression from right to left recruitment of neural regions across development has been observed (Spironelli & Angrilli, 2009). This hypothesis in the numerical domain is supported through work by Holloway et al. (2013), who examined symbolic number processing using an adaptation task with Arabic digit as well as Chinese numerical symbols. Two groups of participants were included: one that could understand the Arabic digits but not the Chinese symbols (English – non-Chinese bilinguals), and one that could understand both symbol sets (English – Chinese bilinguals). A parametric effect was observed in the left IPS for the Arabic digits, regardless of group. However, only the group that could understand Chinese symbols demonstrated a parametric effect in the Chinese symbol condition of the task. This parametric effect was found in the right IPS. Arguably, those who were familiar with the Chinese numerical symbols still were less familiar with these symbols than they were with using Arabic digits. Therefore, it is possible that the left IPS was recruited for the very familiar format that the entire sample would be considered an expert in (i.e., Arabic digits). The right IPS was recruited by the group that could understand the meaning of the Chinese symbols, however who were perhaps less practiced using this format to represent numerical information (Holloway et al., 2013). Perhaps recruitment of both hemispheres of the IPS could indicate an intermediate stage in the development of symbolic number representation. In other words, perhaps the recruitment of both hemispheres is a reflection of a lack of automaticity within the sample of children for representing number symbolically. This suggests these regions could be working in similar ways in this age range to support symbolic number representation. Further research is needed to understand the mechanisms that underlie symbolic number representation, and how this may develop and change as children become more fluent with using symbols to represent quantities. The role of the left vs. the right IPS in symbolic numerical representation remains an open question.

3.4.2 Spatial reproducibility within the IPS

Both the current study and Vogel et al. (2015) found a parametric response to number within the right IPS. However, when the distance between the peak coordinates of the right IPS parametric effect from the current study and that of Vogel et al. (2015) was calculated, the parametric effect was actually found in areas of the right IPS that could be considered spatially different. This was also the case for the left IPS peak coordinates from the current study and the left parietal cluster found in Vogel et al. (2015) for the age correlation. This suggests that even though the right IPS demonstrated a parametric effect across both studies, the effects were spatially distinct. Hong et al. (2019) found that out of 135 fMRI studies that supposedly replicated previous results, about 43% of those obtained peak coordinates that were greater than 15mm away from the coordinates reported by the original study. This is problematic, as defining replication by gross anatomical region, as opposed to finer-tuned criteria such as voxel-based measures, leads to imprecise claims of replication between regions that may actually be functionally distinct. The IPS, for example has been demonstrated in monkeys to be comprised of five regions that can be considered functionally distinct (Grefkes & Fink, 2005). Therefore, although both the current study and Vogel et al. (2015) obtained a parametric effect within the right IPS, the spatial distance between these regions suggests they could be functionally different regions. It should be noted that Vogel et al. (2015) normalized their data into Talairach space, whereas the current study used MNI space. It is possible that these differences in normalization contributed to the differences observed between the studies in terms of quantitative differences in the location of peak voxels within the right IPS, even after the coordinates from Vogel et al. (2015) were translated into MNI space (Lancaster et al., 2007). Further research is needed to understand the involvement of these potentially functionally distinct regions within the IPS and their involvement in symbolic numerical processing.

3.4.3 Developmental trajectories of symbolic numerical representation

The current study failed to replicate one of the central findings of Vogel et al. (2015): the correlation between age and the parametric effect within the left IPS. Why might this be the case? Symbolic numerical processing as measured by an adaptation task resulted in a robust parametric effect, but an effect that, according to the results presented above, is age-invariant in the current sample. It is possible that in the included age range (6-14), symbolic numerical processing is already sufficiently developed to be similar to that of older children. Cantlon et al. (2006) found that their sample of four-year-olds demonstrated brain activation that was comparable to that of adults using a passive non-symbolic task. Specifically, adults and children showed activation in overlapping regions in the right IPS and SPL. However, adults showed this effect bilaterally, while children had right-lateralized IPS activity (although left IPL was also observed for the children). When adults and children were directly contrasted, age differences were observed, with adults demonstrating greater activity in comparison to children bilaterally in the IPS, while children demonstrated greater bilateral SPL activity in comparison to adults. Therefore, although there were some similarities in the patterns of activation when comparing 4-year-olds and adults in a non-symbolic adaptation task, important differences were also observed. In the current study, similar to previous research with adults, children recruited the left IPS for number processing. However, children also recruited the right IPS, demonstrating divergence with the adult patterns of activation.

Given the simplicity of the adaptation measure in terms of task demands, perhaps the task is relatively insensitive to developmental changes that would be captured in an active task that requires processes such as selecting a response. This is a key benefit of the adaptation method, as it can be said to allow researchers to capture neural correlates that could be considered a “purer” measure of numerical processing. This is why it is of particular interest that developmental changes in the parametric effect were not observed in the current sample. This suggests that symbolic numerical representation in the brain may already be quite stable by age six. Performing different operations with symbolic number (such as comparison, ordering, arithmetic) undergoes development in elementary school-aged children, however the underlying representations that are used for these operations may be well-formed by age six. This could also explain why we did not find evidence for an association between the parametric effect and math achievement or number comparison. It remains a question for future studies whether including children who are first beginning to learn symbolic numbers would lead to observing an age difference in the parametric effect captured with the symbolic adaptation task.

3.4.4 The effect of sample size on the stability of correlation coefficients

Critically, in the present study, we failed to replicate one of the main findings of Vogel et al. (2015) – an association between age and the parametric effect in the left IPS. Despite using the same task and age range as the original study, a correlation with age was not found at the whole-brain or ROI level. Furthermore, a Bayesian correlation analysis at the ROI level suggested substantial evidence for a lack of association between age and the parametric effect in the IPS. This could suggest that the original finding of an age correlation within the left IPS was spurious, although it is difficult to discuss the absence of an effect.

While the current study strove to include a larger sample size – more than doubling the original sample – the included sample size could still be considered relatively small, depending on the true effect size of any correlation between the parametric ratio effect and brain activation. Neuroimaging studies, especially developmental neuroimaging studies, are constrained by practical issues such as budget and time; making large sample sizes difficult to attain. Unfortunately, these small samples sizes contribute to the particularly high false positive rates within cognitive neuroscience research (Szucs & Ioannidis, 2017). Effect sizes reported for cognitive neuroscience journals are between d = 0.34 – 1.22 (25th and 75th percentile; Szucs & Ioannidis, 2017). However, these effect sizes are likely to be inflated due to low power as a consequence of small sample sizes. More specifically, Szucs and Ioannidis (2017) calculated that overall, cognitive neuroscience has demonstrated in the literature statistical power of less than 0.234 to detect a small effect.

Considering one of the main findings from Vogel et al. (2015) was the result of a correlation analysis, what would the optimal sample size be to provide an accurate estimate of a correlation in the general population? The magnitude of a correlation can vary in small sample sizes, to the point where it may cycle between significance and non-significance, or even significance in the opposite direction before stabilizing (Schönbrodt & Perugini, 2013). This is clearly highly problematic when trying to draw conclusions from a correlation analysis. To explore this issue, Schönbrodt and Perugini (2013) ran Monte-Carlo simulations to assess the necessary sample size for a correlation to stabilize. To define stability in terms of a correlation, the authors established a "corridor of stability": an interval based on a chosen effect size that determines the maximum acceptable range of values for a correlation to fluctuate within and still be considered stable. The "point of stability" then, is the minimum sample size at which the trajectory of the correlation stays within the corridor of stability. Using a bootstrapping method that repeatedly takes subsets of data from a sample, Schönbrodt and Perugini (2013) mapped the trajectories of correlations to determine a critical point of stability: a sample size at which one can be confident that a correlation estimate will stay within the corridor of stability. The ideal sample size varied according to the magnitude of the actual correlation as well as what the researcher considers acceptable in terms of level of accuracy (i.e., the width of the corridor of stability) and confidence (i.e., the level of confidence that the correlation trajectory will stay within the corridor of stability). However, the authors concluded that in general a sample size of n = 250 should be used. This is a far cry from the usual degrees of freedom reported by studies in cognitive neuroscience journals (df = 10-28) or even psychology journals (df = 17-60; Szucs & Ioannidis, 2017). Although the current study used a sample size that could be considered relatively large for the field of cognitive neuroscience, based on the parameters established by Schönbrodt and Perugini (2013) it seems very likely that results from this correlation analysis have not stabilized. Therefore, any conclusions drawn from the current study regarding correlations need to be taken with caution.

3.4.5 Conclusions

The current study demonstrated a parametric effect in bilateral IPS across a group of 6 to 14-year-olds in response to symbolic number. This provided a partial replication of Vogel et al. (2015)'s right-lateralized parametric effect in the IPS, although the right IPS identified in Vogel et al. (2015) and the current study are spatially distinct. This finding of the presence of a neural response that seems to be modulated by numerical ratio suggests that childrens' neural representation of symbolic number is qualitatively similar to that of adults. However, children recruited bilateral IPS regions, whereas in adults this response tends to be more left-lateralized (Sokolowski et al., 2017). This finding could reflect an immaturity in the neural representation of symbolic number in younger children. This study failed to replicate the correlation between age and the neural parametric effect demonstrated by the original Vogel et al. (2015), suggesting that the parametric effect in this sample was relatively stable across the age range. In the current climate of the replicability crisis, this study provided further evidence to underline the importance of replication, particularly in the field of cognitive neuroscience where sample sizes and the resultant statistical power to pick up true effects is very low, while false positive rates are very high.

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Chapter 4

4 Does writing handedness affect neural representation of symbolic number? An fMRI Adaptation Study

4.1 Introduction

4.1.1 Neural Correlates of Symbolic Number Representation

Although the ability to manipulate symbolic numerical information is key to daily functioning, little is known about how the human brain comes to assign meaning to arbitrary symbols (Coolidge & Overmann, 2012). Number symbols (e.g., Arabic digits) are a human invention of arbitrary symbols used to represent quantities. Number symbols have emerged over the course of human cultural history (Everett, 2017). Given the relatively recent invention of number symbols, it is highly unlikely that the human brain was adapted over the course of evolution to represent symbolic numbers. More specifically, representing number symbolically occurs with enculturation, and consequently does not occur without learning (Núñez, 2017). Therefore, how the human brain comes to represent symbolic numbers over the course of learning and development is a key question in the field of numerical cognition.

Neuroimaging tools such as functional magnetic resonance imaging (fMRI) have been used to address this question. A large body of evidence implicates specific brain regions in the representation of numerical symbols. For example, regions within the parietal lobes, specifically the left parietal lobe, are consistently activated when participants compare the numerical magnitude of two symbolic numbers (e.g., which of 4 and 6 is numerically larger?; e.g., Bugden, Price, McLean, & Ansari, 2012; Cohen Kadosh et al., 2005; Göbel, Johansen-Berg, Behrens, & Rushworth, 2004). Similarly, activation along the left parietal cortex has been observed when participants are asked to solve arithmetic problems presented in a symbolic format (e.g., 1+3; Arsalidou & Taylor, 2011; e.g., Grabner et al., 2009; Venkatraman, Ansari, & Chee, 2005). Additionally, studies of patients with left parietal lesions find numerical skills are negatively impacted. For example, Cipolotti, Butterworth and Denes (1991) observed an inability to process numbers higher than ‘4’ in a patient with widespread, but left-lateralized, fronto-parietal damage. In a patient with a left parietal lesion, Lemer, Dehaene, Spelke and Cohen (2003) noted issues in various domains of basic numerical abilities, including counting and number comparison. Ashkenazi, Henik, Ifergane and Shelef (2008) found that a patient with a left IPS lesion demonstrated difficulties with basic numerical processing as well as arithmetic.

Furthermore, the left parietal cortex is activated when participants passively look at number symbols (Holloway, Battista, Vogel, & Ansari, 2013; Notebaert, Nelis, & Reynvoet, 2011; Vogel et al., 2015). Such passive paradigms control for confounds such as response selection and motor response and thereby lend stronger support for the notion that activation in the left parietal cortex is correlated with the processing of number symbols (Holloway et al., 2013; Notebaert et al., 2011; Vogel et al., 2015). A recent meta-analysis of the existing fMRI studies of symbolic number processing provided convergent evidence for the association between the activation of the left parietal lobe and symbolic number processing (Sokolowski et al., 2016). More specifically, in comparison to non-symbolic number processing (e.g. numerical comparison of dot arrays) the left superior parietal lobule (SPL) was found to be activated consistently for symbolic number processing.

Although research has revealed underlying neural correlates of symbolic number processing, it remains unclear what mechanisms drive this association. Specifically, the mechanism underlying why the left parietal cortex appears to be more strongly associated with the processing of symbolic number than the right parietal cortex is unknown. A possible key mechanism for this parietal asymmetry during symbolic number processing may be handwriting and, by extension, the handedness of individuals.

4.1.2 Handedness and Cognitive Neuroscience

While a large body of functional neuroimaging experiments have implicated the left IPS in symbolic number processing, it is unclear what might give rise to this relative lateralization of activation. One possible candidate is the handedness of the participants. Consistent with fMRI research across domains, research on symbolic numerical skills has almost exclusively involved right-handed individuals. Of the 27 papers that reported the handedness of participants included in the meta-analysis by Sokolowski et al, 98.4% reported data from right-handed participants and only two out of 57 studies included data from left-handed participants.

Being right-handed is often a mandatory inclusion criterion for fMRI studies in order to exclude handedness as potential confound and thereby reduce unmeasured variability between participants. Yet, approximately ten percent of the population is left-handed (Willems et al., 2014). Therefore, most fMRI studies do not adequately represent this population.

Critically, the few studies that have examined left- as well as right-handed individuals, report that handedness affects the neural laterality of various cognitive constructs. For example, research in embodied cognition demonstrates that the motor system influences word processing (Willems et al., 2010) and visuospatial attention (Cai et al., 2013). Interestingly, handedness has been found to affect the laterality of language processing (Willems et al., 2014). Neuroimaging of language processing has typically revealed left-lateralized patterns of activation (Knecht et al., 2000). However, when taking handedness into account the data appear to be mixed. For example, Cai et al. (2013) revealed that some left-handers exhibited the expected left-lateralization of language production that is typical of studies of right-handed individuals. However, other left-handed individuals showed a right-lateralization of language production. This reversal of the so-called typical lateralization of these important cognitive constructs emphasizes the importance of examining the effect of handedness on lateralization in the brain.

Additional research has shown that the handedness of participants is an important factor with respect to hemispheric lateralization while processing symbols (e.g. letters). For example, Longcamp, Anton, Roth, & Velay (2003) presented a group of right-handed participants with a passive viewing task in which participants saw letters, nonsense symbols or lines. Left ventral premotor activation was found for the letter condition. In a follow-up study, Longcamp, Anton, Roth and Velay (2005) used the same letter viewing task with a group of left-handed participants and revealed right lateralized premotor activation in this group. Longcamp and colleagues (2005) attributed this finding of handedness-dependent laterality to the experience of handwriting. Specifically, the hand that participants use to write affects the visual perception of the letter stimuli. This finding suggests that the neural representation of symbols may be influenced by handwriting (specifically by which hand participants use to write) and that these effects of handwriting on symbolic representations in the brain can be observed using passive tasks.

