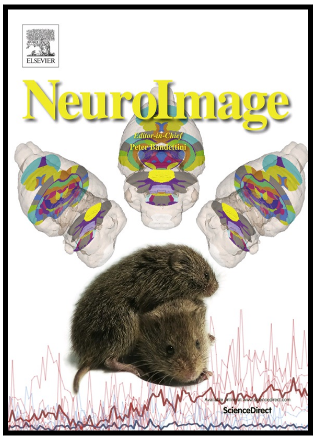

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Common and distinct brain regions in both parietal and frontal cortex support symbolic and nonsymbolic number processing in humans: A functional neuroimaging meta-analysis

H. Moriah Sokolowski[1], Wim Fias[2], Ahmad Mousa[1], Daniel Ansari[1*]

[1] *University of Western Ontario. London, Ontario, Canada*

[2] *Ghent University, Ghent, Belgium*

*Corresponding Author: Numerical Cognition Laboratory, Department of Psychology,
Westminster Hall, Western University, London ON, Canada, N6A 3K7,
daniel.ansari@uwo.ca

Abstract

In recent years, there has been substantial growth in neuroimaging studies investigating neural correlates of symbolic (e.g. Arabic numerals) and non-symbolic (e.g. dot arrays) number processing. However, it remains contested whether number is represented abstractly, or if number representations in the brain are format-dependent. In order to quantitatively evaluate available evidence, we used activation likelihood estimation (ALE) to conduct quantitative meta-analyses using 57 neuroimaging papers. Consistent with the existence of abstract representation of number in the brain, conjunction analyses revealed overlapping activation for symbolic and nonsymbolic numbers in frontal and parietal lobes. Consistent with the notion of format-dependent activation, contrast analyses demonstrated anatomically distinct fronto-parietal activation for symbolic and non-symbolic processing. Therefore, symbolic and non-symbolic numbers are subserved by format-dependent and abstract neural systems. Moreover, the present results suggest that regions across the parietal cortex, not just the intraparietal sulcus, are engaged in both symbolic and non-symbolic number processing, challenging the notion that the intraparietal sulcus is the key region for abstract number processing. Additionally, our analyses indicate that the frontal cortex subserve magnitude representations rather than non-numerical cognitive processes associated with number tasks, thereby highlighting the importance of considering both frontal and parietal regions as important for number processing.

Keywords: Activation Likelihood Estimation Meta-analysis, Frontal Cortex, Nonsymbolic Number, Parietal Cortex, Symbolic Number

1. Introduction

The question of how the human brain represents numbers has been addressed through a multitude of neuroimaging experiments. The overarching results from this rapidly growing body of research are consistent with a large body of neuropsychological evidence (Cipolotti et al., 1991; Dehaene et al., 2003). Specifically, neuroimaging research, like preceding neuropsychological studies, has suggested the bilateral parietal lobes, and specifically the bilateral intraparietal sulci, as important brain regions for processing the quantity of a discrete set of items (i.e. number) (for review see: Dehaene et al. 2003; Nieder 2005; Brannon 2006; Ansari 2008).

Humans have the unique ability to represent numbers either symbolically, such as with Arabic symbols (2) or number words (two), or nonsymbolically, appearing as an array of items (••). The system used to process nonsymbolic numbers (e.g. ••), often referred to as the approximate number system, is thought to be innate, meaning that infants are born with the ability to process nonsymbolic numbers (Cantlon et al., 2009a) and has a long evolutionary history (Brannon, 2006; Dehaene et al., 1998). In contrast, the acquisition of the culturally acquired, uniquely human ability to process abstract numerical symbols (e.g. 2 or two) is a product of learning and development and has emerged recently in human evolution (e.g. Ansari 2008; Coolidge and Overmann 2012). Because different stimulus formats can be used to represent the same quantity, numbers are said to have an abstract (i.e. format-independent) quality. As a result, one of the most dominant theories in the cognitive neuroscience of number processing, namely the three parietal circuits model, states that symbolic and nonsymbolic numbers are subserved by the same underlying neuronal circuitry (Dehaene et al., 2003, 1998). More specifically, the three parietal circuits model (Dehaene et al., 2003) predicts that three distinct neural systems support different aspects of basic number processing. Importantly, the model was based on a qualitative synthesis of previous literature (Dehaene et al., 2003). This qualitative meta-analysis suggests that the bilateral intraparietal sulci supports the processing of abstract numerical magnitudes, the left angular gyrus supports verbal aspects of basic number processing, and the bilateral posterior superior parietal lobules support visual attentional aspects of number processing. To empirically evaluate the parietal circuits model, researchers have canvassed the brain in search of neural responses associated with abstract representations of numbers (e.g. Dehaene et al. 1998, 2003; Brannon 2006; Piazza et al. 2007; Cantlon, Libertus, et al. 2009).

Such efforts have generated a large body of research which has identified bilateral inferior parietal regions as brain regions that respond to numbers across stimulus formats (Dehaene et al., 2003). Specifically, this research revealed that the intraparietal sulcus was activated by numbers when the numerical information was presented symbolically, either as Arabic digits (Ansari et al., 2005; Chochon et al., 1999; Holloway et al., 2010; Pesenti et al., 2000), number words (Ansari et al., 2006b), or nonsymbolically, such as dot arrays (Ansari and Dhital, 2006; Holloway et al., 2010; Piazza et al., 2007, 2004; Venkatraman et al., 2005). This activation in the intraparietal sulcus during number processing was also found when the stimuli were presented visually (Arabic numerals) or auditorily (Eger et al., 2003). Together, these results suggest that the intraparietal sulcus hosts a format and modality independent representation of number. However, the finding that the intraparietal sulcus is consistently activated across varying task types and methodologies does not necessarily imply that number is represented using only an abstract format-independent system.

In recent years, there has been a growing interest in the distinction between the neural correlates of symbolic processing and nonsymbolic processing (Holloway and Ansari, 2010; Lyons et al., 2014; Shuman and Kanwisher, 2004; Venkatraman et al., 2005). Recent empirical research has highlighted striking differences in the brain activation patterns of numerical stimuli based on stimulus format (Ansari, 2007; Cantlon et al., 2009a; Holloway et al., 2010; Piazza et al., 2007; Venkatraman et al., 2005). Right lateralized parietal and frontal regions have been found to show greater activation for nonsymbolic addition compared to symbolic addition (Venkatraman et al., 2005). However, brain regions in the left intraparietal sulcus have been shown to be more finely tuned to numbers presented as Arabic symbols compared to nonsymbolic dot arrays (Piazza et al., 2007). Holloway et al., (2010) directly tested whether the functional neuroanatomy underlying symbolic and nonsymbolic processing is overlapping or distinct. They found overlapping activation for symbolic and nonsymbolic stimuli in the right inferior parietal lobule. They also found that distinct brain regions responded to symbolic compared to nonsymbolic number. Specifically, symbolic number processing recruited the left angular gyrus and left superior temporal gyrus while nonsymbolic number processing recruited regions in the right posterior superior parietal lobule (Holloway et al., 2010). These findings imply that distinct brain regions support format-general and format- specific processing of numbers.

This converging evidence that showed that distinct brain regions support format-specific processing led Cohen Kadosh and Walsh, (2009) to mount a significant challenge to the predominant view in the field that number is represented abstractly in the brain. These authors highlighted caveats associated with studies that conclude that number is processed abstractly. For example, Cohen Kadosh and Walsh, (2009) called attention to the fact that many of the conclusions of these studies are based on null results and point out that shared neural representations may be driven by general task-related processing rather than by shared magnitude representations. The authors subsequently proposed the format-dependent processing hypothesis, postulating that the human brain possesses format-specific semantic representations of number.

Although the primary focus in the field of numerical cognition has been on the relationship between activation in the parietal cortex and number processing, converging evidence has shown that brain regions in the bilateral prefrontal and precentral cortex are also consistently activated during numerical processing (Ansari et al., 2005; Pinel et al., 2001). The frontal cortex has been identified as important for number processing in single-cell recordings from neurons in non-human primates (Andreas Nieder and Miller, 2004; Nieder et al., 2002). Additionally, developmental imaging studies have documented that brain activation during numerical processing shifts from the frontal cortex to the parietal cortex across development (Ansari et al., 2005; Cantlon et al., 2006;

Kaufmann et al., 2006). A quantitative meta-analysis that synthesized studies examining brain regions that are correlated with basic number processing and calculation tasks in adults further supported the idea that the frontal cortex is important for number processing in adults (Arsalidou and Taylor, 2011). This meta-analysis revealed that large regions of activation in both the parietal and frontal cortex support basic number and calculation tasks. Results showed that calculation tasks elicited greater activation in the prefrontal cortex compared to basic number tasks. Consequently, these authors concluded that the prefrontal cortices are essential in number and computational tasks (Arsalidou and Taylor, 2011). Together, these studies suggest that a fronto-parietal network may support the processing of numerical information. Although the large body of research examining numerical processing in adults concluded that the parietal lobes support numerical processing, it remains unclear whether frontal activation is as consistent as parietal activation during numerical processing. One potential explanation that parietal activation is more consistently reported than frontal activation during number processing tasks is that frontal activation may vary more than parietal activation between individuals. Since fMRI methodology cannot measure individual neural firing and requires averaging across many participants (Scott & Wise, 2003), it is possible that frontal activation varies more strongly than parietal activation between individuals. An alternative explanation is that perhaps parietal regions are selected more often than frontal regions in analyses involving region of interest (ROI). This selection bias could perpetuate an erroneous impression that the parietal lobe is more important than the frontal lobe for processing numbers. Consequently, quantitative meta-analytic tools are needed to overcome this potential unintentional bias within numerical cognition.

While converging evidence supports the notion that the processing of symbolic and nonsymbolic numbers relies on both common and distinct brain regions, this evidence has never been quantitatively synthesized. Previous meta-analyses by Dehaene et al. (2003), Cohen Kadosh et al. (2008) and Cantlon, Platt, et al. (2009) examining brain activation patterns underlying number processing in adults did not investigate how the brain activation patterns during number processing differ based on number format (i.e. symbolic vs. nonsymbolic). Instead, these qualitative meta-analyses grouped symbolic and nonsymbolic numerical stimuli into a general term: number (Arsalidou and Taylor, 2011; Dehaene et al., 2003; Houdé et al., 2010; Kaufmann et al., 2011a). However, it is critical to examine symbolic and nonsymbolic numerical stimuli separately since a large body of empirical research has highlighted striking differences in the brain activation patterns of symbolic compared to nonsymbolic number processing (Ansari, 2007; Cantlon et al., 2009a; Holloway et al., 2010; Piazza et al., 2007; Venkatraman et al., 2005). Additionally, despite converging evidence revealing consistent activation in frontal brain regions (such as the medial frontal gyrus, inferior frontal gyrus and precentral gyrus) during number processing tasks (Ansari et al., 2005; Pinel et al., 2001), previous qualitative analyses focused exclusively on parietal regions (Cantlon et al., 2009b; Cohen Kadosh et al., 2008; Dehaene et al., 2003). Moreover, these previous meta-analyses used Caret software (Cohen Kadosh et al. 2008; Cantlon, Platt et al. 2009), a tool that is widely used to visualize neuroimaging data by projecting the spatial mappings of brain activation patterns onto a population-averaged brain (Van Essen, 2012; Van Essen et al., 2001). This method of merging foci from several contrasts into a single figure or table has been the most common approach that researchers have used to combine data across studies (Turkeltaub et al., 2002). Visualization-based methods like Caret may be safely used for presenting the results of a few studies, however it should not be used for large sets of studies. The use of this technique requires judgments of convergence or divergence across studies that are largely subjective. This subjectivity is undesirable for rigorous evaluation of the convergence of neuroimaging findings. Therefore, quantitative meta-analytic tools, such as activation likelihood estimation (ALE) are critical for synthesizing studies with varying methodologies and inconsistent findings (Eickhoff et al., 2009b; Turkeltaub et al., 2012, 2002).

1.1 The Present Meta-analysis

There has been an emergence of quantitative meta-analytic techniques that use coordinate-based approaches to statistically determine concordance across functional imaging studies (Eickhoff et al., 2009b; Turkeltaub et al., 2012, 2002). These methods minimize subjectivity of meta-analyses by using statistical models to determine inter-study trends. The present study uses activation likelihood estimation (ALE) to examine brain activation patterns underlying symbolic and nonsymbolic number processing. The aim of an ALE meta-analysis is to quantify the spatial reproducibility of a set of independent functional magnetic resonance imaging (fMRI) studies. ALE identifies 3D-coordinates (foci) from independent studies and models probability distributions that are centered around foci. The unification of these probability distributions produces statistical whole brain maps (ALE maps) that show statistically reliable activity across independent studies (Eickhoff et al., 2012, 2009b; Laird et al., 2005; Turkeltaub et al., 2012, 2002). The current study is the first study to use ALE to objectively examine brain activity that is overlapping and distinct for symbolic and nonsymbolic numbers. This study aims to reveal which brain regions support abstract and format dependent number processing.