4.1.3 Handwriting and Hemispheric Lateralization

A meta-analysis by Planton, Jucla, Roux and Demonet (2013) that included 18 studies of unspecified handedness indirectly provides support for this idea that handwriting plays a role in number representation. Planton et al. (2013) found that the left IPS, an area commonly engaged by symbolic numerical tasks, was part of a network of areas involved in handwriting. James (2010) provides further support for the notion that handwriting is an important experience that contributes to the development of brain representations. Specifically, James (2010) scanned two groups of right-handed, non-literate preschool children before and after two letter training interventions. One group of children practiced handwriting letters, the other group practiced visually recognizing letters. Both groups of children showed left-lateralized activation in response to letters. However, the group of children that practiced hand-writing letters also showed increased activation in the left fusiform gyrus and right anterior fusiform gyrus. This indicates that the experience of practicing letter writing affected the development of the visual systems' response to the presentation of the letters. These data provide further evidence that handwriting may be integral to the way symbols such as letters are represented in the brain and, critically, in areas that are not associated with the motor processes engaged during handwriting.

Given the evidence for effects of handedness on laterality of various cognitive functions including embodied cognition, attention, and language it can be predicted that handedness will affect laterality in other domains of neurocognitive processing (Willems et al., 2014). Moreover, the finding by Longcamp and colleagues (2005) of different lateralization in left- and right-handers for premotor activity in response to letters suggests that handedness could similarly affect the processing of number symbols. Throughout education, children are taught to copy symbols, engage in tracing and perform rudimentary calculation using paper and pencil. We predict that these activities may shape the lateralization of neural representations of number symbols. Therefore, it is critical to empirically test whether including only right-handed individuals is biasing results in numerical cognition to find left lateralization for symbolic number. Handwriting experience with the right-hand could account for the left lateralized parietal activation consistently observed in right-handed individuals (Sokolowski et al., 2016). Against this background, the current study addressed the following question: is hand preference for writing associated with the functional architecture underlying symbolic number processing?

4.1.4 The Current Study

The aim of the current study was to examine whether hand preference in writing is related to the representation of symbolic number in the brain. One way to test this is to compare brain activation patterns in right-handed individuals with left-handed individuals. However, tasks commonly used in numerical cognition research such as number comparison and arithmetic verification require participants to make a response (e.g., choose a response and press a button). This introduces confounds such as response selection and motor responses. These confounds severely compromise our ability to draw inferences specifically regarding the effect of handedness, independently of the response. These confounds are particularly problematic if participants use their dominant hand to respond. For example, if right-handed individuals show greater left lateralization during symbolic number comparison (deciding which of two numbers is numerically larger) than left-handed individuals, this could simply reflect the fact that they are responding with their dominant hand.

fMRI-Adaptation (fMRI-A) uses a passive design to measure neural correlates of interest without requiring participants to make motor responses. Generally, fMRI-A uses repeated presentations of a stimulus. Regions of the brain that are involved in the representation of this stimulus tend to show decreased activation with the repeated presentations (for example a region involved in processing faces would be expected to show decreases following the repeated presentation of faces). Following this period of adaptation, a stimulus that differs in some way of interest is presented. Brain regions that are involved in encoding this specific stimulus attribute tend to show a rebound in activation in response to this deviation from the adaptation period. Throughout the adaptation paradigm, participants are simply asked to passively view the stimuli. The use of these passive tasks mitigates confounds that are inherent to active tasks.

This technique has been used to investigate neural representation in research domains such as face and object processing (Grill-Spector, Henson, & Martin, 2006). For example, Grill-Spector and Malach (2001) presented participants with various faces that were either identical, presented in a different position, a different size, a different rotation or scrambled. Brain regions that are insensitive to variations in these variables will show decreased activation with repeated presentations of the face stimuli. However, if activation in a certain region rebounds with a change in, for example, position, it can be inferred that this region is involved in the processing of position for this stimulus (or positional information more generally). What this study revealed is that within the lateral occipital cortex (LOC), more neural adaptation was reserved for faces that changed in position and size, but less adaptation was observed for faces that were rotated (Grill-Spector & Malach, 2001). This suggests that activity in the LOC was more invariant to changes in position and size of the face stimuli and more sensitive to changes in rotation.

fMRI-A has also been used to study the representation of symbolic numbers in the brain. (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Holloway et al., 2013;

Notebaert, Nelis, & Reynvoet, 2010; Notebaert, Pesenti, & Reynvoet, 2010; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Vogel, Goffin, & Ansari, 2015, Vogel et al., 2017). In fMRI-A studies of symbolic number, the same number is repeatedly presented during a so-called adaptation phase and areas involved in numerical processing are expected to show decreased activation (i.e., there is adaptation to the repeated stimuli). Following the adaptation phase, a different number (a deviant number) is presented. The presentation of the deviant number is hypothesized to result in a rebound of activation in regions that are involved in symbolic number processing (i.e., the region that is coding for numerical symbols is hypothesized to recover from adaptation when the stimulus property to which this region adapts is changed). Previous research has demonstrated that activity in the left IPS is modulated by the numerical ratio between the adaptation number and the deviant number (Holloway et al., 2013; Notebaert, Pesenti, & Reynvoet, 2010; Vogel et al., 2015). In other words, more rebound in activation in the left IPS was observed for numbers for which the ratio between adaptation and deviant number is smaller (e.g., 0.50) compared to instances where this ratio is relatively larger (e.g., 0.83).

It has been argued that such ratio effects reflect the representational similarity or overlap between number symbols (Notebaert, Pesenti, et al., 2010). Specifically, larger ratios between the adaptation and deviant numbers are hypothesized to correspond to greater representational overlap/similarity. In other words, the more the deviant stimulus differs from the adapted stimulus in the variable of interest (in this case numerical magnitude), the greater the expected rebound brain response. For example, the representation of 3 is more similar to the representation of 4 than it is to the representation of 5. From this, it follows that the presentation of the digit 3 will lead to greater co-activation of the representation of 4 than that of 5 (i.e., the rebound in brain response should be less for the deviant 4 compared to the deviant 5).

Measuring the effect of deviant number/adaptation number ratio is purported to reveal regions that are sensitive to semantic representation of number. Regions that respond to all deviants irrespective of ratio may include brain areas that are important for the visual processing of the number symbols in a way that does not necessarily reflect the processing of the numerical magnitude represented by the symbols. Therefore, measuring how the neural response to deviants depends on the ratio between the adaptation and deviant numbers allows for more specific inferences about the underlying processes to be made.

This left-lateralized rebound effect observed in passive symbolic numerical tasks is relatively consistent across the literature (Sokolowski et al., 2016). However, to date, only right-handed participants have been included in these studies (notably, one included study did not report participant handedness). Therefore, the current study tested whether the rebound effect in passive symbolic number is systematically related to the handedness of the participants. For this purpose, a group of right-handed participants and a group of left-handed participants were recruited. fMRI-A using Arabic numerals was used to compare the lateralization of symbolic number representation in right- vs. left-handed participants.

Consistent with existent findings, our first hypothesis was that the right-handed group would show the previously demonstrated left-lateralized effect in the parietal lobe. In contrast, based on evidence that finds an important effect of handwriting on representation and of handedness on neural laterality, our second hypothesis was that the left-handed group would show relatively greater right hemispheric lateralization of the neural rebound effect in the parietal lobe. Related to this, our third hypothesis predicted group differences when the left- and right-handers were compared directly, whereby the left-handed participants would show greater activation in the right parietal region in comparison to the right-handed group, and the right-handed group would show greater activation in the left parietal region. This finding would significantly inform our understanding of the mechanisms underlying numerical representation and would suggest that the process of handwriting plays an important role in how humans come to represent numerical symbols. This finding could provide novel insights into how the experience of handwriting is a key mechanism that scaffolds the culturally acquired symbolic number processing system.

In our fourth hypothesis, we examined the laterality of the neural rebound effect at the individual level, and examined the proportion of participants in each group that showed left-lateralization. These proportions were compared between the left- and right-handed groups. If no difference in laterality between left and right handed participants is found, this indicates that either the null hypothesis is true, which would suggest that handedness in the way it is measured in the current study does not play a role in the left-lateralization of number symbol processing in the brain, or that we have not yet accumulated enough evidence to reject the null hypothesis. To distinguish between these possibilities, the proportion of participants who show a left-lateralized parametric effect in response to symbolic number will be compared between the two groups using a Bayesian test of proportions. We predicted that a larger proportion of individuals in the left-handed group, compared to the right-handed group, would show right-lateralization.

4.2 Methods

4.2.1 Power Analyses

To calculate the sample size needed for an adequately powered sample, we used G*Power. Holloway et al., (2013) used a numerical adaptation task and a between-subjects design. They had two groups of participants: bilingual in English and Chinese, and fluent in English but not Chinese. This study used a numerical adaptation task that is almost identical to the one used in the current study. The main difference between Holloway et al., (2013) and the current study is that Holloway et al., (2013) included two conditions: an Arabic digit and Chinese numeral condition.

To calculate power for the analyses that address Hypotheses 1 and 2, we used the means and standard error values provided on p. 395 for the whole brain contrast of Chinese group for the parametric effect in the Chinese numerical adaptation condition > 0 (M = 0.406, SE = 0.101). The effect size from the between-groups contrast for the Chinese numeral condition was used because group differences in the adaptation effect were found in this condition. These values were used to calculate the standard deviation (SD = 0.364) and then an effect size of 4.02. This effect size was entered into a G*power analysis for a power of .9 and an alpha of .001 for an A priori power analysis to compute the required sample size needed for a one sample t-test. This analysis revealed that we need a sample size of n = 6 per group for each of the first and second hypotheses.

For Hypothesis 3, we used means and standard errors for the whole brain contrast of Chinese > control (*M* = 0.153, *SE* = 0.089, calculated *SD* = 0.321) for the Chinese ideograph condition from p. 395-396 of Holloway et al., (2013) to calculate a between-group effect size (d = 2.657). This effect size with power of .9 and an alpha <.001 was entered into a G*power A priori power analysis to compute the required sample size needed for a one-tailed independent t-test. This analysis revealed that we need a sample size of n=16 in total (n = 8 per group).

Critically, it has been demonstrated by Holloway et al. (2013) that this adaptation task has been used to successfully identify group differences with a sample size as small as 13 per group. However, to be conservative, we exceeded the average sample size of studies that have demonstrated a parametric adaptation effect in response to symbolic stimuli: Notebaert et al., 2010, n = 13; Piazza et al. (2007), n = 14; Holloway et al., (2013), n = 26; Vogel et al. (2017), n = 20 and n = 34, Chapter 2 of current dissertation, n = 24. Therefore, our study included 25 participants per group, for a total of 50 participants.

Finally, with regards to Hypothesis 4, because the analysis used to investigate the laterality of the parametric effect at the individual level was carried out using Bayesian statistics, a power analysis was not required. Power analyses are only necessary for frequentist statistics.

4.2.2 Measures

4.2.2.1 Adaptation.

Because we were interested in examining the left lateralized parametric effect observed in right-handed participants in previous studies, the adaptation task used was taken from the numerical cognition adaptation literature. More specifically, it was the same adaptation task used in Vogel et al., (2015) and experiment 1 of Vogel et al. (2017). This task has been demonstrated to show the expected left lateralized parametric effect in the parietal region in right-handed adults, as well as an age-related left lateralized parametric effect in children. Participants were adapted to number ‘6’. The number ‘6’ was repeated between 5 and 9 times (with an average repetition of 7 presentations) during the adaptation period. This creates a jitter in the presentation intervals so that the haemodynamic response is oversampled. The repeated presentation of the number 6 was randomly interspersed with 18 presentations of deviant numbers (3, 4, 5, 8, 9, 12), 8 catch trials and 4 null trials per run (see Figure 4.1). The ratio between the adaptation and deviant number was varied (see Table 4.1). The catch trials consisted of the presentation of a number in red font (R-G-B values 255, 0, 0). Catch trials are used to ensure the participants are attending to the stimuli. In the ‘null trials’, the adaptation period is followed by the presentation of another ‘6’. These null trials are used to model the adaptation effect. In other words, we expected that activation in response to these ‘null trials’ would be lower than for any of the deviant trials, providing us with a means to estimate the effect of repetition on the neural response to the adaptation number.

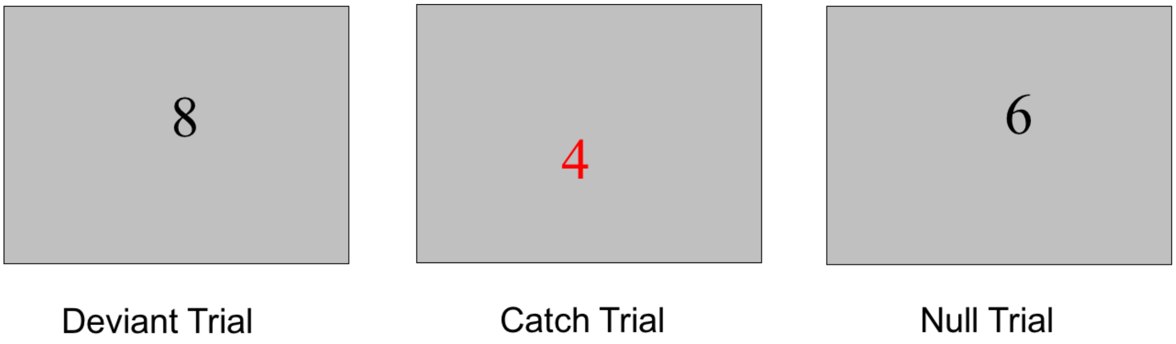

Figure 4.1: Examples of trial types. Deviant trials differ by small, medium or large ratio from ‘6’. Catch trials were presented in red font, and participants were required to press a button when they appeared on the screen. Null trials are a repeated presentation of the adapted value (‘6’) and were used to model the adaptation effect.

Table 4.1: Deviants used in adaptation task

Deviant	Ratio from adapted value (‘6’)	Ratio Bin	Parametric Weight
3	0.5	Small	2
4	0.67	Medium	1.5
5	0.83	Large	1.25
8	0.75	Large	1.25
9	0.67	Medium	1.5
12	0.5	Small	2

Stimuli were presented in black (R-G-B values 0, 0, 0) font (size 40 pt) on a grey (R-G-B values 192, 192, 192) background. Two techniques were used to reduce lower-level perceptual adaptation effects: varying font type and spatial location. Two font types (Times New Roman and Courier New) were used. Six different spatial locations were used, in which the number was presented two degrees from the centre of the screen (x, y coordinates: 435/300, 365/300, 375/325, 425/325, 375/275 and 425/275). Each number remained on the screen for 200ms, followed by a blank screen for 1200ms (see Figure 4.2). Participants were asked to attend to the stimuli on the screen for the duration of the task, and to respond by pressing a button with their index finger whenever they saw a red number. The hand that participants used to make their response was counterbalanced within the handedness groups (i.e., an approximately equal number of participants in both the left and right handedness groups responded to catch trials with their left and right index fingers). Participants completed four runs of the 6 minute 26 second task.

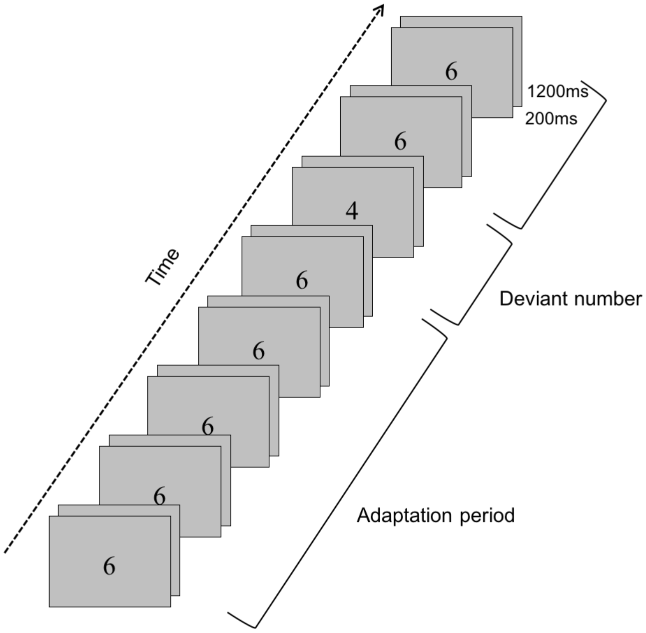

Figure 4.2: Adaptation task design. Adaptation periods were followed by deviant number, catch trials or null trials.