2. Materials and Methods

2.1 Literature Search and Article Selection

A stepwise procedure was used to identify relevant al research articles. First, the literature was searched using a standard search in the PubMed (http://www.pubmed.gov) and PsychInfo (http://www.apa.org/psychinfo/) databases. Combinations of the key terms "magnitude", "number*", "symbol*", "nonsymbolic", "PET", "positron emission", "fMRI", "functional magnetic resonance imaging", "neuroimaging" and "imaging" were entered into these databases. Second, the reference list of all relevant papers found in the first step and all relevant review papers were reviewed. A study was considered for inclusion if it included a passive or active symbolic number task, a passive or active nonsymbolic number task or both symbolic and nonsymbolic number passive or active tasks. The term 'study' refers to a paper and the term 'contrast' is defined as an individual contrast reported within a paper.

2.2 Additional inclusion/exclusion criteria:

1. Studies had to use at least one of the following tasks: comparison, ordering, passive viewing, numerical estimation, numerosity categorization, counting, matching, size congruity, naming or target detection.
    - These studies were chosen to include both explicit and automatic magnitude processing. Studies with tasks that required cognitive processing (such as calculation) were excluded in order to have activation that is specifically related to format-independent or format-dependent magnitude processing.

2. Studies had to include a sample of healthy human adults.
3. Brain imaging had to be done using fMRI or PET.
    - PET and fMRI studies were included because these imaging methods have comparable spatial uncertainty (Eickhoff et al., 2009a).
4. Studies had to use whole-brain group analyses with stereotaxic coordinates in Talairach/Tournoux or Montreal Neurological Institute (MNI) space.
    - Contrasts that used only region of interest analyses were excluded.
    - Contrasts that used only multivariate statistical approaches were excluded.
5. Studies had to have a sample size > 5 participants.
6. Studies had to be written in English.

Fifty-seven studies met the inclusion criteria, providing data on 877 healthy subjects. All of these studies included at least one symbolic and one nonsymbolic number task. See tables 1 and 2 for a detailed description of the main characteristics of each selected study. Together, these studies reported 575 activation foci obtained from 121 contrasts. The studies were reported in either Talairach or MNI spaces. Studies that reported data in MNI space were transformed into Talairach space using the Lancaster transformation tool (icbm2tal) (Laird et al., 2010; Lancaster et al., 2007).

2.3 Analysis Procedure

Quantitative, coordinate based meta-analyses were conducted using the revised version of the ALE method (Eickhoff et al., 2012, 2009b; Turkeltaub et al., 2012). ALE analyses were conducted using GingerALE, a freely available application by Brainmap (http://www.brainmap.org). ALE assesses the overlap between contrast coordinates (i.e. foci) by modeling the coordinates as probability distributions centered on coordinates to create probabilistic maps of activation related to the construct of interest. Specifically, foci reported from contrasts were combined for each voxel to create a modeled activation (MA) map. An ALE null-distribution is created by randomly redistributing the same number of foci as in the experimental analysis throughout the brain. To differentiate meaningful convergence of foci from random clustering (i.e. noise), an ALE algorithm empirically determines whether the clustering of converging areas of activity across contrasts is greater than chance as shown in the ALE null-distribution. In most empirical studies, a single group of subjects perform multiple similar tasks. Therefore, as most studies report many different contrasts, these contrasts use the same participants in the same scanning session. Consequently, the activation patterns produced by different contrasts do not represent independent observations. The ALE algorithm was modified to address this issue (Eickhoff et al., 2009; Turkeltaub et al., 2012). Additionally, an alternative approach of organizing datasets according to subject group (rather than by contrasts) was implemented (Turkeltaub et al., 2012). The current study used the modified ALE algorithm and organizational approach to prevent subject groups with multiple contrasts from influencing the data more than studies in which only a few contrasts are reported from the same group of participants (Turkeltaub et al., 2012).

Two separate ALE maps were created: One for symbolic numbers and one for nonsymbolic numbers. The current study examined brain regions that were active during each of symbolic (both Arabic and verbal) number processing and nonsymbolic number processing. A conjunction ALE analysis was then computed to examine brain regions that were active during both symbolic and nonsymbolic number processing. Contrast analyses were computed between the symbolic number map of activation and the nonsymbolic number map of activation to determine which regions symbolic and nonsymbolic numbers specifically activated.

2.4 Single Dataset ALE Maps

Two separate ALE meta-analyses were conducted to examine convergence of foci for: 1) symbolic number processing and 2) nonsymbolic number processing. These two ALE maps used both active and passive contrasts. In addition, three separate ALE meta-analyses were conducted to examine convergent foci for passive number processing: 1) all passive number processing (passive), 2) passive symbolic number processing (passive symbolic), 3) passive nonsymbolic number processing (passive nonsymbolic). All papers were coded using Scribe (either version 2.3 or version 3.0.8). Coordinates were compiled using Sleuth (version 2.4b). ALE meta-analyses were conducted using GingerALE (version 2.3.6). Of the 57 studies, 31 were used to create the symbolic map of activation (477 subjects, 69 contrasts, 265 foci) (cf. Table 1) and 26 were used to create the nonsymbolic map of activation (400 subjects, 52 contrasts, 310 foci) (cf. Table 2). 13 studies were used to create the passive map of activation (184 subjects, 30 contrasts, 139 foci) (cf. Table 3), of which 5 were used to create the passive symbolic map of activation (cf. Table 3), and 7 to create the passive nonsymbolic map of activation (cf. Table 3). One of the studies only included a conjunction analysis with both symbolic and nonsymbolic stimuli and therefore was not used to create the passive symbolic or passive nonsymbolic map. All ALE analyses were performed in GingerALE using a cluster-level correction that compared significant cluster sizes in the original data to cluster sizes in the ALE maps that were generated from 1000 threshold permutations. This was in order to correct for false positive clusters that could arise as a result of multiple comparisons within the same voxel. Specifically, these maps had a cluster-level threshold of p<.05 and a cluster-forming (uncorrected) threshold of p<.001. The ALE maps were transformed into z-scores for display. This recently developed thresholding technique provides a faster, more rigorous analytical solution for producing the null-distribution and addresses the issue of multiple-comparison corrections (Eickhoff et al., 2012). All single dataset ALE maps (symbolic, nonsymbolic and passive) were created using this correction.

Table 1. Studies Included in the Symbolic Meta-Analysis.

1st Author	Year	Journal	N	Imaging Method	Mean Age	Gender	Task(s)	Contrast Name	Loc
Ansari D	2005	NeuroReport	12	fMRI	19		Comparison	Distance effect (small>large) adults	12
Ansari D	2006	NeuroImage	14	fMRI	21	8F 6M	Size Congruity	Main effect: distance (small > large)	10
								Main effect of distance in the neutral condition (small>large)	7
Ansari D	2007	Journal of Cognitive Neuroscience	13	fMRI	21.5		Comparison	Conjunction of Small and Large symbolic number	8
Attout L	2014	PLoS ONE	26	fMRI	21	15F, 11M	Order Judgment	Distance effect of numerical order	7
Chassy P	2012	Cerebral Cortex	16	fMRI	28	16M	Comparison	Positive Integers<Negative Integers	1
Chen C	2007	NeuroReport	20	fMRI	22.7	10F, 10M	Delayed-number-matching	Unmatched Numbers > Matched Numbers	8
Chochon F	1999	Journal of Cognitive Neuroscience	8	fMRI		4F, 4M	Naming, Comparison	Digit Naming vs. Control	2
								Comparison vs. Control	13
								Comparison vs. Digit Naming	1
Damarla S R	2013	Human Brain Mapping	10	fMRI	25.5	7F, 3M	Passive Viewing	Stable Parietal lobe voxels in Digit-object mode	2
Eger E	2003	Neuron	9	fMRI	27.9	5F, 4M	Target-detection	Modality-related effects: Auditory	2

								Numbers >Visual Numbers (fixed-effect)	
								Modality-related effects: Auditory Numbers >Visual Numbers (random-effect)	4
								Modality-related effects: Auditory Numbers >Visual Numbers	5
								Modality-related effects: Auditory Numbers >Visual Numbers (random-effect)	4
								Numbers > Letters and Colours (fixed-effect)	4
								Numbers > Letters and Colours (random-effect)	2
								Numbers > Letters (fixed-effect)	2
								Numbers > Letters (random-effect)	2
								Numbers > Colours (fixed-effect)	4
								Numbers > Colours (random-effect)	3
Fias W	2003	Journal of Cognitive Neuroscience	18	PET	23	18M	Comparison	Number comparison vs Nonsymbolic Stimuli	13
Fias W	2007	Journal of Neuroscience	17	fMRI		9F, 8M	Comparison	Comparison (Number comparison-number dimming) - (letter comparison-letter dimming)	3
Franklin M S	2009	Journal of Cognitive Neuroscience	17	fMRI	21.8	10F, 7M	Ordering Task	Magnitude Near>Far (common regions with Order Near>Far)	1
								Order Far>Near (common regions with Magnitude Near>Far)	1
								Magnitude Near>Far (Unique regions)	3
								Order Far>Near	1

								(Unique regions)	
Fulbright R K	2003	American Journal of Neuroradiology	19	fMRI	24	8F, 11M	Order, Identification	Number vs Shapes	0
He L	2013	Cerebral Cortex	20	fMRI	21	8F, 12M	Comparison	Symbolic > Nonsymbolic	2
								Digit-digit > cross notation trials	1
								Overlap between (Symbolic>nonsymbolic) and (small>large)	2
Holloway I D	2010	Neuroimage	19	fMRI	23.5	10F, 9M	Comparison	(symbolic - control) - (non-symbolic - control)	2
Holloway I D	2013	Journal of Cognitive Neuroscience	26	fMRI	25	22F, 4M	Passive Viewing	Adaptation to Hindu-Arabic Numerals for both groups	2
Kadosh R	2005	Neuropsychologia	15	fMRI	28	7F, 8M	Comparison	Numerical vs. Size	7
								Numerical vs. Luminance	8
Kadosh R C	2007	NeuroImage	17	fMRI	31	7F, 10M	Stroop	Numerical Distance	3
								Numerical Distance (IPS)	2
								Notation Adaptation	2
								Quantity Adaptation	1
								Notation x Adaptation	1
Kadosh R C	2011	Frontiers in Human Neuroscience	19	fMRI	26.3	12F, 7M	Passive Viewing	Magnitude Change Digits	10
								Magnitude Change Digits>Dots	3
Kaufmann L	2005	Neuroimage	17	fMRI	31	7F, 10M	Stroop	Numerical comparison > physical comparison	5
								Numerical comparison (Distance 1 > Distance 4, only neutral trials)	5
Le Clec'H G	2000	Neuroimage	5	fMRI	37	5M	Compare to 12	Numbers > Body Parts (Block)	4
			6	fMRI	27	3F, 3M	Compare to 12	Numbers > Body Parts (Error)	3
Liu X	200	Journal of	2	fMRI		7 F,	Stroop	Distance of 18 vs.	6

	6	Cognitive Neuroscience	3			5M		Distance of 27	
Lyons I M	2013	Journal of Cognitive Neuroscience	35	fMRI		16F, 17M	Comparison	Symbolic: Number Ordindal > Lumimance Ordinal	3
								Symbolic: Number Ordinal > Luminance Ordinal and Number Cardinal >Luminance Cardinal	10
Notebaert K	2011	Journal of Cognitive Neuroscience	13	fMRI		6F,7 M	Passive Viewing	Ratio 1.25 Below > Ratio 1	1
								Ratio 1.5 Below > Ratio 1	1
								Ratio 2 Below > Ratio 1	1
								Ratio 2 Below > Ratio 1.25 Below	1
								Ratio 1.5 Above > Ratio 1	1
								Ratio 2 Above > Ratio 1	1
								Ratio 2 Above > Ratio 1.25 Above	1
Park J	2012	Journal of Cognitive Neuroscience	20	fMRI	23.4	11F, 9M	Visual matching task	Number > Letter	1
Pesenti M	2000	Journal of Cognitive Neuroscience	8	PET		8M	Comparison	Comparison vs. Orientation, Digits	7
Pinel P	1999	NeuroReport	11	fMRI	26	2F, 9M	Compare to 5	Arabic Number > Verbal Number	1
								Close Distance > Far Distance	1
								Far Distance > Close Distance	1
Pinel P	2001	Neuroimage	13	fMRI			Comparison	Verbal vs. Arabic	3
								Arabic vs. Verbal	6
								Distance Effect	7
Pinel P	2004	Neuron	15	fMRI	24	18 F, 6M	Stroop	Number Comparison vs. Size Comparison	5
								Number Comparison Small Distance vs. Number Comparison Large	3

Price G R	2011	Neuroimage	19	fMRI	22.17	6F, 13M	Passive Viewing	Distance (Conjunction) Arabic digits>Letters and Arabic digits>Scrambled digits	1
Vogel S E	2013	Neuro-psychologia	14	fMRI	25	7F, 7M	Number line estimation	Number > Control	10
								Number Specific Activation	5

Loc, number of locations reported in contrast; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; ; N, sample size of each study; M – Male, F – Female.