Because this task used in Vogel et al. (2015) and Vogel et al. (2017) was originally designed to be used with children, the methodology described above included a small alteration: instead of a “smurf” image signifying a catch trial, a change of font colour from black to red signified a catch trial. This type of catch trial has been used in previous number adaptation research with adults (Kadosh et al., 2011; Vogel et al., 2017). This change should not impact results in any way, as catch trials are not modelled as part of the parametric effect of interest.

4.2.2.2 Handedness.

Handedness was measured using the Edinburgh Handedness Inventory. This self-report measure asks the participants about their hand preference for several activities (e.g., writing, throwing, toothbrush). It yields a score that signifies the amount of dominance of one hand over the other using the following formula:

$$(Right_{SUM} - Left_{SUM})/(Right_{SUM} + Left_{SUM})$$

A positive score indicates right-handedness, a negative score indicates left-handedness. This is a commonly used measure of handedness in the literature (Willems et al., 2014).

Although handedness was primarily determined by the results of the Edinburgh Handedness Inventory, we also included a performance measure of handedness to confirm the self-report findings. Because our research question was focused on the potential differences in number representation related to laterality of handwriting of the participant, the performance measure focused on handwriting. Participants were asked to reproduce four different sentences, two with their left hand and two with their right hand as fast but also as neatly as possible. The sentences chosen used every letter in the English alphabet at least once and were matched on number of words and number of letters (see Appendix D). The order of administration of the sentences was counterbalanced across participants. The experimenter used a stopwatch to record the time it took for each participant to copy the sentences using their right hand and their left hand. Two blind raters rated the quality of each sentence from 1 (Very Neat) to 5 (Illegible) using the handwriting quality scale pictured in Table 4.2. Finally, the speed and quality scores for each hand were combined using an inverse efficiency formula that combines speed and accuracy scores (Lyons et al., 2014)

$$Handwriting\ performance = Mean\ Speed(1 + ER)$$

ER (Error Rate) was defined by: $1 - \ mean\ handwriting\ quality\ score/5$. In the original formula from Lyons et al., (2014) ER is multiplied by two because the task requires a forced choice between two options (i.e. Performance = MeanSpeed(1+2ER)). However, as the outcome measure of the handwriting task is not a binary forced choice, ER was not multiplied by 2 in the current study. Using this formula, a lower score indicated better performance (higher speed and higher quality). From the performance measure, handwriting handedness was determined by the smaller of the two performance scores. We excluded participants whose performance assessment of handedness conflicted with their self-report assessment of handedness. As such, in the current study, handedness of the participant and hand preference for handwriting were necessarily related. Ambidextrous participants were also excluded from analysis. Participants with a score of 0 on the Edinburgh Handedness Inventory and/or with no difference between hands on the performance measure of handedness were classified as ambidextrous. Our hypotheses surrounding number representation were more specific to hand preference for handwriting (measured by the performance measure) as opposed to general handedness (measured by the Edinburgh Handedness Inventory).

Table 4.2: Handwriting Quality Scale

Score	Label	Description
5	Illegible	Unable to read
4	Barely Legible	Reading takes effort, letters poorly formed
3	Legible	Not neat
2	Neat	Some letters non-uniform, could be slightly slanted
1	Very Neat	All letters uniform size, straight

4.2.3 Participants

Participants were healthy adults (18-35 years old), fluent English-speakers and had normal or corrected-to-normal vision. In the handedness literature a distinction is often made between left-handedness that is associated with early pathologies, and left-handedness that is not associated with early pathology (Satz, Orsini, Saslow, & Henry, 1985). Pathological left-handedness is thought to be distinguishable from familial left-handedness, in that the former is a result of early trauma that resulted in a compensatory shift from right-hand dominance to left-hand dominance, and the latter is related to other factors such as genetics (Llaurens, Raymond, & Faurie, 2009; Ramadhani et al., 2006; Satz et al., 1985). Therefore, only participants who reported no neurological impairments and no early (before age six) trauma were included in the current study, as measured by a Neurological Questionnaire (see Appendix B). As well, we only included left-handed participants who reported having at least one left-handed family member, as measured by the included Familial Handedness Questionnaire (see Appendix C).

Participants were screened for MRI safety and only those who fulfilled the above criteria were invited to participate in the study. Written informed consent was obtained from all participants prior to participation. A total of fifty-five participants consented to participate in the study. Of these fifty-five, two participants did not complete the scanning protocol due to claustrophobia. One participant was excluded because they reported early brain damage in the Neurological Questionnaire, one participant was excluded because their handedness determined by the handedness performance measure conflicted with their handedness determined by the Edinburgh Handedness Inventory, and one participant was excluded because their accuracy was below the cut-off for three out of the four adaptation runs. This left a total of 25 right-handed participants (13 females; M_{age} = 24.16 years; SD_{age} = 4.08) and 25 left-handed participants (13 females; M_{age} = 24.20 years; SD_{age} = 4.26). The left-handed and right-handed groups were matched on age and gender. Scores on the Edinburgh Handedness Inventory and the handedness performance measure were in agreement for all included participants and did not violate normality, with the exception of the right-handers' score on the Edinburgh Handedness Inventory, Shapiro-Wilk = .89, p = .011.

4.2.4 Procedure

Participants were recruited through posters from the University of Western Ontario campus in London, Canada as well as related online avenues (e.g., university Facebook pages). The recruitment poster specified that we were recruiting *both* left- and right-handed participants. After being screened for study exclusion criteria and indicating their handedness informally, participants met the experimenter at Robarts Research Institute. Written informed consent was obtained. The instructions for the adaptation task were explained as follows: “You will see numbers appear on the screen. Please keep your eyes on the screen the entire time. When you see a red number, press the button with the index finger of your (right or left) hand”. Participants were also told about the importance of keeping still in the scanner. Ear plugs were used so that scanner noise was reduced. Participants were made comfortable on the scanner bed and foam padding was used around their heads. The task was presented using Eprime 2.0 software and viewed using a mirror system attached to the scanner head coil.

Four runs of the adaptation task were collected. Two diffusion tensor imaging (DTI) scans were also collected, however this data was not used for the purposes of the registered analyses. The anatomical scan was collected last. Following the scan, participants completed the handedness assessment. The order of the handedness tasks – the Edinburgh Handedness Inventory and the handwriting performance measure- was counterbalanced across participants.

4.2.5 MRI Data Acquisition

MRI and fMRI data were collected using a 3T Siemens Magnetom Prisma scanner with a Siemens 32-channel head coil. A BOLD-sensitive T2* weighted echo planar sequence was used to collect fMRI data. For each volume, 48 slices that covered the whole brain were collected, in an ascending-interleaved method, (voxel size = 2.5 x 2.5 x 2.5, 2.5mm thickness, TR = 1000ms, TE = 30ms, FOV = 208 x 208mm, matrix size = 84 x 84, flip angle = 40°, multiband acceleration factor = 4). For each run of the adaptation task, 386 volumes were collected. The anatomical MRI data were collected in high-resolution T1-weighted images in the sagittal plane (voxel size = 1x1x1mm; 192 slices, TR = 2300ms, TE = 2.98ms, TI = 900ms, flip angle = 9 °). The in-plane resolution was 256 x 256 mm.

4.2.6 fMRI Preprocessing

fMRI data were preprocessed using Brainvoyager QX version 20.6 software (Brain innovation, Maastricht, the Netherlands). Slice scan-time acquisition was corrected for with cubic-spline interpolation. A 2-cycle cut-off, high-pass filter (GLM-Fourier) removed low frequency noise in the data. Trilinear/since interpolation was used for motion correction. Functional runs were excluded if there was motion in excess of 3mm across the entire run or more than a 1.5mm volume-to-volume displacement. A 6mm FWHM Gaussian smoothing kernel was used to spatially smooth the data.

The data was transformed to MNI space for group analysis. As per the analysis used in the original Vogel et al. (2015) study, the deviant numbers were put into four ratio bins (see Table 4.1). These bins were then used to compute a parametric regressor in the GLM. This analysis identified regions of the brain that showed a parametric ratio-dependent recovery effect (see Figure 4.3a). We also modelled the main effect of the recovery effect. For this analysis, all deviants were weighted the same. Therefore, this analysis identified regions of the brain that responded to any deviation in number, regardless of ratio (see Figure 4.3b). Catch trials were modelled separately as predictors of no interest and added to all models. All GLM events were convolved with a 2-gamma hemodynamic response function to predict the blood oxygen level dependent (BOLD) response using random effects (RFX) analysis (Friston et al., 1998b).

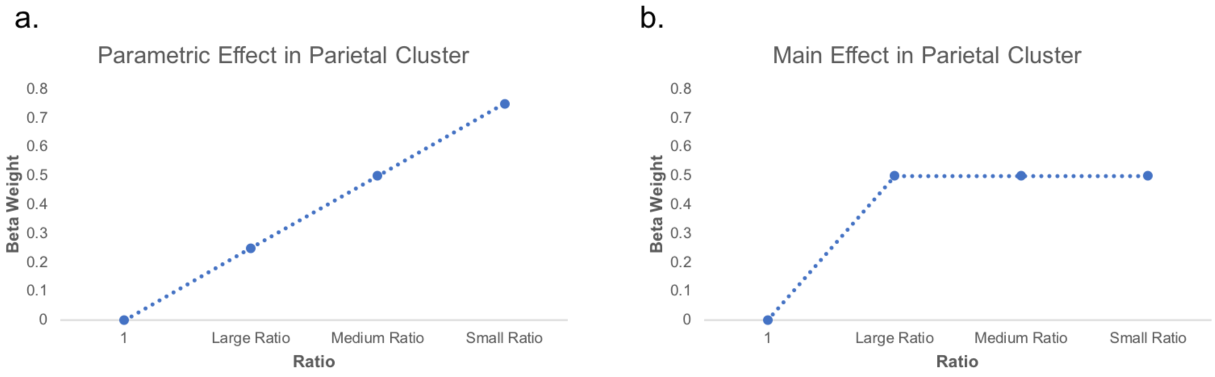

Figure 4.3: Modelling signal change in response to symbolic numerical adaptation task. A) The parametric effect identifies brain regions that show an increase in activation with smaller ratio between the adapted value and deviant value. B) The main effect identifies brain regions that show an increase in activation to any change in numerical stimuli, regardless of ratio.

Consistent with previous studies, an uncorrected threshold of $p < .001$ was first used to identify active brain regions. Then we corrected for multiple comparisons using cluster correction (Forman et al., 1995; Rainer Goebel et al., 2006). A mask of the whole brain was used to limit cluster calculation to voxels within the brain. A Monte-Carlo simulation with 1000 iterations was used to determine the minimum cluster size that would result in a false positive of 5%. Cluster correction then occurred at the whole-brain level, such that only clusters that survived the $p < .05$ threshold were considered significant.

4.3 Planned Analyses

4.3.1 Behavioural Data

First, accuracy for each functional run was calculated for each participant. To be included in the analyses, 6 of the 8 (75%) presented catch trials must have been "caught" for each run. This criterion was used to ensure participants were attending to the stimuli throughout the run (Vogel et al., 2015; Vogel et al., 2017).

4.3.2 Imaging Data

Our alternate hypothesis was that handwriting handedness plays a role in symbolic number representation, and therefore, that the laterality of the parametric recovery effect is related to handedness. To examine these hypotheses, the following analyses were used. To identify neural regions that demonstrated a ratio dependent recovery effect, the parametric regressor described above was contrasted against the baseline brain activation at the whole-brain level. For hypothesis one, we sought to replicate the finding of a left-lateralized parietal region (Sokolowski et al., 2016) in the group of right-handed participants (parametric effect > baseline). To test our second hypothesis, we tested the alternative hypothesis and looked at the same analysis in the group of left-handed participants. We expected to see right lateralization of the parietal ratio-dependent parametric effect in the group of left-handed participants. In other words, our second hypothesis was that the left-handed group would show significant right lateralization of the rebound effect. For a more stringent analysis, we also looked for regions of the brain that were activated for the conjunction of the main effect and parametric effect (main effect > baseline ∩ parametric effect > baseline) for each of the right- and left-handed groups separately.

Next, to test our third hypothesis, the left-handed and right-handed groups were directly compared using the following analyses: parametric rebound effect of left-handers > parametric rebound effect of right-handers and parametric rebound effect of right-handers > parametric rebound effect of left-handers. These contrasts were computed using an independent samples t-test in Brain Voyager. These analyses identify regions of the brain that show a ratio dependent rebound effect and are more activated for the left-handed group and the right-handed group, respectively. Finally, we checked whether there were any common regions that show a parametric effect in both the left- and right-handed participants: parametric rebound effect of left handers ∩ parametric rebound effect of right handers.

To assess the fourth hypothesis, we were interested in the extent to which brain activation is lateralized according to handedness. Therefore, we examined the contrast parametric rebound effect > baseline at the individual level using fixed-effect analysis. For this analysis, we defined two ROI's in the left and right parietal regions using the superior parietal lobule cluster defined in the passive maps of Sokolowski et al. (2017). The ROI's were defined by a sphere with a radius of 10mm centered on the peak voxel from Sokolowski et al. (2017; Tal coordinates (x, y, z): -30, -66, 36, MNI coordinates (x, y, z): -30, -69, 38 and 30, -69, 38). Next, we calculated a Laterality Index (LI) for each participant, which quantified at the individual level the left vs. right hemispheric lateralization for the parametric effect (Cai et al., 2013; Seghier et al., 2004). The following formula (Seghier et al., 2008) was used to calculate the LI's:

$$LI = (Left\ Hemisphere - Right\ Hemisphere)/(Left\ Hemisphere + Right\ Hemisphere)$$

The left hemisphere and right hemisphere values were defined as the number of above threshold voxels (p = .001, uncorrected) within the left and right ROI's respectively, for the parametric effect (Chlebus et al., 2007; Seghier et al., 2008). A positive value indicates left hemisphere dominance and a negative value indicates right hemisphere dominance.

The LI for the parametric effect in the parietal lobe was recorded for each participant within each group. Then, the proportion of right-handers that showed the expected left-lateralization was calculated with the following formula: $LI\ Proportion_{RIGHT} = (number\ of\ participants\ in\ right - handed\ group\ that\ show\ left\ lateralization)/n$

The same calculation was also made for the left-handers: $LI\ Proportion_{LEFT} = (number\ of\ participants\ in\ left - handed\ group\ that\ show\ left\ lateralization)/n$. In accordance with previous research, we predicted that the right-handed group would show strong left lateralization for the symbolic number parametric effect (Holloway et al., 2013; Notebaert, Pesenti, et al., 2010; Vogel et al., 2017). In addition, in accordance with the alternate hypothesis, we predicted that the left-handed group would show a more right-hemisphere-dominated parametric effect, as per our expectation that handedness of handwriting plays a significant role in symbolic number representation. To test this, a z-test of proportions was conducted, whereby LI $\text{Proportion}_{\text{RIGHT}}$ was compared to LI $\text{Proportion}_{\text{LEFT}}$.

As stated above, the null hypothesis was that the left-handed group would show no differences in lateralization for the parietal distance-dependent parametric effect in comparison to the right-handed group. As previously stated, this would suggest either that handedness does not play a role in the left-lateralization of number symbol processing in the brain, or that we have not yet accumulated enough evidence to reject the null hypothesis. Therefore, if the test of proportions reveals no difference, a Bayesian test of proportions will be carried out using the bayes.prop.test function in the R statistical software (R Core Team, 2013). The current analysis tests how much more likely the right-handed group is to show left-lateralized parametric activation compared to the left-handed group.