Table 2. Studies Included in the Nonsymbolic Meta-Analysis.

1st Author	Year	Journal	N	Imaging Method	Mean Age	Gender	Task(s)	Contrast Name	Loc
Ansari D	2006	Brain Research	16	fMRI	20.4	16M	Passive Viewing	Number Change Effect	4
Ansari D	2006	Journal of Cognitive Neuroscience	9	fMRI	19.8	6M, 3F	Comparison	Distance Effect in Adults	7
Ansari D	2007	Journal of Cognitive Neuroscience	13	fMRI	21.5		Comparison	Small Nonsymbolic > Large Nonsymbolic	1
								Large Nonsymbolic > Small Nonsymbolic	2
								Conjunction of small nonsymbolic and large nonsymbolic	3
Cantlon J F	2006	PLoS Biology	12	fMRI	25	5F, 7M	Passive viewing	Number > Shape (Adults)	2
Castelli F	2006	PNAS	12	fMRI	24	4F, 8M	Comparison	Estimating Numerosity: In space and time	7
								Difficulty Effect Estimating Numerosity: Space	2
								Difficulty Effect Estimating Numerosity: Time	2
Chassy P	2012	Cerebral Cortex	16	fMRI	28	16M	Comparison	Disk > Dots	1
Damarl	20	Human	1	fMRI	25.	7F,	Passive	Stable Parietal lobe	6

a S R	13	Brain Mapping	0		5	3M	Viewing	voxels in Pictoral Mode	
Demeyere N	2014	Human Brain Mapping	12	fMRI	26	9F, 3M	Passive Viewing	Adaptation to categories (repeated pairs vs. different pairs)	4
								Repetition of small category versus large category (large < small)	1
								Repetition of small category versus large category (small < large)	9
								Numerosity specific repetition [Repetition-Category > (Repetition-numerosity + Repetition-Exact)]	14
								Interaction Small/Large with Category/Numerosity/Exact	3
								Small numerosity < Small category	4
Dormal V	2009	Human Brain Mapping	14	fMRI	21	14M	Numerosity Categorization	Numerosity Processing - Reference for Numerosity	9
Dormal V	2012	Human Brain Mapping	15	fMRI	21	15M	Numerosity Categorization	Numerosity - Reference for Numerosity	5
								(Numerosity - Reference for Numerosity) - (Duration vs Reference for Duration)	1
Dormal V	2010	Neuroimage	15	fMRI	21	15M	Numerosity Categorization	[Simultaneous Numerosity]-[Reference Simultaneous Numerosity]	6
								[Sequential Numerosity]-[Reference Sequential Numerosity]	6
								[Simultaneous Numerosity– Reference for Simultaneous Numerosity]-	4

								[Sequential Numerosity–Reference Sequential Numerosity]	
								[Sequential Numerosity-Reference Sequential Numerosity]-[Simultaneous Numerosity-Reference Simultaneous Numerosity]	3
								[Sequential Numerosity]-[Reference Sequential Numerosity] and [Simultaneous Numerosity]-[Reference Simultaneous]	3
Eger E	2009	Current Biology	10	fMRI	23	5F, 5M	Comparison	Number Comparison Same List	8
								Number Comparison Different List	10
Hayashi M J	2013	Journal of Neuroscience	27	fMRI		14F, 12M	Comparison	Main Effect of Numerosity Task	13
He L	2013	Cerebral Cortex	20	fMRI	21	8F, 12M	Comparison	Nonsymbolic > Symbolic	8
								Dot-dot > cross-notation trials	4
								Overlap between (nonsymbolic>symbolic) and (large>small)	6
Holloway I D	2010	Neuroimage	19	fMRI	23.5	10F, 9M	Comparison	(nonsymbolic-control)-(symbolic-control)	7
Holloway I D	2013	Journal of Cognitive Neuroscience	26	fMRI	25	22F, 4M	Passive Viewing	Nonsymbolic Comparison	6
Jacob S N	2009	European Journal of Neuroscience	15	fMRI			Passive Viewing	Dot Proportion full brain analysis	1
								Adaptation to Dot Proportion	27
								Numerosity full brain analysis	1

Kadosh R C	2011	Frontiers in Human Neuroscience	19	fMRI	26.3	12F, 7M	Passive Viewing	Magnitude Change Dots	10
								Magnitude Change Dots>Digits	6
Leroux G	2009	Developmental Science	9	fMRI	23	9M	Number-length interference	(Interference-reference interference) AND (Covariation-Reference covariation)	10
Lyons I M	2013	Journal of Cognitive Neuroscience	33	fMRI		16F, 17M	Comparison	Nonsymbolic: Number ordinal>Luminance Ordinal	7
								Dot Ordinal >Luminance Ordinal (dot) and Dot Cardinal >Luminance Cardinal (dot)	10
Piazza M	2002	Neuroimage	9	PET	29	9M	Count	All 6-9 > All 1-4	8
								6-9 Random > 1-4 Random	6
								6-9 Canonical > 1-4 Canonical	5
Piazza M	2004	Neuron	12	fMRI	23		Passive Viewing	Regions Responding to Deviations in Number	7
Piazza M	2006	Brain Research	10	fMRI		3F, 7M	Estimation, Counting	Estimation > Matching	9
								Counting > Matching	14
								Counting > Estimation	7
Roggeman C	2011	Journal of Neuroscience	23	fMRI	25.8	23M	Passive Viewing	Large vs. Small Numerical Deviants	2
								Far vs. Close Numerical Deviants	1
Santens S	2010	Cerebral Cortex	16	fMRI	22.2	13M, 1F	Match-to-numerosity	conjunction: (Numerosity large > Numerosity medium) and (Numerosity medium > Numerosity small)	6
Shuman M	2004	Neuron	9	fMRI		2F, 7M	Comparison	Experiment 1: Nonsymbolic number comparison > Nonsymbolic color comparison	2

Loc, number of locations reported in contrast; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; N, sample size of each study; M – Male, F – Female.

Table 3: Studies Included in the Passive Meta-Analyses.

1st Author	Year	Journal	N	Imaging Method	Mean Age	Gender	*Symbolic or Nonsymbolic	Contrast Name	Loc
Ansari D	2006	Brain Research	16	fMRI	20.4	16M	Nonsymbolic	Number Change Effect	4
Cantlon J F	2006	PLoS Biology	12	fMRI	25	5F, 7M	Nonsymbolic	Number > Shape (Adults)	2
Damarla S R	2013	Human Brain Mapping	10	fMRI	25.5	7F, 3M	Nonsymbolic	Stable Parietal lobe voxels in Pictoral Mode	6
							Symbolic	Stable Parietal lobe voxels in Digit-object mode	2
Demeyere N	2014	Human Brain Mapping	12	fMRI	26	9F, 3M	Nonsymbolic	Adaptation to categories (repeated categories pairs vs. different categories pairs)	4
								Repetition of small category versus large category (large < small)	1
								Repetition of small category versus large category (small < large)	9
								Numerosity specific repetition [Repetition-Category > (Repetition-numerosity + Repetition-Exact)]	14
								Interaction Small/Large with Category/Numerosity/Exact	3
								Small numerosity < Small category	4
Holloway I D	2013	Journal of Cognitive Neuroscience	26	fMRI	25	22F, 4M	Symbolic	Adaptation to Hindu-Arabic Numerals for both groups	2

Jacob S N	2009	European Journal of Neuroscience	15	fMRI			Nonsymbolic	Line Proportion full brain analysis	1
								Adaptation to Dot Proportion	27
								Numerosity full brain analysis	1
Kadosh R C	2007	NeuroImage	17	fMRI	31	7F, 10M	Symbolic	Notation Adaptation	2
								Quantity Adaptation	1
								Notation x Adaptation	1
Notebaert K	2011	Journal of Cognitive Neuroscience	13	fMRI		6F,7M	Symbolic	Ratio 1.25 Below > Ratio 1	1
								Ratio 1.5 Below > Ratio 1	1
								Ratio 2 Below > Ratio 1	1
								Ratio 2 Below > Ratio 1.25 Below	1
								Ratio 1.5 Above > Ratio 1	1
								Ratio 2 Above > Ratio 1	1
								Ratio 2 Above > Ratio 1.25 Above	1
Piazza M	2004	Neuron	12	fMRI	23		Nonsymbolic	Regions Responding to Deviations in Number	7
Piazza M	2007	Neuron	14	fMRI			**Symbolic & Nonsymbolic	Overall fMRI Adaptation Effect (Activation decrease with repetition of same approximate quantity)	16
								Distance-Dependent Recovery from Adaptation across conditions (Far>Close)	21
Price G R	2011	Neuroimage	19	fMRI	22.17	6F, 13M	Symbolic	(conjunction) Arabic digits>Letters and Arabic digits>Scrambled digits	1
Roggeman C	2011	Journal of Neuroscience	23	fMRI	25.8	23M	Nonsymbolic	Large vs. Small Numerical Deviants	2
								Far vs. Close Numerical Deviants	1

Loc, number of locations reported in contrast; fMRI, functional magnetic resonance imaging; PET, positron emission tomography
*Symbolic vs. Nonsymbolic column shows whether contrast was used in symbolic or nonsymbolic map for format specific passive viewing maps.
**Study used in the full passive map but not in symbolic or nonsymbolic

2.5 Conjunction and Contrast Analyses

Conjunction and contrast analyses were computed to examine overlapping and distinct brain regions for the two ALE maps that included both active and passive tasks for symbolic and nonsymbolic number processing (Eickhoff et al., 2011). All conjunction and contrast ALE analyses were performed in GingerALE and used an uncorrected threshold of p<.01 with 5000 threshold permutations and a minimum volume of 50mm3. Although the cluster-level correction used to produce the single file ALE maps is the optimal thresholding technique available (Eickhoff et al., 2012), this correction is not yet available for conjunction and contrast analysis. The only available correction available to date for conjunction and contrast analysis is false discovery rate (FDR) thresholding. However, because ALE models the foci as 3D Gaussian distributions and FDR is not recommended to be used with Gaussian data (Chumbley and Friston, 2009), an uncorrected threshold of .01 was used for the conjunction and contrast analyses. Therefore, due to methodological constraints, cluster-level correction was used for the single file maps and uncorrected thresholding for the conjunction and contrast analyses[1,2]. An uncorrected threshold of .01 was appropriate for the conjunction and

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[1] Leading experts on ALE are recommending against using FDR and thus, for the use of uncorrected thresholds when doing conjunction and contrast analyses.
Discussions on the gingerALE forum:
http://www.brainmap.org/forum/viewtopic.php?f=3&t=499&sid=6c3ba03dfecbce73933a22acbd6fe2c1
http://brainmap.org/forum/viewtopic.php?f=3&t=320#p1012
http://brainmap.org/forum/viewtopic.php?f=3&t=485#p1505

[2] The main findings do not change when using an FDR correction of .05 to calculate the conjunction and contrast analyses comparing symbolic and nonsymbolic single file ALE

contrast analyses because the algorithm used by these analyses only includes clusters that have already passed the strict threshold of cluster-level .05 and uncorrected .001, used to create the single file maps. Therefore, this threshold is ideal to ensure that the threshold is stringent without masking any important regions. This threshold was combined with an extent threshold, which suppressed clusters that were smaller than 50 mm^3.

A conjunction analysis was computed to examine similarity of activation between the ALE maps generated by symbolic number processing and nonsymbolic number processing. The voxel-wise minimum value of the input ALE images was used to create the conjunction map. The conjunction was considered to be significant for each voxel if all contributing ALE maps showed significant activation in that voxel at the thresholds described. A conjunction ALE map was created to determine overlapping activation of symbolic and nonsymbolic numbers.

Contrast analyses were computed to compare activation between the ALE maps generated for symbolic and nonsymbolic number processing. ALE contrast images are created by directly subtracting one input image from the other. GingerALE creates simulated null data to correct for unequal sample sizes by pooling foci and randomly dividing the foci into two groupings that are equal in size to the original data sets. One simulation dataset is subtracted from the other and compared to the true data. This produces voxel-wise p-value images that show where the true data sit in relation to the distribution of values within that voxel. The p-value images are converted to Z scores.

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maps with cluster-level threshold of $p<.05$ and a cluster-forming (uncorrected) threshold of $p<.05$.

The following ALE contrasts were computed: 1) symbolic > nonsymbolic, 2) nonsymbolic > symbolic.

It is possible that the activation commonly found across studies is related to top-down task-related brain activations during the explicit processing of number tasks. Although the majority of neuroimaging studies investigating number processing have used active paradigms in which participants have to make a decision about numerical stimuli being presented, there is a growing body of research that has examined the neural processing of symbolic and nonsymbolic numbers in the absence of an explicit numerical processing task (e.g. Piazza et al. 2004, 2007; Ansari, Dhital, et al. 2006; Holloway et al. 2013; Vogel et al. 2014). In order to determine which brain regions support symbolic and nonsymbolic number processing in the absence of task demands, ALE maps were created included papers which exclusively used passive viewing paradigms. Specifically, an ALE map was computed to examine convergent activation of all papers that used a passive viewing paradigm (symbolic and nonsymbolic). Additionally, two separate ALE maps were created using papers that employed passive viewing paradigms: One for passive viewing of symbolic numbers and one for passive viewing of nonsymbolic numbers.

There were not enough papers to conduct conjunction and contrast analyses to examine the overlapping and distinct activation for the passive symbolic and passive nonsymbolic single file ALE maps. Therefore, these maps were compared qualitatively.

2.4 Anatomical Labeling

Anatomical labels from the Talairach Daemon (talairach.org) were determined automatically using GingerALE software for each of the automatically generated peak

ALE locations within all clusters. All (x, y, z) coordinates and anatomical labels of peak ALE values are reported in Table 4, Table 5 and Table 6.

3. Results

This section is organized in the following manner. First, the results are presented for the two meta-analyses that include active and passive tasks: 1) symbolic number processing, 2) nonsymbolic number processing. This is followed by the results of the conjunction analysis for symbolic and nonsymbolic magnitude processing. Following this, the brain regions active for the following contrasts are shown for symbolic>nonsymbolic, nonsymbolic>symbolic. These contrast analyses are repeated using a symbolic map that only includes Arabic digits. Subsequently, the results are presented for the three ALE maps that include only passive tasks: 1) passive (both symbolic and nonsymbolic), 2) passive symbolic and 3) passive nonsymbolic. Finally, reliability analyses for the symbolic and nonsymbolic ALE maps are presented.

3.1 Single Dataset Meta-Analyses (Passive and Active)

Two separate single dataset ALE meta-analyses were conducted to examine convergence of foci for symbolic number processing and nonsymbolic number processing.

3.1.1 Symbolic ALE map.

The symbolic number processing single dataset meta-analysis revealed activation in a widespread fronto-parietal network of brain areas during symbolic number processing (Fig. 1 and Table 4). The largest clusters of converging brain activation across 31 studies (Table 1) were in the left superior parietal lobule, inferior parietal lobule and the precuneus and the right inferior parietal lobule and precuneus. In addition to the parietal lobes, there was convergent activation in the left lingual gyrus and the left middle occipital gyrus as well as in the right superior frontal gyrus.

3.1.2 Nonsymbolic ALE map

The nonsymbolic number processing single dataset meta-analysis also revealed activation in a widespread fronto-parietal network of brain areas during nonsymbolic number processing (Fig. 2 and Table 4). Convergent brain activation across 26 studies (Table 2) was found in the a region spanning the right inferior parietal lobule, superior parietal lobule, precuneus and middle occipital gyrus, as well as a region spanning the left superior parietal lobule and the precuneus. Convergent activation was also found in the, right medial frontal gyrus and cingulate gyrus, the right insula, right precentral gyrus, and left middle occipital gyrus.

Table 4: Single Dataset Analyses (Active and Passive).

Hemisphere	Brain Area	BA	X	Y	Z	ALE	Vol/mm
Symbolic							
L	Superior Parietal Lobule	7	-28	-58	42	0.026	8944
L	Superior Parietal Lobule	7	-26	-54	44	0.026	
L	Inferior Parietal Lobule	40	-38	-48	48	0.022	
L	Inferior Parietal Lobule	40	-40	-44	38	0.021	
L	Inferior Parietal Lobule	40	-34	-52	36	0.020	
L	Precuneus	31	-20	-72	30	0.014	
R	Inferior Parietal Lobule	40	34	-44	40	0.031	6208
R	Precuneus	19	30	-64	38	0.028	
R	Precuneus	7	22	-52	46	0.021	
L	Lingual Gyrus	18	-22	-74	-4	0.017	1096
L	Middle Occipital Gyrus	18	-26	-86	2	0.014	
R	Superior Frontal Gyrus	6	2	10	48	0.021	768
Nonsymbolic							
R	Inferior Parietal Lobule	40	44	-40	46	0.032	10448
R	Precuneus	7	28	-50	48	0.030	
R	Superior Parietal Lobule	7	28	-58	46	0.026	
R	Precuneus	7	18	-64	50	0.026	
R	Middle Occipital Gyrus	19	30	-78	18	0.020	
R	Precuneus	31	28	-72	24	0.018	
R	Middle Occipital Gyrus	18	34	-84	4	0.013	
L	Superior Parietal Lobule	7	-30	-54	46	0.032	5472
L	Precuneus	19	-26	-70	30	0.019	
L	Precuneus	7	-22	-64	36	0.018	
L	Precuneus	7	-20	-58	54	0.017	
L	Precuneus	7	-20	-62	44	0.016	
L	Superior Parietal Lobule	7	-26	-52	60	0.012	
R	Medial Frontal Gyrus	32	4	10	46	0.032	3464
L	Cingulate Gyrus	32	-6	12	40	0.013	
R	Insula	13	32	20	8	0.034	1888
R	Precentral Gyrus	6	42	2	28	0.036	1704
L	Middle Occipital Gyrus	19	-26	-88	18	0.020	824

X, Y and Z – x,y,z values of the location of the maximum ALE value

ALE - maximum ALE value observed in the cluster

Vol/mm^3 - volume of cluster in mm3

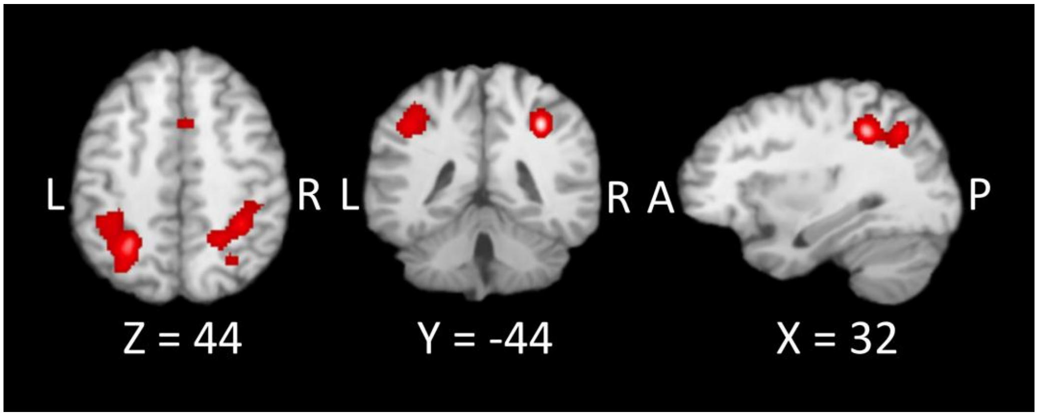

Figure 1: Single Dataset ALE map of symbolic number processing. The ALE analysis revealed significant clusters of convergent brain clusters (cf., table 4). Activations were identified using a cluster-level threshold of *p*<.05 with 1000 threshold permutations and an uncorrected *p*<.001 Brain slices are shown at coordinates (x, y, z) in Talairach space.

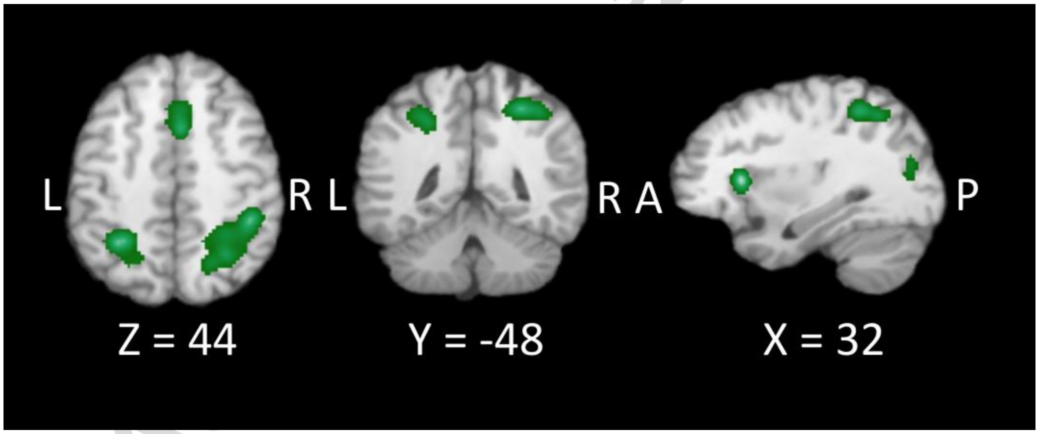

Figure 2: Single Dataset ALE map of nonsymbolic number processing. The ALE analysis revealed significant clusters of convergen brain clusters (cf., table 4). Activations were identified using a cluster-level threshold of *p*<.05 with 1000 threshold permutations and an uncorrected *p*<.001 Brain slices are shown at coordinates (x, y, z) in Talairach space.

3.2 Conjunction and Contrast Analyses

3.2.1 Conjunction ALE Map

A conjunction analysis was conducted to reveal brain regions with convergent clusters of activation between the symbolic and nonsymbolic single dataset ALE maps. Significant clusters of activation for symbolic and nonsymbolic number processing converged in the bilateral inferior parietal lobules, bilateral precuneus, left superior parietal lobule, as well as the right superior frontal gyrus (Table 5 Figure 3).

3.2.2 Contrast ALE Maps

To assess which brain regions were specifically activated for symbolic and nonsymbolic number processing, contrast analyses were conducted to compare the symbolic and nonsymbolic single dataset ALE maps. These contrast analyses revealed significant clusters of activation in the right supramarginal gyrus and inferior parietal lobule as well as the left angular gyrus for symbolic>nonsymbolic (Table 5, Figure 3). There were significant clusters of activation in a right lateralized frontal parietal network including the superior parietal lobule, inferior parietal lobule, precuneus, insula, superior frontal gyrus, and middle occipital gyrus for nonsymbolic>symbolic (Table 5, Figure 3).

Table 5: Conjunction and Contrast Analyses.

Hemisphere	Brain Area	BA	X	Y	Z	ALE	Vol/mm
Symbolic and Nonsymbolic							
L	Superior Parietal Lobule	7	-26	-54	44	0.026	2544
L	Inferior Parietal Lobule	40	-34	-48	44	0.016	
R	Precuneus	7	22	-52	46	0.021	2464
R	Inferior Parietal Lobule	40	36	-46	44	0.020	
R	Inferior Parietal Lobule	40	38	-42	42	0.020	
R	Inferior Parietal Lobule	40	32	-46	44	0.019	
R	Precuneus	19	30	-62	42	0.017	
R	Superior Frontal Gyrus	6	2	10	48	0.021	728
L	Precuneus	7	-28	-66	32	0.014	184
L	Precuneus	7	-26	-64	36	0.013	
L	Precuneus	19	-24	-72	30	0.012	
R	Precuneus	7	22	-66	38	0.012	24
R	Precuneus	7	24	-66	36	0.012	8
Symbolic > Nonsymbolic							
R	Supramarginal Gyrus	40	36	-48	32	2.911	304
R	Inferior Parietal Lobule	40	34	-52	34	2.820	
L	Angular Gyrus	39	-36	-60	36	2.878	240
Nonsymbolic > Symbolic							
R	Precuneus	7	18	-61	51	2.848	1128
R	Precuneus	7	15.5	-64.5	52	2.820	
R	Superior Parietal Lobule	7	21.3	-66.7	51.3	2.794	
R	Insula	13	38	20	11	3.156	648
R	Insula	13	32	20	14	2.636	
R	Inferior Parietal Lobule	7	34	-56	46	3.156	440
R	Inferior Parietal Lobule	40	34	-48	54	2.794	
R	Superior Frontal Gyrus	6	8	22	50	3.156	408
R	Inferior Parietal Lobule	40	46	-44	49	2.652	328
R	Middle Occipital Gyrus	19	34	-80	12	2.687	200

X, Y and Z – x,y,z values of the location of the maximum ALE value
ALE – conjunction analysis: maximum ALE value observed in the cluster, contrast analyses: maximum z-score observed in the cluster
Vol/mm^3