4.4 Results

4.4.1 Behavioural Results

Three runs were removed as they exceeded the motion criteria mentioned above, and one run was removed due to the participant failing to follow task instructions. For the remaining runs, accuracy on the catch trials was examined in order to ensure a minimum amount of attention throughout the paradigm. Of the fifty included participants, all runs met the minimum accuracy cut-off (at least 6/8 catch trials), $M_{ACC} = 7.94$, $SD_{ACC} = 0.25$. Therefore, a total of 196 runs were included in the analyses (98 runs for the right-handers, 98 runs for the left-handers). These data, study materials and the preregistration are available on the Open Science Framework page for this study: https://osf.io/buqcm/.

4.4.2 Imaging Results

To label significant neural clusters, the peak voxel and center of gravity coordinates in MNI space were entered in FSLview using the MNI standard map (avg152T1_brain.nii.gz; Smith et al., 2004). The labels were then taken from the Jülich Histological Atlas (Eickhoff et al., 2005). The Harvard-Oxford Cortical Structural Atlas was used if no label was found using the Jülich Histological Atlas. Imaging data are available on the OpenNeuro page for this study: https://openneuro.org/datasets/ds001838/versions/1.0.0.

4.4.2.1 Hypothesis 1.

Our first hypothesis was that the data from the right-handed group would replicate the previously found left-lateralized parametric effect in the IPS (Sokolowski et al., 2016). The contrast parametric effect > baseline was run at the whole-brain level at the threshold of .001. After cluster correction, four clusters remained significant, including a region in the left IPS (Table 4.3 and Figure 4.4). To test if the IPS cluster survived a more stringent contrast, the conjunction of the main and parametric effect was also examined (main effect > baseline ∩ parametric effect > baseline). Three of the four clusters identified in the parametric > baseline contrast were significant, including the left IPS.

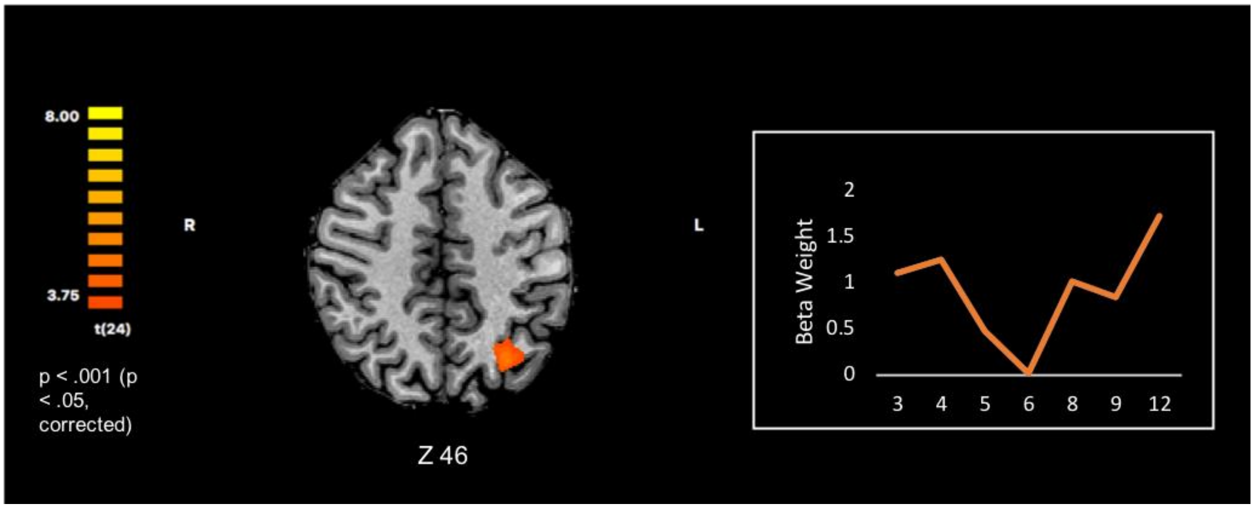

Figure 4.4: Parametric effect > baseline contrast for the right-handers reveals a cluster in the left anterior IPS. The graph represents beta weights extracted from this cluster for each of the number stimuli. The beta weights in this region follow the predicted pattern of increasing rebound of activation as the number deviant presented differs more from the adaptation value of 6.

4.4.2.2 Hypothesis 2.

Our second hypothesis was that the left-handed group would show reversed lateralization of the parametric effect, i.e., a right-lateralized parametric effect within the IPS. To this end, the contrast parametric effect > baseline was run at the whole-brain level at the threshold of .001. One cluster within the inferior temporal gyrus survived cluster correction (Table 4.4). Therefore, at the initial threshold of .001 the left-handed group did not demonstrate a parametric effect within the IPS.

4.4.2.2.1 Exploratory analysis.

Because the left-handed group did not demonstrate a parametric effect in the IPS, we ran an exploratory analysis to assess whether a more lenient threshold would identify a parametric effect within the IPS for the left-handed group. To this end, a follow-up analysis was run wherein the initial uncorrected threshold to identify clusters at the whole-brain level was increased from .001 to .005. For the new threshold, the contrast parametric effect > baseline yielded five significant clusters after correction (Table 4.5).

Notably, a cluster within the right IPS was identified (Figure 4.5). The right IPS remained significant in the conjunction between the main and parametric effect.

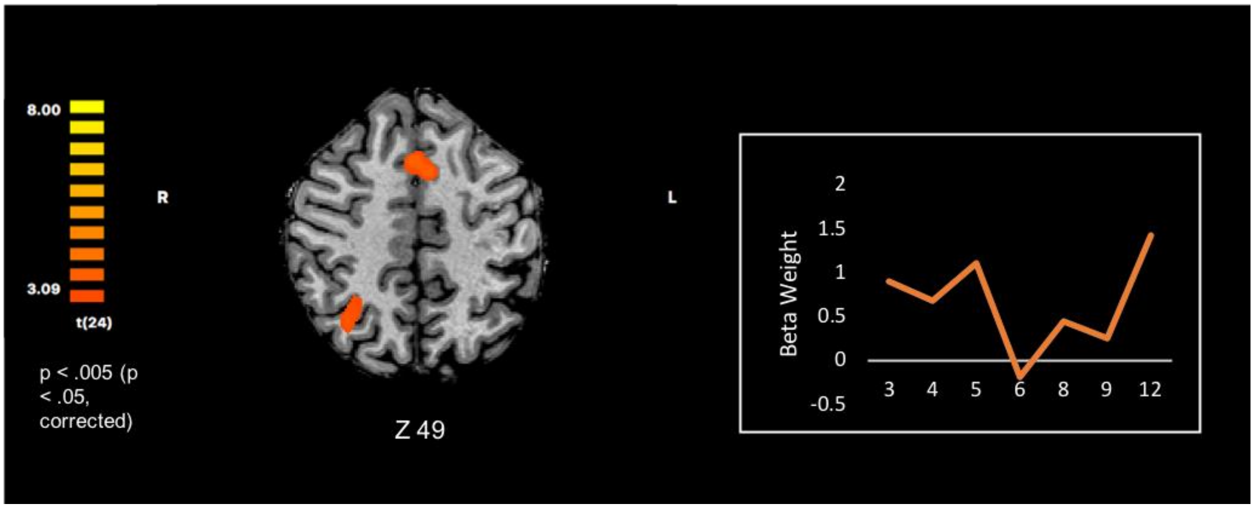

Figure 4.5: Parametric effect > baseline contrast for the left-handers reveals a cluster in the right anterior IPS. The graph represents beta weights extracted from this cluster for each of the number stimuli. The beta weights in this region follow the predicted pattern of increasing rebound of activation as the number deviant presented differs more from the adaptation value of 6.

4.4.2.3 Hypothesis 3.

For the third hypothesis, the right-handed and left-handed groups were compared directly. A more left-lateralized parametric effect was expected for the right-handed group in comparison to the left-handed group, while the reverse was expected for the left-handed group. Independent samples t-tests were run for the following: parametric rebound effect of left- handers > parametric rebound effect of right-handers and parametric rebound effect of right- handers > parametric rebound effect of left-handers. No significant clusters were identified. As well, the conjunction analysis between the left- and right-handed groups (parametric rebound effect of left-handers > baseline ∩ parametric rebound effect of right-handers > baseline) revealed no significant regions.

Table 4.3: Locations of center of gravity and peak voxels for significant clusters identified at the whole-brain level for the parametric effect in the right-handed group.

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Broca's area BA45	Right	46.17	32.88	20.71	3.05	4.87	5.36	1771	Broca's area BA45	45	35	16	5.457367	.000013
Broca's area BA44	Right	39.83	8.37	29.96	3.11	2.42	3.01	846	Broca's area BA44	39	8	28	4.659448	.000099
Premotor cortex BA6	Left	-1.95	14.93	50.97	3.3	3.31	1.45	442	Premotor cortex BA6	-6	11	49	4.852976	.00006
Anterior intraparietal sulcus hIP3	Left	-30.56	-61.46	45.41	3.4	4.08	4.43	1943	Anterior intraparietal sulcus hIP3	-30	-64	46	5.253391	.000022

Cluster size is given in total number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005).

Table 4.4: Locations of center of gravity and peak voxels for significant clusters identified at the whole-brain level for the parametric effect in the left-handed group (initial threshold .001).

Region - Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region - Peak Voxel	x	y	z	t	p
Inferior temporal gyrus, temporooccipital part*	Right	48	-57.67	-13.29	3.34	4.21	2.75	1175	Inferior temporal gyrus, temporooccipital part*	48	-58	-14	5.246243	0.000022

Cluster size is given in total number of voxels. The region was identified using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

Table 4.5: Locations of center of gravity and peak voxels for significant clusters identified at the whole-brain level for the parametric effect in the left-handed group (initial threshold .005).

Region – Center of Gravity	Hemisphere	mean x	mean y	mean z	stdev x	stdev y	stdev z	Cluster size	Region – Peak Voxel	x	y	z	t	p	Hemisphere
Inferior temporal gyrus, temporooccipital part*	Right	46.99	-56.8	-13.38	4.1	5.77	3.56	2887	Inferior temporal gyrus, temporooccipital part*	48	-58	-14	5.246243	.000022	Right
Visual cortex V4	Right	34.57	-85.33	-4.58	2.43	2.32	2.97	678	Visual cortex V4	36	-85	-5	4.198338	.000319	Right
Anterior intra-parietal sulcus hIP3	Right	31.51	-55.62	48.58	2.4	3.44	3.45	1062	Anterior intra-parietal sulcus hIP3	33	-58	49	4.382221	.0002	Right
Premotor cortex BA6	Right	2.38	15.26	47.71	6.95	3.48	4.11	1162	Premotor cortex BA6	-3	14	52	4.938403	.000049	Left
Occipital fusiform gyrus*	Left	-41.42	-65.79	-10.25	2.74	4.3	2.54	1175	Lateral occipital cortex, inferior division*	-42	-67	-11	4.729256	.000083	Left

Cluster size is given in total number of voxels. Regions were identified using the Jülich Histological Atlas (Eickhoff et al., 2005), regions marked with * were identified using the Harvard-Oxford Cortical Structural Atlas (Harvard - Oxford Cortical Structural Atlas, RRID:SCR_001476).

4.4.2.4 Hypothesis 4.

The fourth hypothesis was that the left- and right-handed groups would differ in the proportion of participants whose parametric effects were left-lateralized. Again, we expected greater left lateralization as opposed to right lateralization in the right-handed group, compared to the left-handed group. Laterality indices were calculated from the ROIs as described above for the uncorrected threshold of .001 for participants who had active, above threshold voxels for the parametric effect > baseline. Table 4.6 shows the categorization of left-lateralization and right-lateralization for this analysis. A one-tailed z-test of proportions was conducted to determine whether the left- and right-handed groups differed in the proportion of individuals who exhibited left-lateralization. There was no significant difference between the left- and right-handed groups, $z = .08$, $p = .468$. In view of the unexpected finding that many participants did not demonstrate activation in either the left or right ROI, an additional one-tailed z-test of proportions was run to compare the left- and right-handed proportions in right-lateralization. The groups did not differ in their proportion of right lateralized participants either, $z = -.08$, $p = .468$.

Table 4.6: Laterality categorization of the parametric effect for the left and right handed groups (p = .001)

	Left Handers	**Right Handers**
Left Lateralization	9	8
Right Lateralization	6	5
Total	15	13

The z-tests of proportions were not significant, therefore we followed up these null results with Bayesian tests of proportions. The Bayesian test of proportions uses Bayesian estimation to determine the frequency of success of one group compared to another group. In the first Bayesian analysis, success was defined as left-lateralization. The Bayesian test of proportions provides theta (θ) values, defined as the “relative frequency of success” for that particular group, along with a 95% credible interval. The relative frequency of left-lateralization was determined to be larger for right-handers ($\theta = 0.60$, 95% credible interval [0.37, 0.83]) by a probability of .532 and larger for left-handers (θ = 0.59 [0.37, 0.81]) by a probability of .468. The same analysis was run for right-lateralization, and the relative frequency of right-lateralization was larger for right-handers (θ = 0.39 [0.16, 0.64]) by a probability of .469, and larger for left-handers (θ = 0.41 [0.20, 0.65]) by a probability of .531. From these analyses it is unclear whether the parametric effect for the right- and left-handed groups differs in the likelihood to be left or right lateralized.

4.4.2.4.1 Exploratory analyses.

A large number of participants – 44% of our total sample – did not exhibit any above-threshold voxels in the left or right ROIs at the preregistered threshold of .001. Consequently, our test of proportions did not include a large portion of our sample. As a follow-up exploratory analysis, we increased the threshold from .001 to .05 in the ROI analysis. Because the ROI analysis is done at the individual level, .05 is an acceptably lenient threshold because there is no need to account for multiple comparisons across the entire brain but only within the ROI, and therefore a threshold of .001 could actually be considered too stringent. Increasing the threshold to .05 allowed the inclusion of 86% of our participants, and participants were categorized according to their LI’s as above (Table 4.7). A one-tailed z-test of proportions was conducted to examine group differences in proportions for left-lateralization. The z-test was significant, with the right handers showing a higher proportion of left-lateralization than the left-handers, $z = 1.67$, $p = .047$. Although the majority of the sample was included in these analyses, there were still several participants who did not exhibit any active voxels. Therefore, a z-test was also run to examine group differences in proportions showing right-lateralization. The proportion of left-handers showing right-lateralization was significantly higher than the proportion of right-handers showing right-lateralization, $z = -1.67$, $p = .047$.

Table 4.7: Laterality categorization of the parametric effect for the left and right handed groups (p = .05)

	Left Handers	**Right Handers**
Left Lateralization	8	13
Right Lateralization	14	8
Total	22	21

The Bayesian test of proportions were also implemented, to provide a comprehensive description of any group differences at the .05 threshold. The bayes.prop.test analysis was carried out as described above, first considering the likelihood of left-lateralization. The relative frequency for left-lateralization was larger for right-handers by a probability of .95 ($\theta = .61$, [0.42, 0.80]) and larger for left-handers ($\theta = 0.37$ [0.19, 0.56]) by a probability of .05. The probability of right-lateralization was also examined, and the relative frequency for right-lateralization was larger for the right-handers ($\theta = 0.39$ [0.20, 0.58]) by a probability of .05, and larger for left-handers ($\theta = 0.63$ [0.43, 0.80]) by a probability of .95. These exploratory analyses indicate that, when compared to the left-handed group, the right-handed group was more likely to show left-lateralization. Likewise, in comparison to the right-handed group, the left-handed group was more likely to show right-lateralization.

To further examine hypothesis 4, average beta weights for the parametric effect for each participant were extracted from the left and right IPS ROIs that were independently defined from Sokolowski et al. (2017). This analysis allowed for inclusion of all participants. Using these beta weights, an independent t-test and a Bayesian independent t-test comparing the right and left-handed groups were carried out within the left IPS ROI and the right IPS ROI using JASP (JASP Team, 2019). Bayesian t-tests provide additional information over and above the frequentist independent t-test. More specifically, Bayesian t-tests were used so that the strength of the evidence obtained under the null could be quantified. For the Bayesian independent t-test, we reported the Bayes Factor in favour of the null hypothesis (no significant group difference) over the alternate hypothesis (significant group difference). This Bayes Factor (BF_{01}) gives an indication of the probability of the data occurring under the null hypothesis as opposed to under the alternate hypothesis.

Within the left IPS ROI, the beta weights for the parametric effect for the right-handed group (M = 0.64, SD = 1.02) were not significantly different from the left-handed group (M = 0.34, SD = 0.92), t(48) = -1.10, p = .276, BF_{01} = 2.15. The BF_{01} indicates that the strength for the null hypothesis is anecdotal (Jeffreys, 1961). Similarly, within the right IPS ROI, the beta weights for the right-handed group (M = 0.68, SD = 1.27) were not significantly different from the left-handed group (M = 0.50, SD = 1.16), t(48) = -0.51, p = .610, BF_{01} = 3.17. The BF_{01} indicates that the strength for the null hypothesis is anecdotal to substantial (Jeffreys, 1961). In summary, the beta weights for the parametric effect are not indicative of differences between the left- and right-handers in either the left or the right IPS.

4.5 Discussion

A key question in the field of numerical cognition is: how does the human brain represent numerical symbols? A frequently reported finding in the field is that numerical symbols are represented in a left lateralized region in the parietal lobe (Sokolowski et al., 2016). Critically, all previous studies that have reported this left lateralized activation in response to number symbols were conducted using an exclusively right-handed sample of participants. However, studies in other fields that have included left- as well as right-handed participants have reported that handedness affects the neural laterality of various constructs, such as word processing, visuospatial attention, language and letter processing (Willems et al., 2014). Therefore, in the present study, we hypothesized that the formation of representations of number symbols may be related to the handedness of the participants. More specifically, we predicted that the left lateralization of the parietal region associated with number processing may be related to processes involved in handwriting. The current study sought to address whether the left lateralized region associated with symbolic number processing is indeed linked to handedness by comparing brain activation during the passive processing of numerical symbols in a sample of right-handers and left-handers. We predicted that processes involved in handwriting are associated with the development of symbolic number processing, and therefore that right-handed and left-handed participants would show differences in neural lateralization for number representation.

Results revealed that, at the whole-brain level, the left-lateralized parametric effect within the IPS was indeed replicated in the right-handed group in the current study. This was the first pre-registered replication of this finding. In contrast, the left-handed group did not show a parametric effect in the IPS at the preregistered initial threshold of .001. However, an exploratory analysis revealed that in the left-handed group, passive symbolic number processing was associated with a right-lateralized parametric effect at a more lenient threshold (.005). This finding lends some support to the idea that left-handers may show a reverse lateralization for symbolic number representation, however it seems this effect may be noisier than that observed in the right-handers. When the groups were compared directly, there were no regions that demonstrated group-level differences.

In a follow-up region of interest analysis within the left and right parietal lobes, we calculated laterality indices for each participant. At the preregistered threshold, the groups did not differ in their probability to be left or right-lateralized. Critically, nearly half of the sample did not exhibit activation above this preregistered threshold. An exploratory analysis that used a threshold of .05, provided preliminary evidence that the right-handed group was more likely to show left-lateralization than the left-handed group, and the left-handed group was more likely to show right-lateralization than the right-handed group. However, using the beta weights extracted from the left and right IPS ROIs, we found no evidence of group differences. In summary, we did not find evidence of reverse lateralization in left-handers for symbolic number representation. Therefore, the data did not support the hypothesis that writing handedness plays a role in the neural laterality of symbolic number representation.

4.5.1 A role for sensorimotor processes in symbolic number representation?

In the current study, right-handers did not demonstrate exclusively left-lateralization. Similarly, left-handers did not demonstrate exclusively right-lateralization. These mixed results suggest that there could be several factors important for the representation of number symbols that affect neural laterality. In other words, if handedness for writing could fully explain the laterality of the parametric effect for numbers, we would have expected robust lateralization in both the left- and right-handed groups. Given the lack of findings for number laterality in relation to writing handedness in the current study, is it possible that there are other motor mechanisms that support symbolic number representations that involve both hands? For example, previous work has provided support for the importance of the motor system in counting (Andres, Olivier, & Badets, 2008; Tschentscher, Hauk, Fischer, & Pulvermüller, 2012). Relatedly, finger gnosis (defined as having a mental representation of one’s fingers) has been shown to be related to numerical and math skills (Penner-Wilger et al., 2007). The IPS is recruited for both finger and numerical tasks (Andres, Michaux, & Pesenti, 2012; Krinzinger et al., 2011). It has been proposed that the neural underpinnings involved in finger representation are redeployed in number representation (Penner-Wilger & Anderson, 2013). Finally, the use of hand gestures has been shown to facilitate math learning (Novack, Congdon, Hemani-Lopez, & Goldin-Meadow, 2014). Hand gestures may represent motor involvement in the solving of calculation questions (Brooks, Barner, Frank, & Goldin-Meadow, 2018; Frank & Barner, 2012). Therefore, gesture during problem solving represents an additional way in which motor processes could be involved in numerical processing. However, this potential relation between gesture and symbolic number representations cannot be addressed with the current data

People are usually dominant in one hand for writing, however for processes such as counting and gesture, both hands are involved. In the current study, not all right-handers showed left lateralization, and not all left-handers showed right-lateralization. It is possible that lateralization of numerical representation could be related to a combination of sensorimotor factors; some of which involve both hands. However, the results of the current study cannot speak to this hypothesis, and the involvement of sensorimotor processes in symbolic number representation remains an open question.

4.5.2 Language and neural lateralization

Although writing handedness was not found to play a role in number representation lateralization, other culturally acquired abilities, such as language, may play a role in the lateralization of number representation. In the brain, language has been demonstrated to engage a largely left-lateralized network (Willems et al., 2014). Both right-handers and left-handers are more likely to recruit left-lateralized regions, however left-handers are more likely than right-handers to show reverse lateralization or bilateral activation for language tasks (Willems et al., 2014). An interesting question then is why some left-handers show reverse lateralization for language, while others show more typical left-lateralization. This question is also highly relevant to the current study, as we found some left-handers who displayed right-lateralization for number, while others showed more typical left-lateralization.

Cai et al., (2013) investigated language production and visual-spatial attention in a group of left-handers who had demonstrated right-lateralization for language production, as well as a group of left-handers who had demonstrated left-lateralization for language production. Interestingly a pattern emerged wherein participants who showed left-lateralization for language tended to have right-lateralization for visual-spatial attention, whereas those who showed the more right-lateralization for language also were likely to show left-lateralization for visual-spatial attention (Cai et al., 2013). The authors suggest that these results are in line with a causal hypothesis of brain lateralization, in which language and spatial attention are usually each lateralized to a single hemisphere because they are highly complex functions, and can function more efficiently if they do not recruit regions from the contralateral side of the brain (Kosslyn, 1987). Related processes may be contained in the same hemisphere to increase efficiency of communication, whereas less related constructs may be more likely to be represented in different hemispheres

(Wang, Van der Haegen, Tao, & Cai, 2018). For example, word reading and speech tend to co-occur in the same hemisphere (usually the left). When one of these processes is right-lateralized, the other tends to be right-lateralized as well (Van der Haegen, Cai, & Brysbaert, 2012). Therefore, it seems as if lateralization of language is related to the handedness of an individual (left-handed participants are more likely to show right-lateralization/bilateralization than right-handers), and also to the functional organization of other constructs in the brain.

What does this mean for the lateralization of number representation? A language system is a necessary component of the use of a symbolic system for number representation (Dehaene, 1997; Núñez, 2017) and language skills have been shown to be important for developing numerical skills such as arithmetic (Simmons & Singleton, 2008; Zhang et al., 2014). Given the tendency for tasks engaging language processing to engage left-lateralized regions, is it possible that symbolic number representation tends towards left-lateralization due to links with the language system? The current study did not determine neural laterality for language. Given the findings surrounding the co-occurrence of language processes in a single hemisphere, and complementary hemispheric specialization for language and visual spatial attention, an interesting open question is whether left-handers who show right-lateralization for language also show right-lateralization for number. The finding that language lateralization is more variable in left-handers could provide one explanation for the lack of clear-cut lateralization for number representation in left-handers in the current study.

4.5.3 Summary and conclusions

Symbolic number representation has been shown to rely on left parietal regions (Sokolowski et al., 2016), yet the factors that might account for such left-lateralization remain poorly understood. The goal of the current study was to test the hypothesis that writing handedness is related to the neural laterality of symbolic number representation, thereby providing an explanation for the left-lateralization of symbolic number. In the right-handed sample, the oft-reported finding of a left-lateralized numerical ratio-dependent rebound effect was replicated. Ad hoc analyses were not indicative of a difference in lateralization between the left- and right-handers. In one post-hoc analysis there was some evidence that the left-handed sample showed a more right-lateralized effect. However, a further post-hoc analysis examining beta weights for the right and left IPS found no evidence of group differences. Overall, we did not find evidence for a role of handedness in the laterality of symbolic number representation. However, the beta weights extracted in a post-hoc ROI analysis indicated only weak evidence for the lack of a group difference, which demands further inquiry into this question. Therefore, a key question that should be addressed in future studies is whether the lateralization of symbolic number representation is related to a complex interplay of multiple factors, including sensorimotor as well as language processes.

4.6 References

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Chapter 5

5 General Discussion

The precise mechanisms underlying the uniquely human ability of representing number symbolically are unknown, and the topic of significant inquiry and debate. For example, how, over the course of learning and development, do humans connect the Arabic digit ‘3’ with the non-symbolic magnitude of three items? The approximate number system (ANS) -- an analog system for representing numerical magnitudes -- has been theorized to be the basis of symbol abstraction for number (Dehaene, 1997). This account that has been used to explain how numerical symbols get their meaning over the course of learning and development largely rests on a body of literature that examined magnitude representation in a wide range of animal species (e.g., Cantlon & Brannon, 2006; Dehaene, 1997), as well as human infants (e.g., Xu & Spelke, 2000). This body of findings indicates the presence of distance effects for non-symbolic numerical tasks in animals and humans. Furthermore, distance effects are also apparent in symbolic numerical tasks (Moyer & Landauer, 1967). From this research, it has been concluded that there is phylogenetic and ontogenetic continuity in the way in which non-symbolic numerical magnitude is processed (Cantlon & Brannon, 2006; Dehaene, Dehaene-Lambertz, & Cohen, 1998). Moreover, it has been theorized that symbols are grounded in this ANS. This suggests we are born with an analog system for the representation of numerical symbols.

However, the notion that the ANS is an evolutionary precursor to symbolic numerical representation and that, therefore, the development of number representation in humans involves the grounding of symbols in the ANS has also been disputed. It has been argued that the ability of animals to perform non-symbolic numerical tasks cannot be considered a natural ability, and the ability of animals and human infants to discriminate magnitudes may actually be based on non-numerical properties such as the surface area of the stimuli used (Leibovich, Katzin, Harel, & Henik, 2017; Núñez, 2017). Furthermore, symbolic and non-symbolic numerical representation has been demonstrated to diverge in important ways that may speak against a shared system. For example, common effects (e.g., ratio effects) from symbolic and non-symbolic tasks do not necessarily correlate (Krajcsi, 2017; Lyons, Nuerk, et al., 2015), and differences in representation at the neural level have been identified (Lyons, Ansari, et al., 2015; Sokolowski et al., 2016). In general it seems that the predictions of the ANS, although potentially appropriate for characterizing non-symbolic magnitude representation, do not necessarily provide the best hypothesis for how symbols become representations of numerical magnitude over the course of learning (Krajcsi et al., 2018). Therefore, studies that investigate mechanisms for symbolic number representation are needed.

5.1 Discussion, implications and limitations of findings from the current dissertation

Neuroimaging tools have provided valuable insight in the quest to understand symbolic numerical representation (Matejko & Ansari, 2018). Through the use of neuroimaging techniques, such as fMRI, symbolic number processing has been demonstrated to recruit a network of fronto-parietal regions (Houdé et al., 2010; Sokolowski et al., 2016, 2017). In particular, the intraparietal sulcus (IPS) has been theorized to be integral to symbolic and non-symbolic number representation (Dehaene, Dehaene-Lambertz, et al., 1998; Nieder & Dehaene, 2009; Piazza, Pinel, Le Bihan, & Dehaene, 2007). Although activity in the IPS is shown to correlate with various numerical tasks, the mechanisms that underlie the nature of symbolic number representation in the IPS remain poorly understood (e.g., Arsalidou & Taylor, 2011; Cohen Kadosh et al., 2005; Dehaene et al., 2003).

This principle aim of this thesis was to shed further light onto how symbolic number is represented in the human brain. Specifically, I explored the neural correlates of symbolic number using fMRI-Adaptation (fMRI-A). fMRI-A offers advantages compared to active tasks traditionally used in numerical cognition research, such as the number comparison task (e.g., where participants have to determine which of two numerical stimuli is numerically larger). Namely, fMRI-A involves the passive presentation of stimuli, which reduces response selection, task difficulty and decision-making confounds (Göbel et al., 2004). Confounds such as response selection could be considered particularly troublesome to research in number processing, as number representation and response selection may share neural substrate in the parietal lobe (Göbel et al., 2004). Furthermore, research with active tasks often make use of a control task in order to subtract processes that would not be considered of interest in order to isolate the process of interest. However, the extent to which this subtraction logic is effective has been criticized (Church et al., 2010; Logothetis, 2008).

As discussed in Chapters 1-4, fMRI-A allows for a more pointed investigation of numerical processing, and has been used in previous research to address questions relevant to how symbolic numbers are represented in the human brain (Holloway, Battista, Vogel, & Ansari, 2013; Reynvoet, Notebaert, & Nelis, 2010; Vogel, Goffin, & Ansari, 2015; Vogel et al., 2017). Building on this previous work, in three related, empirical studies, I used fMRI-A to address questions surrounding symbolic numerical representation, namely:

- Chapter 2: Could general ordinal relationships between symbols explain symbolic numerical representation?
- Chapter 3: How might symbolic number representation change across development?
- Chapter 4: Does handwriting relate to the representation of number symbols?

5.1.1 Chapter 2.

In Chapter 2, we asked: can ordinal relationships – i.e., serial position relationships -- account for the way in which the parietal cortex responds to symbolic number? Twenty-four adults completed an adaptation task using number symbols and letter symbols. Letters, as a symbol system with no magnitude association, were used in an attempt to determine whether ordinal relationships between symbols (as in the alphabet for letters, or the count sequence for symbolic numbers) could account for the ratio-dependent rebound effect observed within the IPS. Given the lack of magnitude associations for letters, if the parietal cortex demonstrates a parametric rebound effect for letters, this would speak against the ANS explanation of symbolic number representation. More specifically, because letters do not have associated magnitudes, but do have ordinal relations, finding a parametric rebound effect for letters would have meant that the ANS theory is not necessary for explaining the rebound effect observed in numerical adaptation tasks. Contrary to our predictions, only numbers demonstrated a distance-dependent rebound effect, whereas letters did not demonstrate this effect anywhere in the brain. In contrast, a follow-up behavioural study (n = 184) using an active ordinality task demonstrated that the letter stimuli used in the adaptation task generated a behavioural distance effect, despite the absence of a distance-dependent effect at the neural level. What does this pattern of results suggest for number representation? Three, non-mutually-exclusive possibilities were suggested:

1. There are different mechanisms at play for behavioural vs. neural distance effects. i.e., the parametric rebound effect and the behavioural distance effect result from different mechanisms.
2. Different mechanisms may explain number and letter distance effects. i.e., perhaps letter distance effects arise due to response selection mechanisms, while number distance effects (both neural and behavioural) reflect a more number-specific mechanism.
3. Mechanisms for the neural distance-dependent parametric effect, behavioural number distance effect and behavioural letter distance are all different.