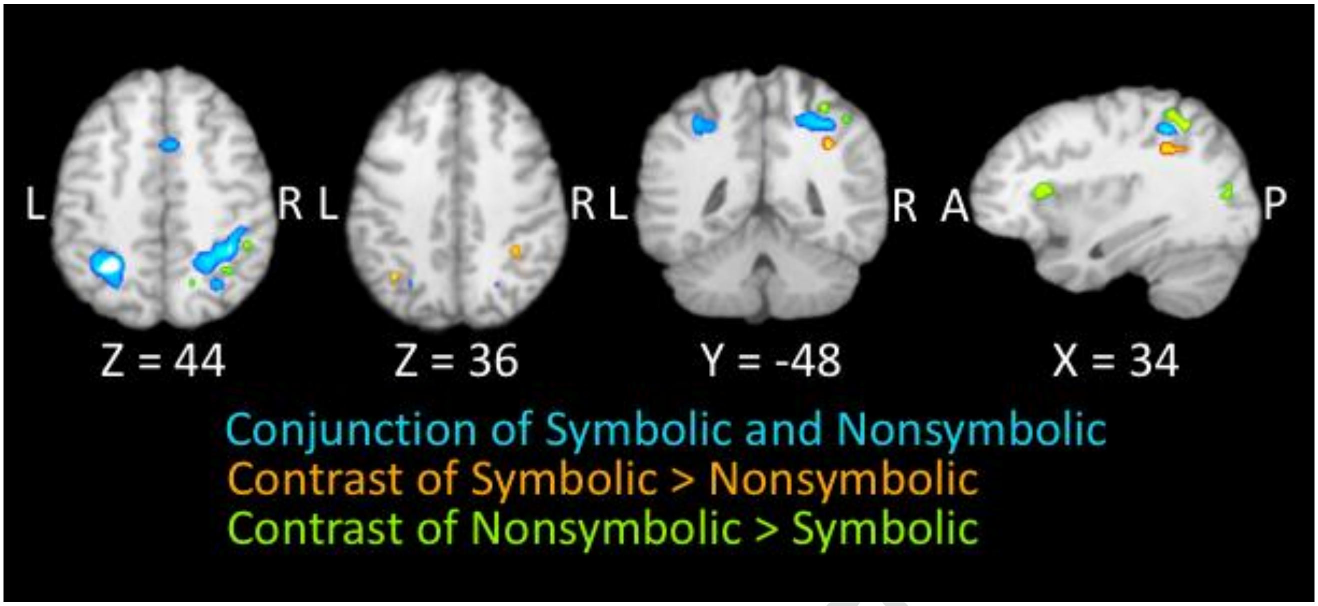

Figure 3: ALE maps of the conjunction and contrasts between the symbolic and nonsymbolic single dataset ALE maps (described in Table 4, Fig 1 and Fig 2). The ALE conjunction analysis revealed significant clusters of convergence between symbolic and nonsymbolic (blue). ALE contrast analyses reveal specific activation for symbolic>nonsymbolic (orange) and nonsymbolic>symbolic (green). Conjunction and contrast analyses were conducted using an uncorrected $p<.01$ with a minimum volume of 50mm^3. Brain slices are shown at coordinates (x, y, z) in Talairach space.

3.2.3 Contrast ALE Maps (Arabic Digits Only)

Of the 31 studies, which were included in the symbolic single file ALE map, 24 studies visually presented Arabic digits. Of the remaining 8 studies, 2 visually presented either number words or a combination of number words and Arabic digits, and 6 studies used both visual and auditory presentations of numbers. In order to determine whether the significant clusters of activation revealed by the symbolic vs. nonsymbolic contrast analyses were driven by the diversity of the symbolic number formats, a single dataset

ALE map was created containing papers that contrasted Arabic digits (24 papers, 399 subjects, 43 contrasts, 172 foci). To assess which brain regions were specifically activated for Arabic digits and nonsymbolic number processing, contrast analyses were conducted to compare the Arabic digit and nonsymbolic single dataset ALE maps.

These contrast analyses revealed significant clusters of activation in the left inferior parietal lobule and precuneus for Arabic digits>nonsymbolic (Table 6, Figure 4). There were significant clusters of activation in a right-lateralized frontal-parietal network including the superior parietal lobule, insula, and medial frontal gyrus, nonsymbolic>Arabic digits (Table 6, Figure 4).

Table 6: Contrast Analyses: Arabic Digits vs. Nonsymbolic.

Hemisphere	**Brain Area**	**BA**	**X**	**Y**	**Z**	**ALE**	**Vol/mm**
Arabic Digits > Nonsymbolic							
L	Inferior Parietal Lobule	39	-35	-62	40	2.590	152
L	Precuneus	19	-30	-62	40	2.576	
Nonsymbolic > Arabic Digits							
R	Superior Parietal Lobule	7	23.1	-62.5	53.3	3.719	2064
R	Superior Parietal Lobule	7	38	-57	48	3.540	
R	Inferior Frontal Gyrus	13	38	24	8	2.948	416
R	Insula	13	38	20	12	2.911	
R	Insula	13	36	24	12	2.848	
R	Medial Frontal Gyrus	8	9.3	21.3	48.7	2.794	208

X, Y and Z – x,y,z values of the location of the maximum ALE value
ALE – conjunction analysis: maximum ALE value observed in the cluster, contrast analyses: maximum z-score observed in the cluster
Vol/mm^3 - volume of cluster in mm3

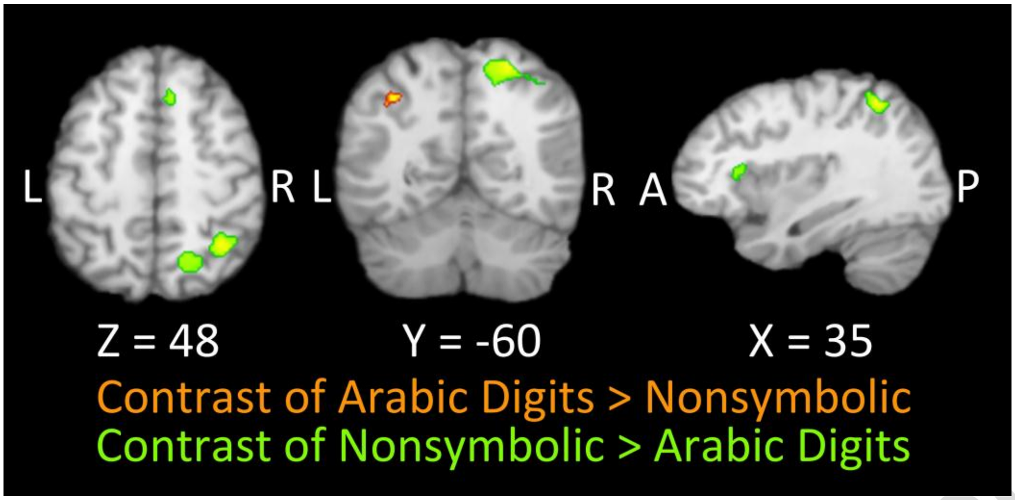

Figure 4: ALE maps of contrasts between the Arabic digits and nonsymbolic single dataset ALE maps. ALE contrast analyses reveal specific activation for Arabic digits>nonsymbolic (orange) and nonsymbolic>Arabic digits (green). Contrast analyses were conducted using an uncorrected *p*<.01 with a minimum volume of 50mm^3. Brain slices are shown at coordinates (x, y, z) in Talairach space.

3.3 Single Dataset ALE Maps (Passive only)

In order to determine which brain regions support symbolic and nonsymbolic number processing in the absence of task demands, ALE maps were created that only included papers that used passive viewing paradigms (Table 7, Figure 5).

3.3.1 Passive (symbolic and nonsymbolic) ALE Map

The passive single dataset meta-analysis revealed a fronto-parietal network of brain areas that qualitatively overlaps with many of the regions that were found in the ALE maps from the conjunction and contrast analyses (Table7, Figure 5, Figure 6). Specifically, the single dataset ALE map for passive symbolic and nonsymbolic revealed convergence of activation in the left superior parietal lobule, precuneus and middle temporal gyrus, the right inferior parietal lobule and precuneus, and left cingulate gyrus.

3.3.2 Passive Symbolic ALE Map

The single dataset meta-analysis for passive symbolic revealed a large cluster of brain activation in the left precuneus and in the left fusiform gyrus (Table 7, Figure 6).

3.3.3 Passive Nonsymbolic ALE Map

The single dataset meta-analysis for passive nonsymbolic revealed brain activation in the right precuneus, superior parietal lobule, and middle occipital gyrus (Table 7, Figure 6).

Table 7: Passive Single Dataset Analyses.

Hemisphere	Brain Area	BA	X	Y	Z	ALE	Vol/mm
Symbolic and Nonsymbolic							
L	Precuneus	19	-30	-66	36	0.022	3736
L	Precuneus	7	-22	-66	36	0.015	
L	Superior Parietal Lobule	7	-26	-62	48	0.014	
L	Superior Parietal Lobule	7	-32	-66	52	0.014	
L	Middle Temporal Gyrus	39	-26	-52	34	0.014	
L	Superior Parietal Lobule	7	-30	-54	44	0.012	
R	Precuneus	7	24	-52	48	0.017	2128
R	Inferior Parietal Lobule	40	36	-48	48	0.013	
L	Cingulate Gyrus	24	-8	6	46	0.015	640
Symbolic							
L	Precuneus	19	-30	-66	36	0.014	1016
L	Fusiform Gyrus	37	-46	-48	-12	0.014	560
Nonsymbolic							
R	Precuneus	7	26	-50	50	0.014	1272
L	Superior Parietal Lobule	7	-28	-54	44	0.011	688
L	Superior Parietal Lobule	7	-28	-62	48	0.010	
L	Middle Occipital Gyrus	18	-24	-88	2	0.013	608

X, Y and Z – x,y,z values of the location of the maximum ALE value
ALE - maximum ALE value observed in the cluster
Vol/mm^3 - volume of cluster in mm$_3$

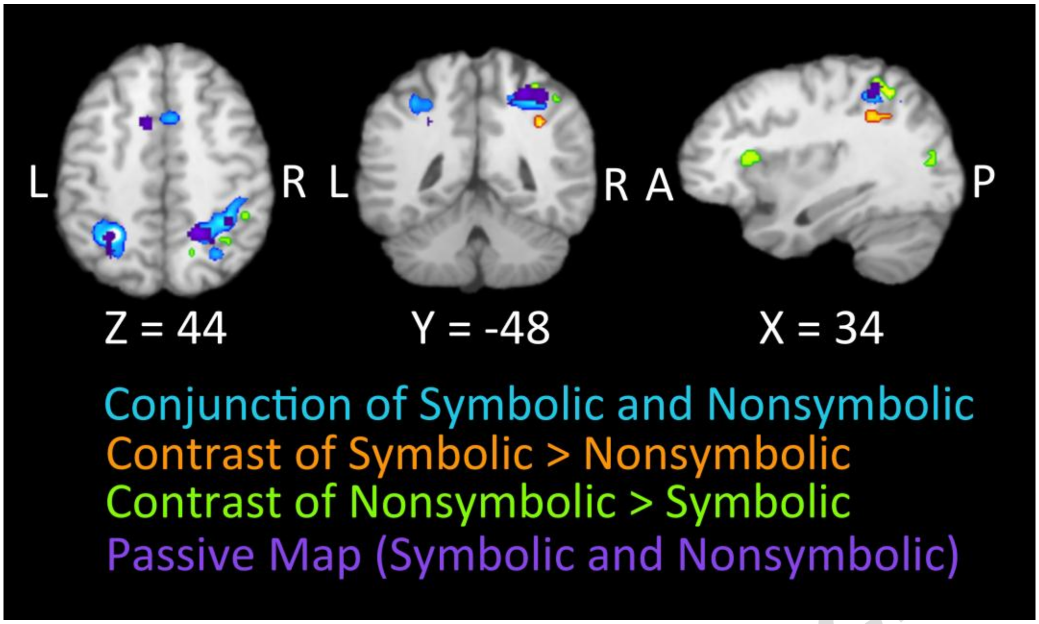

Figure 5: Single file ALE map using only studies with a passive design (purple) overlaid on top of Figure 3. Activations of passive ALE map were identified using a cluster-level threshold of *p*<.05 with 1000 threshold permutations and an uncorrected *p*<.001 Brain slices are shown at coordinates (x, y, z) in Talairach space.

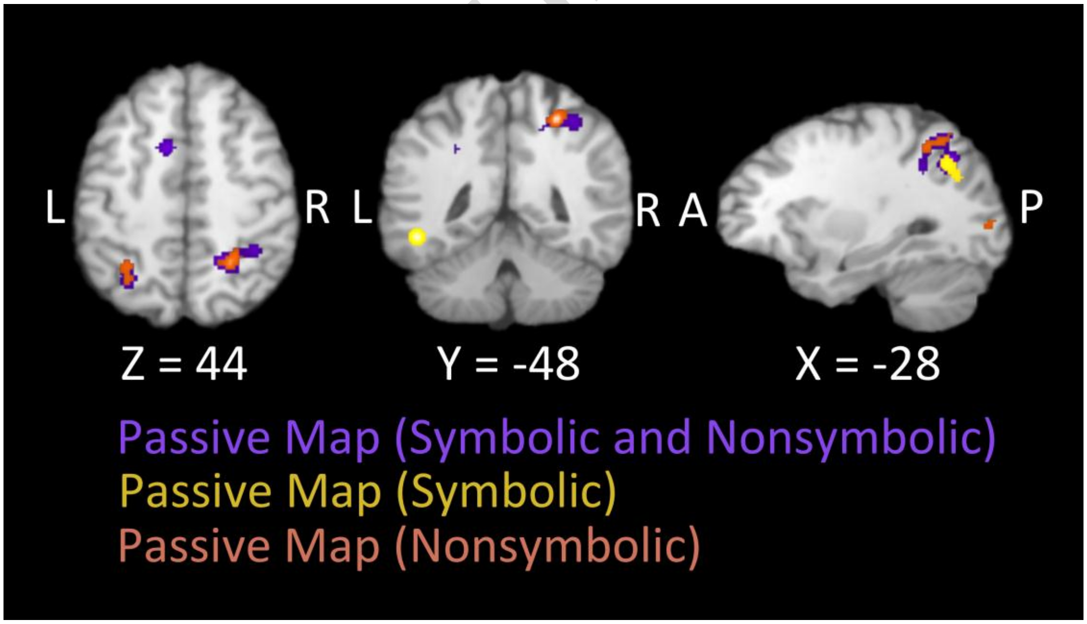

Figure 6: Single file ALE map of all studies (symbolic and nonsymbolic) that used a passive design (purple). Single file ALE maps of studies using passive design studies with symbolic stimuli (orange) and nonsymbolic stimuli (yellow) are overlaid. Activations of passive ALE maps were identified using a cluster-level threshold of *p*<.05 with 1000 threshold permutations and an uncorrected *p*<.001 Brain slices are shown at coordinates (x, y, z) in Talairach space.