The data for Chapter 2 cannot speak to which of these possibilities may provide the best explanation. In order to distinguish between these possibilities, a within-subjects design that includes behavioural measures of ordinality with numbers and letters, and adaptation with numbers and letters, would be helpful. It would also be informative to include active fMRI ordinality tasks with numbers and letters. This within-participant design would allow investigation into the relationships between distance effects generated from letters and numbers in both passive and active tasks, at the behavioural and neural level. For example, it could be the case that distance effects from the letter and number active ordinality tasks correlate with one another, at both the behavioural and neural levels. However, the distance effect from numbers from the passive task does not correlate with the distance effects from the active tasks, and the letters do not generate a distance effect in the passive task (similar to the current study). This would suggest that the distance effect from the active tasks may reflect a non-number-specific process, such as response selection. Alternatively, perhaps the distance effects for numbers and letters would not be associated at the neural or behavioural level (option 2 above). This might suggest that the distance effects for letters could reflect response selection mechanisms, while the distance effects for numbers may reflect a more number-specific process. A further possibility is that none of the effects correlate with one another, which would support option 3 above. Unfortunately in Chapter 2, the follow-up study in Experiment 2, which I designed after the neural data had been analyzed, was made up of a sample independent to that of Experiment 1, and I did not include an active ordinality task in the scanner, therefore this remains a question for future research.

In one such study that examined the relationship between parametric effects from active and passive numerical tasks, Holloway et al. (2013) had participants complete an adaptation task with number symbols (Arabic digits and Chinese ideographs) and a non-symbolic comparison task. Holloway et al. (2013) investigated the relationship between IPS regions that demonstrated a parametric effect in response to numerical symbols (Arabic digits and Chinese ideographs) and IPS regions that exhibited a ratio effect in the non-symbolic comparison task. The right IPS regions found for the non-symbolic comparison task and the Chinese numeral adaptation condition did partially overlap. However, the left IPS regions found for the non-symbolic comparison task and the Arabic digit condition of the adaptation task did not overlap. Given the lack of overlap in the left IPS for Arabic symbols and non-symbolic comparison, this pattern of findings could be suggestive of different mechanisms underlying the neural ratio effects in active and passive tasks (Hong et al., 2019). However, this should be tested directly by examining correlations between the ratio effect in a symbolic numerical comparison task and symbolic numerical adaptation task.

There is a lack of research examining the relationship between neural distance effects generated from passive and active numerical tasks, therefore currently it is unclear if these distance effects are tapping into the same system of representation. At the level of behavioural distance effects, research has suggested that distance effects exhibited in number comparison tasks may reflect more domain-general processes, as opposed to mechanisms of number representation. In a behavioural study, Van Opstal, Gevers, De Moor and Verguts (2008) used letters to test the theory that representational overlap underlies the distance effect from the number comparison task. Participants completed a priming comparison task with number symbols and letters. In this task, a prime (either a number or a letter, depending on the condition) was followed by a target (number or letter) and participants were asked to indicate whether the target number was larger or smaller than a standard number, or whether the target letter came before or after a standard letter. From this task, two effects were calculated: a comparison distance effect and a priming distance effect. In the priming distance effect, participants demonstrate faster and more accurate responses to a target stimulus when the prime that preceded the target is numerically closer (e.g., a prime of 1 followed by a target of 3), compared to numerically further (e.g., a prime of 6 followed by a target of 3; Dehaene et al., 1998). Similarly to the previously defined comparison distance effect, the priming distance effect has been attributed to overlapping distributions in number representation (Van Opstal et al., 2008). An alternative hypothesis is that the priming distance effects does arise from overlapping distributions, however the comparison distance effect is better explained by responses selection processes (Van Opstal et al., 2008). As predicted, Van Opstal et al. (2008) found both a comparison distance effect and priming distance effect for the number condition, however only a distance effect for the letter condition. The comparison distance effect therefore seemed to be due to response selection, instead of magnitude representation (Van Opstal et al., 2008). Therefore, the ANS was not necessary to explain the comparison distance effect, as evidenced by the obtainment of the effect using letter (i.e., non-numerical) stimuli, whereas an effect that was hypothesized to be specific to numerical magnitude representation (the priming distance effect) was not observed with letters. Therefore, at the behavioural level, the active decision-making component of the comparison task has been demonstrated to fit better with a response selection mechanism, while the non-task relevant aspect (the prime), has been demonstrated to potentially reflect more specific numerical processing. Examining distance effects generated from different types of stimuli (e.g., numbers and letters) and levels of awareness (e.g., active symbol comparison vs. priming) can provide insight into the mechanisms underlying numerical processing.

Although the nature of distance effects observed at the behavioural and neural level in numerical cognition research is still an open question, data from Chapter 2 suggest that general ordinal relationships may not account for the distance-dependent adaptation to symbolic number in the IPS. Although distance effects are obtained at the behavioural level, it seems that mechanisms such as response selection, or perhaps a sort of interaction of response selection mechanisms with number representation, may account for this pattern as opposed to the ANS, given that distance effects were obtained for both letter and number stimuli (Van Opstal et al., 2008).

5.1.2 Chapter 3.

Chapter 3 asked: how do we develop symbolic number representations? Specifically, I set out to replicate the important finding from Vogel, Goffin and Ansari (2015) demonstrating a whole-brain correlation between age and the ratio-dependent rebound effect in the left IPS (n = 19). The same adaptation task and age range (6-14) was used, with a larger sample size (n = 45). I found a significant parametric effect across the entire age group bilaterally in the IPS, however there was no association between this effect and age anywhere in the brain. Therefore, the original Vogel et al. (2015) findings were not replicated. This preregistered study speaks to the importance of conducting replication research. Replicating new findings is a necessary, yet often overlooked, aspect of advancing science (Zwaan et al., 2018).

The lack of an association between age and the ratio-dependent effect could suggest that basic symbolic number representations may be fairly stable by age six. Given the lack of age-dependent results, previous research that demonstrated age-related changes in number representation (Houdé et al., 2010; Mussolin et al., 2013) may actually be capturing the development of more domain-general processes, or the interaction of domain-general processes with number representation, as opposed to changes just to symbolic number representation. For example, executive functions are related to early math skills (Bull, Espy, Wiebe, Sheffield, & Nelson, 2011; Verdine, Irwin, Golinkoff, & Hirsh-Pasek, 2004) and early number processing skills, such as number comparison and counting (Zhang, 2016). Language skills are also related to number comparison (Lefevre et al., 2010). Since executive functions develop rapidly over the course of elementary school, it is difficult to disentangle the effects of the development of these skills from the development of numerical representation using tasks that require the use of a combination of these skills (Cragg & Nation, 2008; Davidson, Amso, Anderson, & Diamond, 2006). Furthermore, some research has demonstrated that young children have a very limited understanding of terms such as “more”, “less” or “equal” (Warren, 2006). This could indicate that asking children to perform magnitude comparisons is taxing their language skills in a way that would not be the case for older children or adults, again complicating the picture of developmental changes in number representation (Church et al., 2010). Therefore, the use of passive designs to study number representation is particularly important when asking questions about developmental processes. The lack of an effect of age on the parametric effect in the current study could be because the fMRI-A paradigm allows us to probe the correlates of number representation, without the interference of constructs such as executive functions. Of course, the lack of a finding of developmental changes in number representation in the current study, and the positive correlation between age and the parametric effect in Vogel et al. (2015) could also be due to the relatively small sample sizes used in both studies (Schönbrodt & Perugini, 2013).

An interesting question for future research would be to examine symbolic numerical adaptation in even younger children; children who are at an age where symbolic number representations are just being learned. Even at age six, the children in our sample had symbolic numerical representations that were quite well-formed, as indicated by their ability to perform basic arithmetic. Between the ages of 3-5 children are actively learning single-digit numbers (Siegler & Lortie-Forgues, 2014). Therefore, perhaps in order to observe a measurable effect of age in symbolic number representation using a passive task, children as young as four should be included. To address the question of the development of symbolic number representation more thoroughly, it would also be of interest to follow a group of children longitudinally, starting at a young age. Given the open questions surrounding the contribution of the left and right IPS for number representation, including a younger age range and examining the neural correlates of symbolic number representation longitudinally using fMRI-A could provide valuable insight.

5.1.3 Chapter 4.

Is there a relation between handedness for handwriting and symbolic number representation? In Chapter 4, I examined the role of a potential sensorimotor mechanism in relation to symbolic number representation using the registered report format. The rationale behind this was based on:

1. The large bias in cognitive neuroimaging research to include only right-handed participants (Willems et al., 2014).
2. The finding that handedness is associated with cognitive constructs such as spatial attention and language (Cai et al., 2013; Van der Haegen et al., 2012), and that handwriting has been shown to affect the representation of letter symbols in the brain (James, 2010).
3. The convergent evidence suggesting that symbolic number representation is left-lateralized in the parietal lobe (Sokolowski et al., 2016).

A right-handed (n = 25) and left-handed (n = 25) group each completed a symbolic numerical fMRI-A task. Preregistered whole-brain and ROI analyses examining the laterality of the parametric effect found no evidence of a difference in laterality between the groups. More specifically, there were no significant regions found when the left and right-handers' parametric effect was compared directly, and using ROIs defined independently using Sokolowski et al. (2016) revealed no difference between the groups in the tendency of the parametric effect to be left or right-lateralized. Post hoc analyses provided conflicting evidence for a role of handedness in laterality of symbolic number representation. At the whole-brain level an increased threshold of .005 revealed activation in the right IPS for left-handers. Exploratory analyses where the threshold used in the ROI analysis was lowered indicated that the left-handers were more likely than the right-handers to demonstrate right IPS activity for the parametric effect. However, an additional ROI analysis using extracted beta weights indicated evidence for no difference in laterality between the groups. Overall, the preregistered analyses were not indicative of an association between handedness and symbolic number representation laterality, however the inconclusive results of the post hoc analyses could indicate that further exploration of this hypothesis is warranted.

Practice with symbol writing is one mechanism through which sensorimotor functions may contribute to number representation. Generally, people use either their left or right hand for handwriting. However, other sensorimotor processes that could be related to numerical processing can involve the use of both hands (e.g., counting and gesture). Given the finding in the current study that neither the left- or the right-handed groups showed categorical neural lateralization, it could be that a combination of sensorimotor factors are related to numerical representation; writing, which is dominated by one hand, as well as other processes that involve both hands, for example counting, finger gnosis and gesture.

In a series of experiments investigating the contribution of the motor system to counting, Andres, Seron and Olivier (2007) presented participants with dot arrays to count. Participants were asked to either count the dots or designate a letter to each dot and provide the letter for the last dot (i.e., "count" the dots using letter labels). Corticospinal excitability of the hand muscles was measured in participants as transcranial magnetic stimulation (TMS) was applied to the left primary motor cortex during the completion of the counting tasks. Greater corticospinal excitability was found in the hand muscles during both the number and letter counting tasks, compared to a non-counting control task (Andres et al., 2007). Therefore, the hand motor circuits seem to play an important role in the process of counting (Andres et al., 2008).

Using fMRI, Tschentscher, Hauk, Fischer and Pulvermüller (2012) compared motor cortex involvement for processing of single digit numbers in two groups of right-handed adults: a group that preferred to start counting on their left hand and a group that started counting on their right hand. Arabic digits and number words (1-9) were passively viewed by participants. ROI analyses in the precentral gyrus showed activation in this region was contralateral to the hand used for starting to count for the numbers 1-5 (Tschentscher et al., 2012). In other words, for the numbers 1-5, participants who tended to start counting these numbers with their left fingers showed right premotor activation when presented with these numbers, while those who counted starting with their right fingers showed left premotor activation. Together, results from Andres et al. (2007) and Tschentscher et al. (2012) provide support for a strong link between motor processes and symbolic number representation, and that counting may play a key role in this link for small numbers.

Finger gnosis is another sensorimotor construct that has been shown to be important in number processing (Penner-Wilger et al., 2007). Finger gnosis is defined as having a mental representation of one’s fingers, and is usually measured by testing the ability to differentiate between one’s fingers without looking at them. There is a relationship between finger gnosis and numerical and math abilities (Penner-Wilger et al., 2007). Finger gnosis is also predictive of later arithmetic skills in children (Fayol, Barrouillet, & Marinthe, 1998). Furthermore, in a TMS study with adults, Rusconi, Walsh, and Butterworth (2005) found that TMS applied to the left angular gyrus led to worse performance on both finger gnosis and numerical processing tasks. Additionally, conjunction analyses between finger gnosis tasks and basic numerical and arithmetic tasks has demonstrated IPS activity for numerical and finger tasks (Andres et al., 2012; Krinzinger et al., 2011). These results provide evidence for an overlapping neural substrate for finger gnosis and numerical processing.

Hand gestures are a further sensorimotor function that has shown links with numerical skills (Novack et al., 2014). Gestures appear to represent motor involvement in the solving of calculation questions, as motor interference tasks have been shown to worsen performance during specific methods of calculation, while verbal interference tasks show little effect (Brooks et al., 2018; Frank & Barner, 2012). Also, children's math learning is facilitated if they are shown and asked to produce gestures when solving math problems (Novack et al., 2014). The finding that gesture can facilitate numerical problem solving provides further evidence for a connection between sensorimotor processes and numerical processes.

The association between various manual sensorimotor processes and numerical abilities suggests that there could be shared mechanisms underlying these constructs. Sensorimotor involvement in number processing could occur through several avenues, such as writing, counting, finger gnosis and gesture. A number of theories have been put forth to explain this relation between numerical processing and sensorimotor processes. For example, some have suggested that the use of early techniques such as finger counting and adding using fingers leads to the linkage of finger sensory information and numerical representation (Butterworth, 1999). In the redeployment view, the neural circuitry for finger gnosis and numerical representation is shared (Penner-Wilger & Anderson, 2013). Therefore, associations that are observed between numerical tasks and finger representation tasks occur because both constructs make use of the same underlying network.

Although the precise mechanisms are unknown, manual sensorimotor functions and numerical representation seem to be linked in some way, providing evidence for the role of sensorimotor processes in number processing. Given the potential for shared neural circuitry between finger and number representation, it is possible that shared circuitry with finger mechanisms could speak to the association between manual sensorimotor processes and number representation (Anderson, 2010). An interesting open question for future research then, is what the contribution of these various sensorimotor processes may be to symbolic number representation. How might circuits involved in writing, counting, finger gnosis and gesture come to be recruited for the representation of symbolic number? It could be that counting, finger gnosis and gesture are related to numerical representation because of common neural circuitry underlying both number representation and these sensorimotor skills that involve finger use (Penner-Wilger & Anderson, 2013).

With regards to the handwriting handedness hypothesis for the laterality of symbolic number representation, a potential limitation of the current study is the use of handedness as a dichotomous variable. Handedness can be viewed as a continuous variable with a bimodal distribution (Willems et al., 2014). In general people tend to be more right-hand dominant or left-hand dominant, however there is variability in the extent to which people show right and left-handedness, as well as some who tend towards ambidextrous. A question for future research then, is whether the extent to which participants are right-hand dominant or left-hand dominant tends to be related to the extent of lateralization for number representation. In Chapter 4, the hypothesis being investigated was based solely on handwriting handedness, therefore the treatment of handedness as a dichotomous variable was warranted. However, with a sufficiently large sample, future research could examine handedness as a continuous variable.