3.4 Split Half Reliability Analyses

The contrast analyses between symbolic and nonsymbolic ALE maps of activation revealed significant differences between symbolic and nonsymbolic number processing at the meta-analytic level (Table 5, Figure 3). Follow-up reliability analyses were conducted in order to determine the extent to which the noise in the data can account for some of the between symbolic versus nonsymbolic activations. Specifically, the contrasts that comprise the symbolic and nonsymbolic number processing ALE maps were each split into two random halves (an ALE map of activation was created for each half). A contrast analysis was run in order to determine regions that were significantly more activated for half one>half two and for half two>half one. This analysis was repeated three times for each symbolic and nonsymbolic ALE map. These analyses revealed that for the symbolic ALE reliability analysis, only one of the six contrasts showed a significant difference between half one and half two. However, for the nonsymbolic ALE reliability analysis, five of the six contrasts showed a significant difference between half one and half two (Table 8a). See Table 8b for a description of which brain regions showed significant differences. Table 8b reports the random regions that come out when contrasting half of the map against the other half. The regions reported in this table are small and random. The purpose of this table is to detail the regions that came out as significant in the reliability analyses in order to highlight that the regions that were different between the two halves are small and span many different regions across the brain.

Table 8a: Reliability Analyses: Number of Significant Regions.

Run	Contrast	Number of Regions
Symbolic		
Run 1	Half 1 > Half 2	0
	Half 2 > Half 1	1
Run 2	Half 1 > Half 2	0
	Half 2 > Half 1	0
Run 3	Half 1 > Half 2	0
	Half 2 > Half 1	0
Nonsymbolic		
Run 1	Half 1 > Half 2	1
	Half 2 > Half 1	1
Run 2	Half 1 > Half 2	3
	Half 2 > Half 1	1
Run 3	Half 1 > Half 2	1
	Half 2 > Half 1	0

Table 8b: Reliability Analyses: Location of Significant Clusters.

Hemisphere	Brain Area	BA	X	Y	Z	ALE	Vol/mm
Symbolic							
L	Inferior Parietal Lobule	40	-39	-55	36	2.652	216
L	Inferior Parietal Lobule	40	-34	-56	36	2.501	
Nonsymbolic							
L	Middle Occipital Gyrus	18	-36	-86	-2	2.794	464
L	Middle Occipital Gyrus	18	-35	-85	2	2.652	
L	Middle Occipital Gyrus	18	-29	-85	2	2.605	
L	Inferior Occipital Gyrus	18	-25	-89	1	2.382	
L	Precuneus	31	-18	-48	39	3.156	504
L	Superior Parietal Lobule	7	-32	-52	52	2.652	512
R	Precuneus	7	28	-54	50	2.794	144
R	Superior Parietal Lobule	7	26	-52	42	2.468	
R	Precuneus	7	20	-60	42	2.727	120
L	Cingulate Gyrus	32	1	16	39	3.719	640
R	Medial Frontal Gyrus	6	8	16	44	2.418	
L	Superior Parietal Lobule	7	-26	-58	56	2.848	120

X, Y and Z – x,y,z values of the location of the maximum ALE value
ALE – conjunction analysis: maximum ALE value observed in the cluster, contrast analyses: maximum z-score observed in the cluster
Vol/mm^3 - volume of cluster in mm$_3$

4. Discussion

The current meta-analysis examined the neural bases of the ability to process symbolic and nonsymbolic numbers. Quantitative meta-analytic techniques were used to address two important questions. First, the study examined whether neural representations of numbers are represented abstractly or if the human brain hosts format-dependent representations for number. This question was addressed by identifying both overlapping and distinct brain regions that are activated by symbolic and nonsymbolic numbers. Second, the study examined whether these converging regions of activation were related to magnitude processing rather than top-down task demands.

The current study represents the first quantitative meta-analysis examining the neural correlates of symbolic and nonsymbolic magnitude processing. Specifically, two ALE meta-analyses were computed to identify the neural correlates of symbolic and nonsymbolic number processing. These meta-analyses revealed that brain regions in the fronto-parietal network were associated with symbolic and nonsymbolic number processing across studies. Activation in regions within the bilateral parietal and frontal cortex was correlated with both symbolic and nonsymbolic number processing. The left middle occipital gyrus was activated during symbolic number processing and the bilateral middle occipital gyri were activated during nonsymbolic number processing. The spatial distributions of the single dataset quantitative ALE maps that were generated for symbolic and nonsymbolic numbers suggest that both overlapping and distinct brain regions are associated with symbolic and nonsymbolic numbers.

4.1 Symbolic vs. Nonsymbolic

In order to quantitatively address whether numbers are represented abstractly or if the human brain hosts format-dependent representations for number, conjunction and contrast analyses were conducted to compare symbolic and nonsymbolic ALE maps. Conjunction analyses revealed that regions along the bilateral inferior parietal lobules and precuneus, as well as the left superior parietal lobule, and right superior frontal gyrus, were specifically activated by the conjunction of symbolic and nonsymbolic numbers. Contrast analyses revealed that the right supramarginal gyrus and inferior parietal lobule as well as the left angular gyrus were specifically activated for symbolic compared to the nonsymbolic numbers. Notably, only the left inferior parietal lobule was significant specifically for Arabic digits compared to nonsymbolic numbers. A right lateralized frontal parietal network including the right superior parietal lobule, inferior parietal lobule, precuneus,, superior frontal gyrus and insula as well as the middle occipital gyrus were specifically activated for nonsymbolic compared to symbolic numbers. These findings are consistent with empirical research suggesting that symbolic and nonsymbolic numbers are processed using both overlapping and distinct neural mechanisms (e.g. Holloway et al., 2010; Lyons and Beilock, 2013; Piazza et al., 2007).

In addition to quantitatively replicating the finding that overlapping and distinct neural populations support different number formats, these conjunction and contrast analyses provide valuable insights into the highly debated question of whether number is processed abstractly (e.g. Ansari, 2007; Cohen Kadosh and Walsh, 2009; Roi Cohen Kadosh et al., 2007; Dehaene et al., 1998; Nieder and Dehaene, 2009; Piazza et al., 2007). The finding that several neural regions were activated by the conjunction of symbolic and nonsymbolic number maps supports the notion that the human brain represents numbers abstractly. This finding implicates the bilateral inferior parietal lobules and precuneus, as well as the left superior parietal lobule, and right superior frontal gyrus, as candidate regions that may support abstract number processing. However, the nature of the overlap between symbolic and nonsymbolic numerical maps is unclear because the statistical algorithms that underlie ALE do not evaluate patterns of activation within overlapping regions. Therefore, while it is possible that the overlap could represent common semantic processing, the overlap could also represent common task demands such as attention or response-selection. In empirical studies, researchers addressed this limitation of coarse spatial resolution by implementing multi-voxel pattern analysis (MVPA) to examine patterns of activation for symbolic and nonsymbolic numbers in the intraparietal sulcus (Damarla and Just, 2013; Eger et al., 2009; Lyons et al., 2014) and at the whole brain level (Bulthé et al., 2014). These studies consistently reported a lack of association between patterns of activation for symbolic and nonsymbolic number processing. Such findings challenge the idea that overlapping activation for symbolic and nonsymbolic numerical processing implies that numbers are processed abstractly. It is important to interpret overlapping activation with caution until data-analysis techniques become available that can analyze patterns of activation across multiple studies.

Meta-analytic contrast analyses revealed that distinct neural mechanisms are activated by symbolic compared to nonsymbolic numbers and supported the theory that numerical representations are dependent on format (Cohen Kadosh and Walsh, 2009; Cohen Kadosh et al., 2011; Roi Cohen Kadosh et al., 2007). In particular, the contrast symbolic>nonsymbolic revealed activation in the right supramarginal gyrus and the inferior parietal lobule, as well as the left angular gyrus. Conversely, the contrast nonsymbolic>symbolic showed that nonsymbolic numbers correlate with activation in the right superior parietal lobule, inferior parietal lobule, and precuneus (as well as right lateralized regions not in the parietal cortex including the insula, superior frontal gyrus, and middle occipital gyrus). Interestingly, regions specifically activated by either symbolic or nonsymbolic stimulus formats seemed to be lateralized within the parietal cortex. Specifically, the right parietal lobule supported both symbolic and nonsymbolic specific processing, while activation in the left parietal lobule was specific to symbolic number processing. However, even though symbolic and nonsymbolic maps both show activation in the right parietal cortex, the localization in the right parietal lobe is different. Specifically, activation nonsymbolic>symbolic activation is more superior, while symbolic>nonsymbolic activation more inferior. In other words, the contrast analyses comparing symbolic and nonsymbolic ALE maps suggest that within the right parietal cortex, symbolic and nonsymbolic number processing are associated with different spatial patterns of activation.

The symbolic ALE map included several symbolic number formats: Arabic digits, written number words, and verbal number words. In contrast, the nonsymbolic ALE map included only visual displays of arrays of objects. One potential explanation for the significant activation revealed by the contrast analyses is that the symbolic number map map consists of not only of visual but also written and auditory stimuli. To test this, a single file ALE map with only Arabic digits was created and compared to the nonsymbolic map. This contrast analysis revealed that the processing of Arabic digits correlated with activity in only the left inferior parietal lobule, while processing nonsymbolic numbers correlated with activity in the right superior parietal lobule, insula and medial frontal gyrus. Therefore, the left inferior parietal lobule may be specific to the processing of arabic digits, while the right supramariginal gyrus and inferior parietal lobule may host more abstract symbolic number representations. The finding that the symbolic passive map reveals left lateralized parietal activation provides converging evidence supporting the notion that the left inferior parietal lobe is important for symbolic number representations.

Significantly, a majority of the papers that were included in the ALE meta-analyses used visual stimuli. Analyzing overlapping and distinct activation for number processing tasks, measured using different modalities at the meta-analytic level, would aid in evaluating abstract number representations. To date, there are not enough studies that measure number in the verbal, or tactile domains to form an ALE map that can be contrasted against a visual number processing maps. Consequently, additional empirical research is necessary to investigate the neural correlates of number processing in non-visual domains.

In addition to these differences in activation, a reliability analyses revealed that the nonsymbolic ALE map has more variability than the symbolic ALE map. More specifically, we examined the extent to which there were significant differences within formats, by randomly splitting the included contrasts in half and contrasting the two halves. One would predict that if the activations are highly consistent, then no differences in such an analysis should be observed. While we found this to be the case for symbolic number processing, the analyses of the nonsymbolic data revealed some significant variability. Specifically, the spilt half analysis of the nonsymbolic data revealed that in five out of the six contrasts revealed greater activation in one half of the nonsymbolic dataset compared to the other half. Given that the data were randomly split, conclusions regarding the potential processing differences between the two halves of the data cannot be made. However, it should be noted that the significant regions within the reliability analyses did not reveal systematic locations (i.e. there were regions across the frontal, parietal, and occipital lobes). This suggests that the lack of reliability in the nonsymbolic map was due to variable data across studies rather than systematic variability within specific brain regions.

The finding from the reliability analyse indicate, that the symbolic ALE map is more reliable than the nonsymbolic ALE map when using equivalent numbers of papers, and the same thresholds suggests that this distinction is a predicament of the data in the field rather than the methodology of the meta-analyses. This finding of differences in reliability of the symbolic and nonsymbolic map should be taken into account when considering the results of contrast analyses contrasting symbolic and nonsymbolic ALE maps. Specifically, regions that are more activated by nonsymbolic numbers compared to symbolic numbers should be interpreted with caution within the context of the current meta-analysis. Additionally, this finding should be considered when evaluating brain regions that correlate with nonsymbolic number processing within empirical studies. Overall, these reliability data provide valuable insights into underlying differences between format-dependent neural responses and set the foundation for future empirical research which needed to disentangle the difference in variability between symbolic and nonsymbolic number processing at the meta-analytic level.

The findings that symbolic numbers activated the bilateral inferior regions of the parietal lobe while nonsymbolic numbers activated right lateralized superior regions of the parietal lobe conflicts with the notion that the brain processes numbers using only a number module that is indifferent to number format. Instead, regions that are format specific may imply differential semantic processing of symbolic and nonsymbolic numbers. However, as meta-analyses do not include experimental manipulations, they cannot determine what brain regions subserve specific processes. This is important to consider with respect to the current meta-analytic contrasts because these contrasts alone cannot confirm that the areas revealed are really engaging in format-specific semantic processing. These regions of activation may reflect other processes that differ between formats. Although it is possible that specific regions activated by symbolic>nonsymbolic and nonsymbolic>symbolic reflect something other than format-specific processing, there are several aspects of the analysis that speak against this. First, all contrasts that were entered into the single file ALE maps contrast basic number processing against a control task that was matched in terms of perceptual and other non-semantic processing dimensions. Second, the symbolic and nonsymbolic passive ALE maps show similar differences. This suggests that the regions that are specifically activated by symbolic and nonsymbolic number processing are likely related to semantic differences between symbolic and nonsymbolic number processing. Ultimately, this question of format specificity in the human brain calls for further experimental investigation in order to understand the process of how the brain represents symbols compared to nonsymbolic numbers. In this way, the present meta-analysis may pave the way for new investigations into the specific nature of format-specific processing in the parietal cortex.

The concept of format-specific hemispheric specialization within the parietal lobes has previously been supported by developmental studies (e.g. Holloway and Ansari 2010). For example, researchers revealed increasing specialization of the left intraparietal sulcus for processing of symbolic numbers across development (e.g. Vogel et al. 2014) but consistent activation across children and adults in the right intraparietal sulcus for nonsymbolic numbers (e.g. Cantlon et al., 2006). The idea that this hemispheric asymmetry in the parietal cortex is a result of developmental specialization is further supported by a developmental quantitative meta-analysis that identified brain regions supporting symbolic and nonsymbolic number processing in children (Kaufmann et al. 2011). The results of this meta-analysis showed that the notation of the number (symbolic vs. nonsymbolic) influenced the location of neural activation patterns both within and outside the parietal lobes (Kaufmann et al. 2011). In accordance with the current meta-analyses, Kaufmann et al., (2011) showed that symbolic number magnitude processing was correlated with bilateral parietal activation while activation during nonsymbolic number processing was lateralized to the right parietal lobe. Together, these findings challenge the notion that the parietal cortex hosts a single system that processes number abstractly. Instead, it is probable that hemispheric specialization for number formats in the parietal cortex emerges over the course of development.

Beyond the parietal cortex, it has long been predicted that the ventral visual stream might house a number form area (NFA, Dehaene and Cohen 1995). In support of this prediction, the ALE passive symbolic map revealed activation in the ventral stream. However, contrary to this prediction, the contrast of symbolic > non-symbolic in the present meta-analysis did not reveal regions in the ventral visual stream that were more active for symbolic than non-symbolic processing of number. Therefore, this meta-analysis does not lend strong support to the NFA as no contrasts were able to reveal symbolic-specific activation. Recently, the existence of an NFA in the ventral stream was revealed using intracranial electrophysiological recording (Shum et al., 2013). This study also reported evidence to suggest that the region that was shown to exhibit category-selectivity for numerals is located within or near a zone in which there is a drop-out of the fMRI signal due to the auditory canal and venous sinus artifacts. Indeed, a recent study in which this fMRI signal drop out was reduced revealed category selectivity for numerals in bilateral regions of the inferior temporal gyri (Grotheer et al., 2016). It is possible, therefore, that the absence of evidence for an NFA in the current meta-analysis stems from an fMRI signal drop out masking category-selective activation for numerals in the ventral stream. Having said that, the evidence for the existence of an NFA is, to date, sparse and there is a need for more evidence using methods that control for the fMRI signal drop out in the inferior temporal gyrus. Once sufficient evidence has been accumulated, a meta-analytic approach, such as the one used in the present paper could be employed to quantify the consistency of evidence for the existence of the NFA.

4.2 The Three Parietal Circuits Model

Several different theories of numerical cognition propose potential mechanisms that may underlie mathematical abilities (Campbell, 1994; Dehaene et al., 2003; McCloskey, 1992). Among these theories is the three parietal circuits model (Dehaene et al., 2003) which is distinct from other theories because it makes specific predictions about the neuroanatomical underlying number processing. This is an influential, highly cited model that is often claimed to be predictive of empirical data (e.g. Neumärker 2000;

Schmithorst and Brown 2004). The current meta-analysis has the potential to further constrain existing theories, such as the three parietal circuits model, that propose potential mechanisms that underlie basic number processing. The three parietal circuits model (Dehaene et al., 2003), predicts that three distinct systems of representation are recruited for basic numerical processing and calculation tasks. These systems include a quantity system (which processes abstract numerical representations that are not related to number format), a verbal system (which represents numbers as words) and a visual system (which encodes numbers as strings of Arabic digits). Dehaene et al., (2003) used three-dimensional visualization software to examine how parietal activation related to this model. Using these qualitative meta-analytic data, they proposed that three distinct but functionally related networks coexist in the parietal lobes, and that these networks are used to support numerical processing. Briefly, the three parietal circuits model suggests that the bilateral horizontal segments of the intraparietal sulci are related to the quantity system, the left angular gyrus is related to the verbal system, and the posterior superior parietal lobules are related to the visual system, and specifically attention processes. For over a decade, this model has driven researchers to examine the neural underpinnings of basic number processing and calculation. This influential model has been both supported and challenged by empirical research (Chassy and Grodd, 2012; Eger et al., 2003; Piazza et al., 2007, 2004; Price and Ansari, 2011). Results of the current quantitative meta-analysis challenge several aspects of the three parietal circuits model. First, the finding from the conjunction analysis that reveals that both symbolic and nonsymbolic number processing activate the regions in the bilateral inferior parietal lobules and precuneus, and left superior parietal lobule challenges the notion put forward by Dehaene et al., (2003) that “the horizontal segment of the intraparietal sulcus (HIPS) appears as a plausible candidate for domain specificity” (p.487). Second, the finding that the left angular gyrus was specifically activated for symbolic numbers supports the idea that the left angular gyrus is related to the verbal system. This was supported by the contrast analysis from the current meta-analyses. However, the right supramarginal gyrus and inferior parietal lobule were also activated by symbolic>nonsymbolic number processing. Therefore, although it is possible that the activation in the left angular gyrus is related to the verbal system, which is likely used more by symbolic compared to nonsymbolic number processing, the activation in the right parietal lobe does not fit with this account. An alternative explanation is that these bilateral parietal regions are part of a format-specific number-processing region for symbolic number processing. Specifically, perhaps the left angular gyrus supports the verbal aspects of number processing while the right supramarginal gyrus and inferior parietal lobule support other aspects of symbolic number processing. In lieu of these results, perhaps the left angular gyrus supports the verbal processing and reading of symbols whereas the right supramarginal gyrus and inferior parietal lobule support processes that use this verbal symbolic knowledge and attentional processes to perform higher-level tasks such as calculation. This suggestion is consistent with results from the calculation meta-analysis (Arsalidou & Taylor, 2011), which report that the right angular gyrus is activated during calculation. Third, findings from the current meta-analysis both support and challenge the idea that activation in the superior parietal lobules is a consequence of attending to visual dimensions of numbers. Evidence from the conjunction analyses of the current meta-analyses showed that the left superior parietal lobule was activated for the conjunction of symbolic and nonsymbolic magnitude processing. Therefore, based on these findings, the left superior parietal lobule is an equally plausible candidate for domain specificity of number processing. Although, this convergence of activation could be due to a visual attention orienting response as proposed by Dehaene et al., (2003), the left superior parietal lobule was also found in the passive meta-analysis. Thus, there is superior parietal lobule activation even when the task demands, and therefore the attentional demands, are reduced. Importantly, the fact that nonsymbolic>symbolic was correlated with activation in the right superior parietal lobule conflicts with the idea that the superior parietal lobule supports only visual attention processes. Instead, these findings reveal hemispheric asymmetry in the bilateral superior parietal lobules that might suggest that the right superior parietal lobule hosts format-dependent representations of nonsymbolic numbers and the left superior parietal lobule hosts and abstract number processing region. One possible explanation for this finding is that the right superior parietal lobule is specifically correlated with visual attentional processes associated with nonsymbolic number tasks. Another possible explanation for the format-specific activation of the right intraparietal sulcus is that this region is associated with processes that are specific to non-symbolic numerical magnitude processing. Using a computational model, Verguts and Fias (2004) trained a neural network to map a symbolic or nonsymbolic numerical visual input onto a place-coded representation. Place-coding is a way of representing the cardinal value of the total number of items in a set by representing the quantity of the set as a place on a number line. In the computational model, symbolic inputs are mapped directly onto a place-coding representation. However, nonsymbolic inputs undergo an intermediate step between the nonsymbolic visual input and a place-coding representation. This intermediate step is referred to as summation coding. In summation coding, the size of the neural representation monotonically varies with the number of objects being presented. During this intermediate step, neurons accumulate proportionally to the number of objects that were visually processed. A large body of neuroscience evidence converges with these computational models suggesting that place-coded neurons exist within the primate brain (for review see, Nieder and Dehaene, 2009 or Nieder, 2013). These studies typically use single-cell recordings, monitoring individual neurons, while non-human primates discriminate between nonsymbolic arrays (e.g. Nieder and Miller, 2004; Nieder and Miller, 2003; Tudusciuc and Nieder, 2007). Overwhelming evidence indicates that the primate brain place codes numerosity (Andreas Nieder and Miller, 2004; Okuyama et al., 2015) even in monkeys that were never trained to discriminate numbers (Viswanathan and Nieder, 2013). Converging evidence from human fMRI adaptation studies revealed that tuned number neurons respond to dot arrays (Jacob & Nieder, 2009; Piazza et al., 2004). These tuned number neurons mirror place-coding neurons within the non-human primate brain (Jacob and Nieder, 2009).

Additionally, the existence of this type of summation coding has been found in humans both behaviourally (Roggeman et al., 2007) and at the neuronal level (Roggeman et al., 2011; Santens et al., 2010). In particular, neuroimaging studies have identified the right superior parietal lobule as a potential region that might support the process of accumulation during summation coding (Roggeman et al., 2011; Santens et al., 2010). Therefore, one possible explanation for activation in the right superior parietal lobule relating specifically to nonsymbolic number processing is that this region supports summation coding. Ultimately, these meta-analytic findings question the idea that the intraparietal sulcus hosts a system that processes numbers abstractly and the superior parietal lobule solely supports visual attentional processing.

It has been over a decade since the initial proposal of the three parietal circuits model. The results of the current quantitative meta-analysis do not converge with the data that support the three parietal circuits model (Dehaene et al., 2003). On the basis of these discrepancies, it is recommended that the three parietal circuits model should be updated. The parietal lobules should be canvased in search of regions that support both format-dependent and format-independent numerical representations. This will illuminate the extent to which format-specific regions reflect various components of format-specific processing including semantic, perceptual and decision making processing. Furthermore, the examination of brain regions that support format-dependent and format-independent numerical representations will clarify which regions in the intraparietal sulcus, inferior parietal lobule and superior parietal lobule are associated with various aspects of basic magnitude processing. This should ultimately illuminate the mechanism underlying magnitude processing in the parietal lobes.