5.1.4 Further questions and final remarks

Evidently, more work is needed to gain a comprehensive understanding of the nature of symbolic number representation in the brain. Although the human brain has evolved circuitry that allowed for the representation of numerical stimuli, it seems highly unlikely that the brain was specifically evolved for this function (Núñez, 2007). Learning and enculturation introduce demands for new uses of existing brain circuitry (Anderson, 2010), meaning that the mechanisms underlying number representation are likely made up of a complex interplay between many factors, including but not limited to sensorimotor processes and domain-general cognitive constructs. Studying the brain can provide key insights into the effects of enculturation, and fMRI provides a useful tool through which to examine questions related to learning and symbol abstraction.

In the current thesis I used fMRI-A to address theoretically-relevant questions surrounding symbolic number representation. Importantly, the distance/ratio-dependent recovery effect in response to symbolic number was replicated consistently in the empirical chapters. Furthermore, Chapters 3 and 4 included the first pre-registered replications of this effect. Through my thesis work, several conclusions can be drawn, and I have identified numerous areas for further investigation.

For example, Chapter 2 demonstrated that letters do not exhibit the same fMRI-A effects as symbolic numbers, despite letters being part of an ordered sequence. This makes it less likely that the adaptation effects for symbolic numbers can be explained by recourse to ordered symbolic sequences alone. Chapter 2 also suggested that there may be different mechanisms for neural and behavioural distance effects that have been theorized to arise from a common system; the ANS. This highlights the need to empirically test assumptions of the ANS for symbolic number representation. More specifically, testing the mechanisms underlying distance effects at the neural and behavioural level may provide a greater understanding of the suitability of the ANS as a system for supporting symbolic number representation.

The findings I reported in Chapter 3 revealed that children as young as six exhibit a ratio-dependent rebound effect for symbolic numbers, and this effect seems to be unrelated to age. When you simplify a numerical task by removing the more domain-general demands, symbolic number representation may actually look quite similar across elementary-school-aged children, and qualitatively similar to that of adults. This emphasizes the pressing need for replication of research findings, and suggests that we still have a lot to learn when it comes to the development of symbolic number representation.

In Chapter 3 I also investigated whether behavioural measures of numerical abilities showed an association with the ratio-dependent rebound effect in the IPS. There was substantial evidence that there was no association between the parametric effect and behavioural math measures. Furthermore, in Chapter 2 there was evidence for divergence between the distance effect demonstrated for symbolic number in the adaptation task, compared to that demonstrated by a behavioural ordinal task, given that letters showed this effect behaviourally but not neurally. These findings from Chapters 2 and 3 seem to demonstrate that there is a disconnect between the parametric effect in numerical adaptation and behavioural measures of number processing. This raises a broader question of what the recovery effect means if it is present at the neural level of analysis, but does not seem to translate in an obvious way to behavioural outcomes.

Chapter 4 found that handwriting handedness was not related to the laterality of symbolic numerical representation in the IPS. This chapter examined a sensorimotor component of number representation, and demonstrated the valuable nature of the registered report format. Chapter 4 also speaks to the exclusion of a potential confound in fMRI-A results, namely that left-lateralization for number representation is due to readiness of the participant to press a button for the catch trials. Given that the handedness of participants was not found to play a key role in the lateralization of number, it seems less likely that anticipating a button press could account for the lateralization observed in previous fMRI-A research with numbers.

Another topic for further inquiry is the finding across all three empirical Chapters of multiple regions outside of the parietal lobe that demonstrated ratio-dependent recovery. Based on previous research demonstrating the particular importance of the IPS for symbolic number representation, the focus of the current dissertation work was on the parietal clusters that demonstrated a parametric effect. However, other neural regions demonstrated parametric modulation by symbolic number, including frontal, premotor and occipital regions. The reasons for this are currently unknown, however it is not unexpected that symbolic number representation recruits a network of regions. Previous work with active tasks has demonstrated that a distributed fronto-parietal network is used for symbolic number representation (Sokolowski et al., 2016). Furthermore, in a map including only studies with a passive design, Sokolowski et al. (2016) found that along with parietal regions, the cingulate gyrus, and middle temporal gyrus were also recruited for symbolic and non-symbolic number across studies. Therefore, it is clear that the IPS is not the only region demonstrating activity that fits with a ratio-dependent rebound effect, although it is the region that receives the most attention due to its theoretical significance (e.g., Dehaene et al., 2003). Symbolic number representation seems to make use of a network of neural regions, which could reflect the recency of its invention. For example, it has been demonstrated that functions that could be considered more recent in terms of evolutionary time, such as language, recruit a more widely distributed network of regions compared to “older” constructs, such as attention (Anderson, 2007). Future research should investigate how this network of regions may work in tandem to form symbolic number representations.

Although the precise mechanisms underlying symbolic numerical processing are still unknown, in this dissertation I have probed the nature of ratio-dependent neural representation and contributed a small piece of understanding to the mystery of symbolic number representation in the brain.

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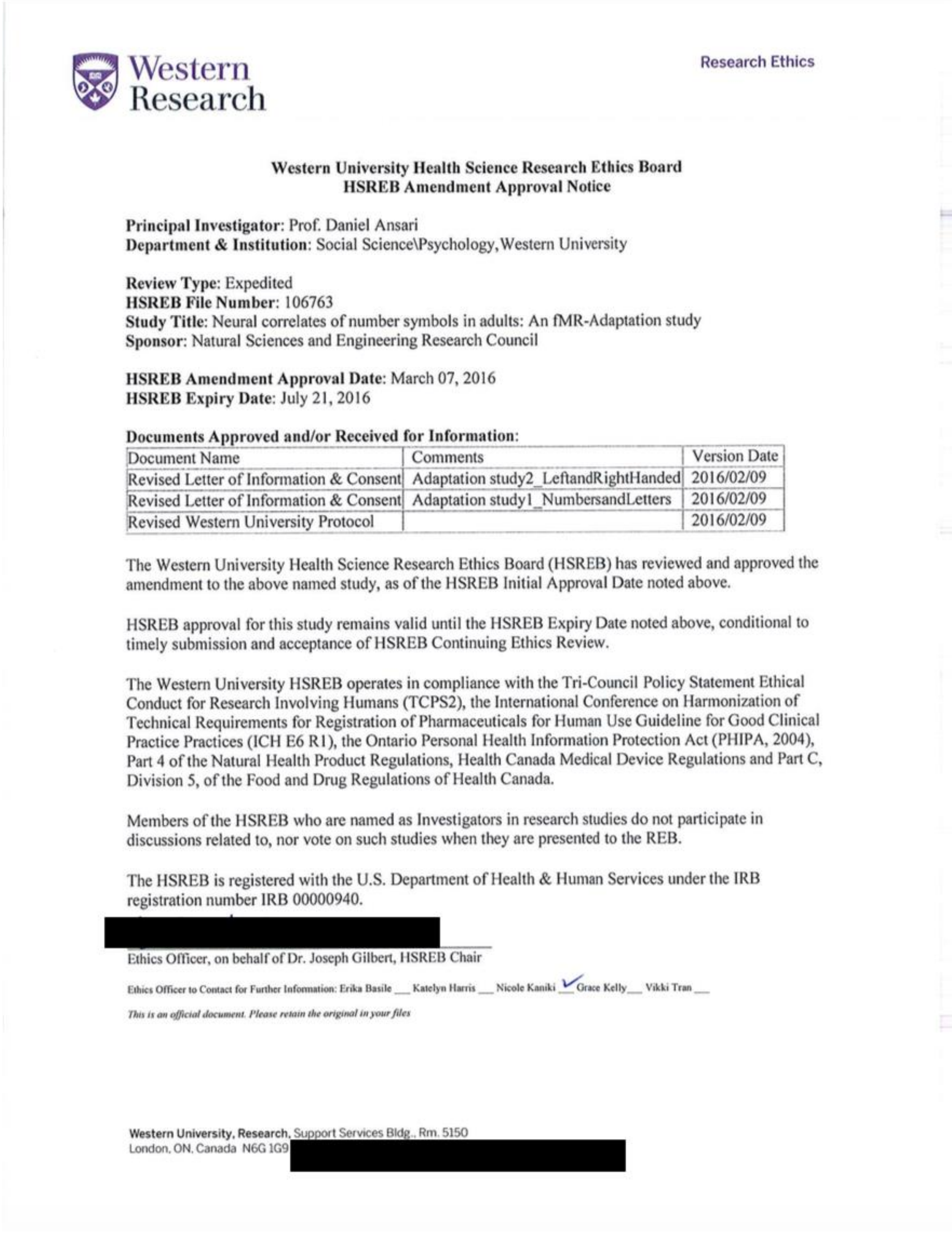
Appendices

Appendix A: Ethics Approval Documentation

Chapter 2



Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Prof. Daniel Ansari
Department & Institution: Social Science\Psychology, Western University

Review Type: Expedited
HSREB File Number: 106763
Study Title: Neural correlates of number symbols in adults: An fMR-Adaptation study
Sponsor: Natural Sciences and Engineering Research Council

HSREB Amendment Approval Date: March 07, 2016
HSREB Expiry Date: July 21, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Letter of Information & Consent	Adaptation study2_LeftandRightHanded	2016/02/09
Revised Letter of Information & Consent	Adaptation study1_NumbersandLetters	2016/02/09
Revised Western University Protocol		2016/02/09

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

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

[redacted]

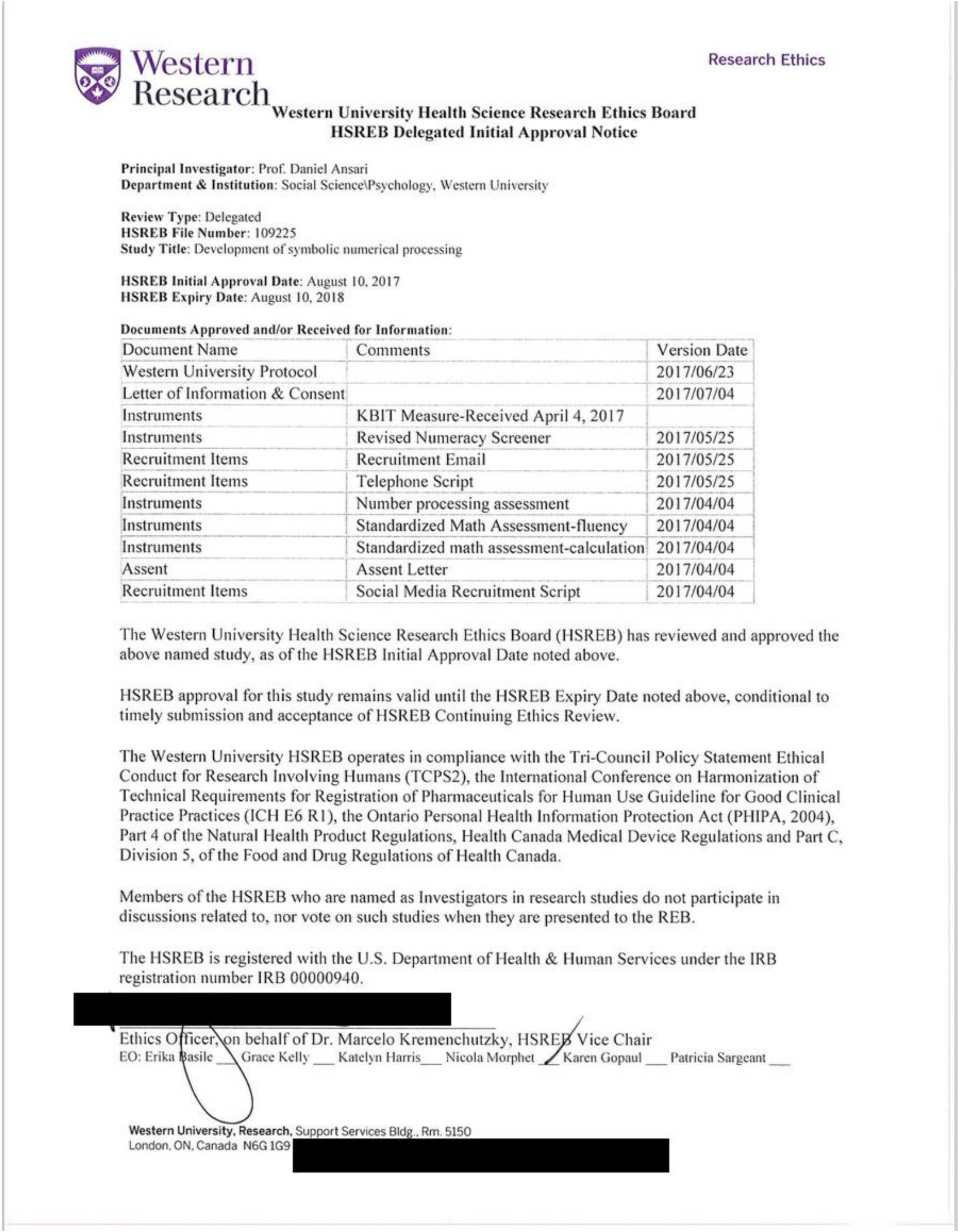
Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information: Erika Basile ___ Katelyn Harris ___ Nicole Kaniki ✓ Grace Kelly___ Vikki Tran ___

This is an official document. Please retain the original in your files

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1G9 [redacted]

Chapter 3



Western Research — Research Ethics

Western University Health Science Research Ethics Board
HSREB Delegated Initial Approval Notice

Principal Investigator: Prof. Daniel Ansari
Department & Institution: Social Science\Psychology, Western University

Review Type: Delegated
HSREB File Number: 109225
Study Title: Development of symbolic numerical processing

HSREB Initial Approval Date: August 10, 2017
HSREB Expiry Date: August 10, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Western University Protocol		2017/06/23
Letter of Information & Consent		2017/07/04
Instruments	KBIT Measure-Received April 4, 2017	
Instruments	Revised Numeracy Screener	2017/05/25
Recruitment Items	Recruitment Email	2017/05/25
Recruitment Items	Telephone Script	2017/05/25
Instruments	Number processing assessment	2017/04/04
Instruments	Standardized Math Assessment-fluency	2017/04/04
Instruments	Standardized math assessment-calculation	2017/04/04
Assent	Assent Letter	2017/04/04
Recruitment Items	Social Media Recruitment Script	2017/04/04

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

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

[redacted]

Ethics Officer, on behalf of Dr. Marcelo Kremenchutzky, HSREB Vice Chair
EO: Erika Basile ___ Grace Kelly ___ Katelyn Harris___ Nicola Morphet ✓ Karen Gopaul ___ Patricia Sargeant ___

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1G9 [redacted]

Chapter 4

Western
Research

Date: 11 July 2018

To: Prof. Daniel Ansari

Project ID: 106763

Study Title: Neural correlates of number symbols in adults: An fMR-Adaptation study

Application Type: HSREB Amendment Form

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 07/Aug/2018

Date Approval Issued: 11/Jul/2018

REB Approval Expiry Date: 21/Jul/2019

Dear Prof. Daniel Ansari ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Familial Handedness Questionnaire	Paper Survey	25/Jun/2018	
Neurological Questionnaire	Paper Survey	25/Jun/2018	
Poster_LeftHanded_26.06.2018	Recruitment Materials	26/Jun/2018	
Poster_RightandLeft_26.06.2018	Recruitment Materials	26/Jun/2018	
Protocol_25.06.2018	Protocol	25/Jun/2018	Clean Copy

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Patricia Sargeant, Ethics Officer [redacted] on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Neurological Questionnaire

Neurological Questionnaire

	Yes	No
1. Do you have a diagnosed neurological condition?	☐	☐
2. Do you have a diagnosed learning disability or attention deficit?	☐	☐
3. Do you have a history of early brain injury (prior to age 6)?	☐	☐

Appendix C: Familial Handedness Questionnaire

Familial Handedness Questionnaire

Please tell us about the handedness of your family. These items only refer to blood relatives (i.e., not step-parents or persons adopted or fostered).

	Yes	**No**
Is anyone in your family (other than you) left-handed?	☐	☐

Please list below your family members who are left-handed, including parents, siblings, grandparents, aunts, uncles and cousins.

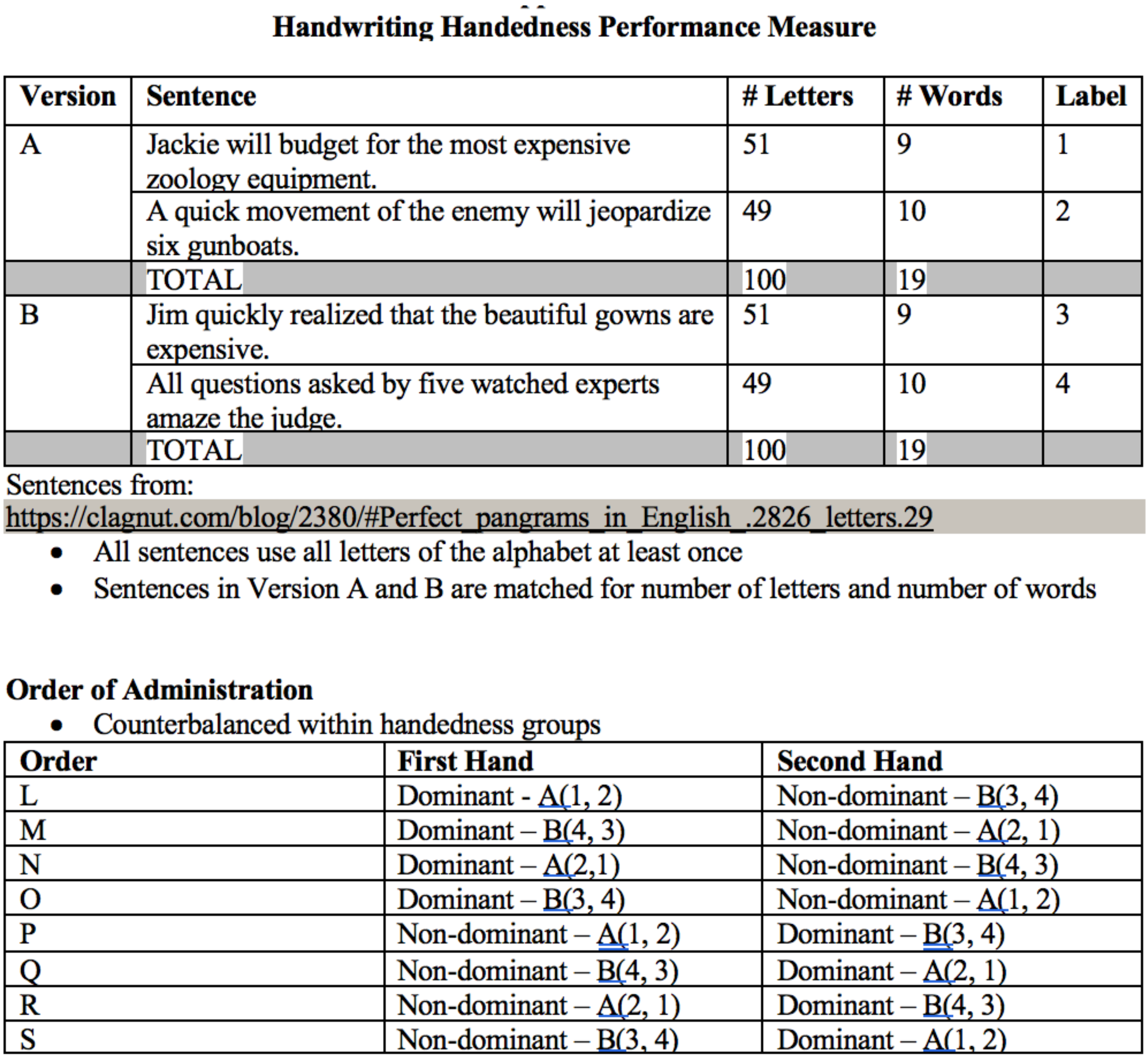
____

____

____

____

Appendix D: Handwriting Handedness Performance Measure



Handwriting Handedness Performance Measure

Version	Sentence	# Letters	# Words	Label
A	Jackie will budget for the most expensive zoology equipment.	51	9	1
	A quick movement of the enemy will jeopardize six gunboats.	49	10	2
	TOTAL	100	19	
B	Jim quickly realized that the beautiful gowns are expensive.	51	9	3
	All questions asked by five watched experts amaze the judge.	49	10	4
	TOTAL	100	19	

Sentences from:
https://clagnut.com/blog/2380/#Perfect_pangrams_in_English_.2826_letters.29

- All sentences use all letters of the alphabet at least once
- Sentences in Version A and B are matched for number of letters and number of words

Order of Administration

- Counterbalanced within handedness groups

Order	First Hand	Second Hand
L	Dominant - A(1, 2)	Non-dominant – B(3, 4)
M	Dominant – B(4, 3)	Non-dominant – A(2, 1)
N	Dominant – A(2,1)	Non-dominant – B(4, 3)
O	Dominant – B(3, 4)	Non-dominant – A(1, 2)
P	Non-dominant – A(1, 2)	Dominant – B(3, 4)
Q	Non-dominant – B(4, 3)	Dominant – A(2, 1)
R	Non-dominant – A(2, 1)	Dominant – B(4, 3)
S	Non-dominant – B(3, 4)	Dominant – A(1, 2)

Curriculum Vitae

Name: Celia Goffin

Post-secondary Education and Degrees:

2015-present	PhD – Developmental Psychology at the University of Western Ontario
2013-2015	Master's of Science – Developmental Psychology at the University of Western Ontario
2008-2012	BA Honors Specialization in Psychology at the University of Western Ontario

Honours and Awards:

2018-2019	Accepted Ontario Graduate Scholarship (OGS) – C$15, 000
2015-2018	Accepted National Sciences and Engineering Research Council of Canada (NSERC) – PGS-D – C$63,000
2017-2018	Doctoral Excellence Research Award (DERA) – C$10, 000
2016-2017	Doctoral Excellence Research Award (DERA) – C$10, 000
2015-2016	Offered Ontario Graduate Scholarship (OGS) – C$15, 000
2015	Awarded Leola E. Neal Award for Best Master's Thesis in Psychology – C$700
2014-2015	Accepted Social Sciences and Humanities Research Council of Canada (SSHRC) – CGS-M – C$17,500
2014-2015	Offered Ontario Graduate Scholarship (OGS) – C$15,000
2012	The McClelland Award for best 4th year thesis ("Reliability and convergent validity of the numerical distance and priming distance effects") – C$500
2011-2012	Faculty Dependents' Tuition Scholarship for University of Western Ontario Students
2008, 2010-2012	Dean's Honor List
2009-2010	Faculty Dependents' Tuition Scholarship for University of Western Ontario Students

Related Work Experience

2018	UWO (Department of Psychology) Graduate Teaching Assistant for 2043A "Exceptional Children: Developmental Disabilities"
2017	UWO (Department of Psychology) Graduate Teaching Assistant for 3442F "Mind, Brain and Education"
2017	UWO (Department of Psychology) Graduate Teaching Assistant for 2035B "Understanding Yourself and Others"
2016	UWO (Department of Psychology) Graduate Teaching Assistant for 2040A "Child Development"
2015	UWO (Department of Psychology) Graduate Teaching Assistant for 2043B "Exceptional Children: Developmental Disabilities"
2014	UWO (Department of Psychology) Graduate Teaching Assistant for

	3301F “Clinical Psychology”
2013-2014	UWO (Department of Psychology) Graduate Teaching Assistant for 2800E “Research Methods in Psychology”
2012-2013	UWO (Department of Psychology) Research Assistant for Dr. Ansari, in Numerical Cognition Lab
2011-2013	UWO (Department of Psychology) Developmental Recruitment at Victoria Hospital (in Post-Natal Care)

Publications:

Goffin, C., Sokolowski, H. M., Slipenkyj, M. & Ansari, D. (In press). Does writing handedness affect neural representation of symbolic number? An fMRI Adaptation Study. *Cortex.*

Colling, L., Holcombe, A. O., … **Goffin, C.**, Sokolowski, H. M., Ansari, D. … (In press). Registered replication report of Fischer, Castel, Dodd, and Pratt (2003). *Psychological Science.* https://osf.io/he5za/

Goffin, C. & Ansari, D. (in press). How are symbols and non-symbolic numerical magnitudes related? Exploring bidirectional relationships in early numeracy. *Mind, Brain, and Education.*

Goffin, C. & Ansari, D. (2018). Can brain training train your brain? Using the scientific method to get the answer. *Frontiers for Young Minds, 6*(26), doi: 10.3389/frym.2018.00026

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

Goffin, C., & Ansari, D. (2016). Beyond magnitude: Judging ordinality of symbolic number is unrelated to magnitude comparison and independently relates to individual differences in arithmetic. *Cognition, 150*(2016), 68-76.

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

Oral Presentations:

Goffin, C., Sokolowski, H. M. & Ansari, D. (2018). Does writing handedness affect neural representation of symbolic number? Research Seminar in Cognitive, Developmental and Brain Sciences, University of Western Ontario, Canada.

Lyons, I. M., Hutchison, J. E., Bugden, S., **Goffin, C**., & Ansari, D. (2018). Kindergarteners reliably mis-classify ordered sequences of non-adjacent numbers. Mathematical Cognition and Learning Society (MCLS), Oxford, U.K.

Goffin, C., Vogel, S. & Ansari, D. (2017). Do general ordinal relationships account for symbolic number representation? An fMR-adaptation study. Research Seminar in Cognitive, Developmental and Brain Sciences, University of Western Ontario, Canada.

Goffin, C., Vogel, S. & Ansari, D. (2016). Do general ordinal relationships account for symbolic number representation? An fMR-adaptation study. Developmental Brown Bag, University of Western Ontario, Canada.

Goffin, C., Ansari, D., Campbell, C., Frid, P., & Mazza, E. (May 2016). Numerical processing in children with cerebral palsy. Child Health Symposium, Thames Valley Children's Centre, London, Canada.

Goffin, C. & Ansari, D. (April 2016). Number processing and math in children with cerebral palsy. Developmental Brown Bag, University of Western Ontario, Canada.

Goffin, C. & Ansari, D. (March 2016). Research update: Numerical processing in children with cerebral palsy. CP-NET Annual Workshop, Toronto, Canada.

Goffin, C. & Ansari, D. (2014). Measuring symbolic numerical processing in adults. Developmental Brown Bag, University of Western Ontario, Canada.

Goffin, C., Vogel, S. & Ansari, D. (2014). Reliability and validity of effects commonly used in numerical cognition research. Numerical Cognition Research Retreat, Bayfield, Canada.

Vogel, S.E., **Goffin, C.** and Ansari D. (2014). Developmental changes in the cortical representation underlying the semantic processing of numerical symbols. Junior Researcher (JURE) Konferenz 2014, European Association for Research on Learning and Instruction (EARLI), Nikosia, Zypern.

Goffin, C. & Ansari, D. (2014). Numerical cognition in children with cerebral palsy. Paediatric Neuroscience Rounds, Thames Valley Children's Centre, London, Canada.

Goffin, C. & Ansari, D. (2013). Numerical cognition in children with cerebral palsy. Developmental Brown Bag, University of Western Ontario, Canada.

Vogel, S. E., **Goffin, C** & Ansari, D (2013). Entwicklungsbedingte Veränderungen der neuronalen Korrelate für die Repräsentation symbolischer Zahlenmenge (Developmental changes of the neural correlates associated with symbolic numerical magnitude representation). Fachgruppentagung für Pädagogische Psychologie, Hildesheim, Germany.

Poster Presentations:

Goffin, C., Sokolowski, H. M., Slipenkyj, M., & Ansari, D. (2019). Is writing handedness involved in the neural representation of symbolic number? Mathematical Cognition and Learning Society (MCLS), Ottawa, Canada.

Goffin, C., Sokolowski, H. M., Matejko, A. A., Bugden, S., Lyons, I. M. & Ansari, D. (2018). Assessing knowledge translation in the field of mind, brain and education in pre-service teachers. International Mind, Brain, and Education Society Conference, Los Angeles, U.S.

Goffin, C., Vogel, S. E. & Ansari, D. (2018). Do general ordinal relationships account for symbolic number representation? Mathematical Cognition and Learning Society (MCLS), Oxford, U.K.

Goffin, C., Vogel, S. E. & Ansari, D. (2017). Do general ordinal relationships account for symbolic number representation in the brain? An fMRI adaptation study. 29th APS Annual Convention, Boston, MA, United States.

Vogel, S. E., **Goffin, C.,** Lyons, I. M., Bohnenberger, J., Koschutnig, K., Reishofer, G., Grabner, R. H. & Ansari, D. (September 2016). The neural correlates of auditory and visual symbolic number processing: Investigations with fMRI adaptation. International Mind, Brain and Education Society Conference, Toronto, Canada.

Goffin, C. & Ansari, D. (2015). Measuring symbolic numerical processing in adults. Inaugural Brain and Mind Institute Symposium, London, Canada.

Goffin, C. & Ansari, D. (2015). Measuring symbolic numerical processing in adults. NIH Math Cognition and Learning Conference, St. Louis, U.S.

Goffin, C. & Ansari, D. (2015). Measuring symbolic numerical processing in adults. Lake Ontario Visionary Establishment (LOVE), Niagara Falls, Canada.

Goffin, C., Vogel, S. E., & Ansari, D. (2014). Reliability and convergent validity of the numerical distance, priming distance and congruency effects. Minds on Minds Symposium, London, Canada.

Goffin, C., Vogel, S. E., & Ansari, D. (2014). Reliability and validity of effects commonly used in numerical cognition research. Banff Annual Seminar in Cognitive Science (BASICS), Banff, Canada.

Vogel, S.E., **Goffin, C.** and Ansari, D. (2014). Developmental specialization of the parietal cortex for symbolic numerical magnitude representation. SIG22 Neuroscience and Education meeting of the European Association for Research on Learning and Instruction (EARLI), Göttingen, Germany.

Vogel, S. E., **Goffin, C.** & Ansari, D. (2013). Developmental changes in the cortical representation underlying the semantic processing of numerical symbols. Brain Plasticity, Learning, and Education Symposium, London, Canada.

Academic Activities:

-Assistant Poster Reviewer of the 2019 Cognitive posters for the 31st APS Annual Convention, Washington, D.C., United States.

-Volunteer at the 2018 International Mind, Brain and Education Society Conference, Los Angeles, United States.

-Assistant Poster Reviewer of the 2018 Cognitive posters for the 30th APS Annual Convention, San Francisco, California, United States.

-Attendee of the 2017 FSL course, organized by FMRIB, University of Oxford - Vancouver, Canada.

-Assistant Poster Reviewer of the 2017 Cognitive posters for the 29th APS Annual Convention, Boston, MA, United States.

-Volunteer at the 2016 International Mind, Brain and Education Society Conference, Toronto, Canada.

-Co-Organizer of the Developmental Brown Bag Series 2013/14 in the Department of Developmental Psychology at The University of Western Ontario, Canada.

Media Contributions:

Goffin, C. & Sokolowski, H. M. (2019). “A Brief Conversation” Radio Interview with Stephen Hurley, *voicEd Radio.*

Goffin, C. (2018). The development of number processing in the brain! Newsletter entry for *Language, Reading, and Math in Children*, Volume 11.