4.3 Frontal vs. Parietal

During the last decade, there has been an intense focus on the parietal lobes as brain regions involved in number processing (e.g. Dehaene et al. 2003; Eger et al. 2003; Fias et al. 2003; Cohen Kadosh et al. 2007b; Cohen Kadosh and Walsh 2009). However, many neuroimaging studies reported activation in regions of the frontal cortex during number processing (e.g. Eger et al. 2003; Cohen Kadosh et al. 2007; Franklin and Jonides 2008; Cohen Kadosh and Walsh 2009; Dormal and Pesenti 2009; Dormal et al. 2012; Hayashi et al. 2013). The importance of the frontal cortex in number processing was revealed in research that used single-cell recordings in animals as well as in pediatric neuroimaging studies. Specifically, invasive single-cell recordings in non-human primates identified putative ‘number neurons’ in the parietal as well as the prefrontal cortex; these neurons responded to specific quantities (such as two dots) while animals performed a number discrimination task (Nieder, 2013; Nieder et al., 2002). These findings suggested that regions of the frontal cortex may host pure magnitude representations. Similarly, pediatric neuroimaging studies showed that young children recruited the prefrontal cortex more than adults during number discrimination tasks. In contrast, intraparietal sulcus activation during number comparison increased across development (Ansari et al., 2005; Kaufmann et al., 2006). Researchers suggested that this frontal to parietal shift from childhood to adulthood may reflect a decrease in the need for domain general cognitive resources such as working memory and attention as children begin to process number symbols automatically (Cantlon et al., 2009a, 2006; Venkatraman et al., 2005). The notion that regions in the frontal cortex are still important for number and calculation tasks among adults is further supported by a quantitative meta-analysis that identified brain regions supporting number processing and calculation in adults (Arsalidou and Taylor, 2011). Unlike the current meta-analysis, Arsalidou and Taylor, (2011) focused on calculation tasks such as arithmetic and subtraction tasks. Their meta-analysis showed that prefrontal regions are essential for number and calculation. Moreover, they revealed that activation in regions along the prefrontal cortex was related to the difficulty of the task. Specifically, IFG was activated during the processing of simple numerical tasks while the MFG and superior frontal gyrus were involved in more complex calculation problems (Arsalidou and Taylor, 2011). In view of this, Arsalidou and Taylor, (2011) suggested that this activation in the prefrontal cortex was a result of domain general processes, such as working memory, that are essential for number and calculation tasks. A common explanation for the consistent activation reported in the frontal cortex during number and calculation tasks was that the frontal cortex is activated in response to general cognitive processes associated with the task (e.g. Cantlon et al. 2006; Arsalidou and Taylor 2011). However, it has also been argued that frontal activation is supporting number representations rather than general cognitive processes (for a review see: Nieder and Dehaene, 2009).

The current meta-analysis lends additional support to the idea that frontal activation is important for number processing during basic number tasks. Results revealed consistent activation in frontal regions during symbolic and nonsymbolic number processing. Moreover, results showed that neural activation in response to number processing is no less consistent in the frontal cortex than in the parietal cortex. In particular, the single dataset ALE maps revealed that the superior frontal gyrus was consistently activated during symbolic magnitude processing and the right medial frontal gyrus and cingulate gyrus were activated during nonsymbolic magnitude processing. The right superior frontal gyrus was also activated in the conjunction analysis of symbolic and nonsymbolic and specifically for nonsymbolic number processing the contrast analyses comparing nonsymbolic>symbolic. The current meta-analysis deliberately included only basic magnitude processing tasks in order to minimize the recruitment of additional cognitive resources typically needed for complex calculation tasks. Additionally, all contrasts included in the current meta-analysis were contrasted against control conditions. These attributes make it likely that the activation revealed in the current meta-analyses is related, at least in part, to magnitude representations. The superior frontal gyrus was also found to activate to complex calculation tasks (Arsalidou & Taylor, 2011), however the location of activity differs such that complex calculations elicit activity in anterior parts of the superior frontal gyrus (BA 10), whereas basic number tasks elicit activity in superior frontal gyrus (BA 6), a region often associated with the premotor cortex. Further evidence for the idea that the frontal cortex may support magnitude representations comes from the contrast analyses, which revealed that the right superior frontal gyrus was specifically activated by nonsymbolic numbers but not by symbolic numbers. The specificity of frontal activation for nonsymbolic numbers suggests that this right lateralized frontal region may be essential for identifying the number of objects within a set. Therefore, similarly to activation in the parietal cortex, the activation patterns within the frontal cortex vary as a function of format (symbolic vs. nonsymbolic. Together, the data from the current meta-analysis offer no reason to think that the parietal cortex is more specialized for number than the frontal cortex.

Although the pattern of frontal activation suggests that the superior frontal gyrus may support basic number processing, the fact that many of the studies included in the symbolic and nonsymbolic meta-analyses were active tasks, and therefore had general cognitive processes such as decision-making, precludes the conclusion that the superior frontal gyrus supports magnitude representations rather than general cognitive processes. To overcome this limitation, single file ALE meta-analyses were computed to examine converging activation of studies that used passive tasks. These single file passive maps are essential to illuminate which brain regions are activated by responding to a task. The brain activation that was associated with passive symbolic and nonsymbolic numerical tasks was consistent with activation revealed in the ALE contrast maps comparing symbolic and nonsymbolic maps of activation that included both passive and active tasks. Specifically, both the active and passive maps and passive only maps revealed bilateral activation in the left superior parietal lobule and precuneus and the right inferior parietal lobule and precuneus as well as the left cingulate gyrus for symbolic and nonsymbolic number processing. Although the current study did not have enough power to statistically contrast the passive symbolic and passive nonsymbolic maps, the qualitative comparison of the passive symbolic and passive nonsymbolic single file ALE maps depicted in Figure 6 is consistent with the contrast analyses symbolic>nonsymbolic and nonsymbolic>symbolic. Specifically, the passive symbolic map reveals activation in the left precuneus and the left fusiform gyrus and the passive nonsymbolic ALE map reveals activation in the right precuneus, left superior parietal lobule, and left middle occipital gyrus. The cluster of activation is larger in the right parietal lobule compared to the left parietal lobule. Therefore, similarly to the contrast analyses that included both passive and active conditions, a qualitative comparison of passive symbolic and passive nonsymbolic single file ALE maps reveals trends of lateralization. Specifically, passive single file ALE meta- analyses suggest that symbolic numbers activate the left parietal lobe and nonsymbolic numbers activate a larger region in the right parietal lobe. Therefore, the passive maps reflect similar patterns of activation to the active and passive single file maps as well as the contrasts for both symbolic and nonsymbolic number processing. Together, these passive maps suggest that activation in the bilateral parietal cortex and the left cingulate gyrus may be related to format-dependent and independent magnitude processing, rather than task demands.

Taken together, the present meta-analysis does not support the argument that frontal regions are involved in task demands while parietal regions are involved in semantic processing. Instead, these data indicate that both the frontal cortex and the parietal cortex may be involved in general cognitive processes associated with number tasks and magnitude representations. Ultimately, the field of numerical cognition needs to acknowledge that frontal regions are consistently engaged, even during basic number processing, and in accordance with this, reduce biases towards parietal activation.

4.4 Limitations and Advantages of ALE

As the present study used ALE methodology, it is important to note several specific limitations with ALE such as difficulty accounting for differences in statistical thresholding approaches across studies and difficulty determining the spatial extent and magnitude of the activation for each focus (for a more detailed discussion of these limitations: Ellison-Wright et al. 2008; Christ et al. 2009; Di Martino et al. 2009; Arsalidou and Taylor 2011). Additionally, as ALE uses data from fMRI and PET studies, it is important to consider that the blood-oxygen-level-dependent (BOLD) signal and the PET signal are indirect signals. Specifically, the PET signal and BOLD response estimate brain activity by detecting changes associated with blood flow (Logothetis, 2003). Moreover, these indirect signals are typically corrected for motion, smoothed, and averaged across participants. Therefore, at best, these signals only reveal mass activation of a brain region, and not individual neuronal firing (see Scott and Wise, (2003) for a more detailed critical appraisal of functional imaging). Since fMRI and PET detect an indirect mass signal that is smoothed across a large number of neurons in the brain, and averaged across subjects, it is likely that one region of activation within a single empirical study, represents several neural networks (Nieder, 2004). This idea is supported by data in primates that revealed that less than 20% of neurons in the intraparietal sulcus responded to numbers(Nieder and Miller, 2004). This is particularly important to consider when examining which brain regions support numbers abstractly versus a format-dependent manner. Therefore, when interpreting the results of the current meta-analysis, it is perhaps more accurate to argue that regions which seem to process numbers abstractly, contain a larger number of "abstract number-selective neurons," whereas regions that are sensitive to number format have a larger number of "format-dependent number-selective neurons." As the field of functioning imaging develops, future research will be needed to more precisely examine abstract and format-dependent regions at the neuronal level in humans.

Despite these limitations, ALE has several important advantages as a tool for synthesizing neuroimaging data. Particularly, the algorithms that underlie ALE allow for the quantification of foci among empirical papers with varying methodologies. For example, this method can account for differences in the number of runs, the duration of the presentation of the stimuli and the type of design (e.g. block vs. event related). It is likely that this diversity in methodologies is one of the main drivers of conflicting findings often reported between studies. Additionally, because neuroimaging research is so costly, the majority of empirical studies have small sample sizes. ALE groups different studies with varying methodologies by domains in order to increase sample sizes and ultimately address broader theoretical questions. Overall, ALE is a valuable meta-analytic tool that can quantitatively integrate large amounts of neuroimaging data to reveal converging patterns of findings.

5. Conclusions

In conclusion, this meta-analysis has reaffirmed the body of research suggesting that the ability to process numbers relies on a large number of brain regions. This quantitative meta-analysis shows that overlapping and distinct regions in the frontal and parietal lobes are activated by symbolic and nonsymbolic numbers, revealing the specific roles of parietal and frontal regions in supporting number processing. The finding that several neural regions were activated by the conjunction of symbolic and nonsymbolic number maps supports the notion that the human brain represents numbers abstractly. This study also illuminates the lateralization of symbolic compared to nonsymbolic number processing within the parietal lobes. Specifically, the left angular gyrus is potentially important for the mapping of symbols onto quantities (nonsymbolic numbers) while the right superior parietal lobule may be important for processing nonsymbolic sets of items. The lateralization of symbolic and nonsymbolic number is an intriguing avenue for future research. Additionally, this research highlights the consistency of activation within the frontal cortex during number processing. Ultimately, the current meta-analysis extends our understanding of the brain regions associated with basic number processing and initiates future research on the neural mechanisms that underlie our essential ability to comprehend numbers.

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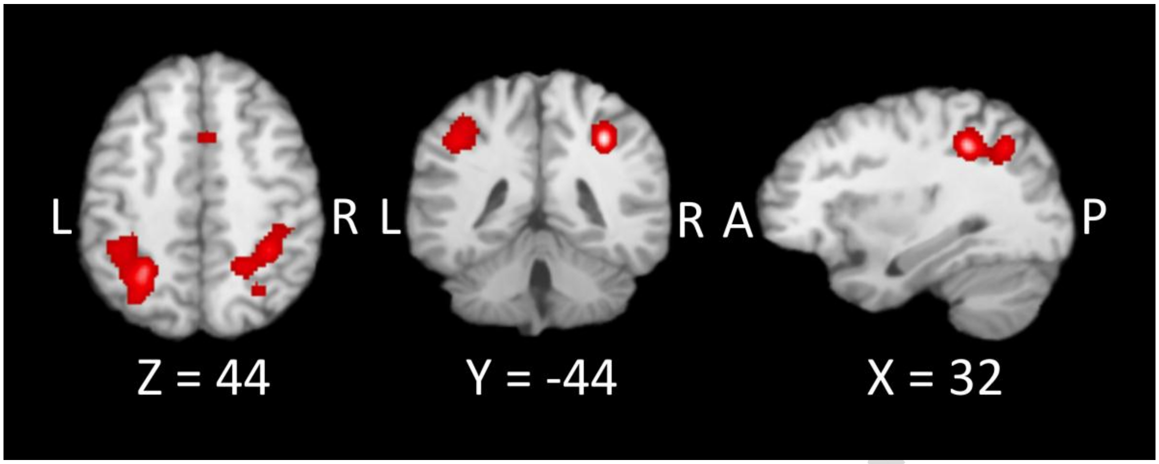
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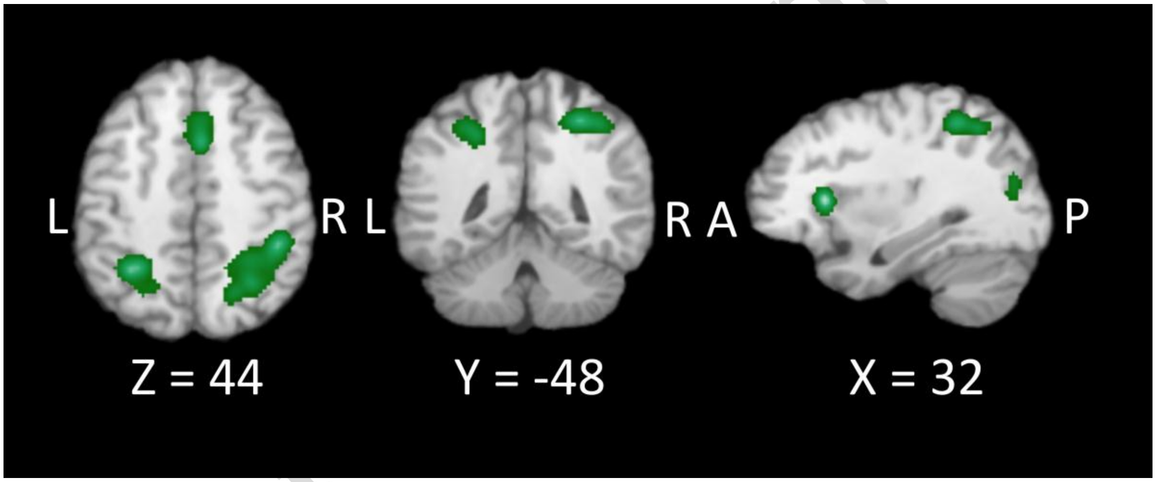
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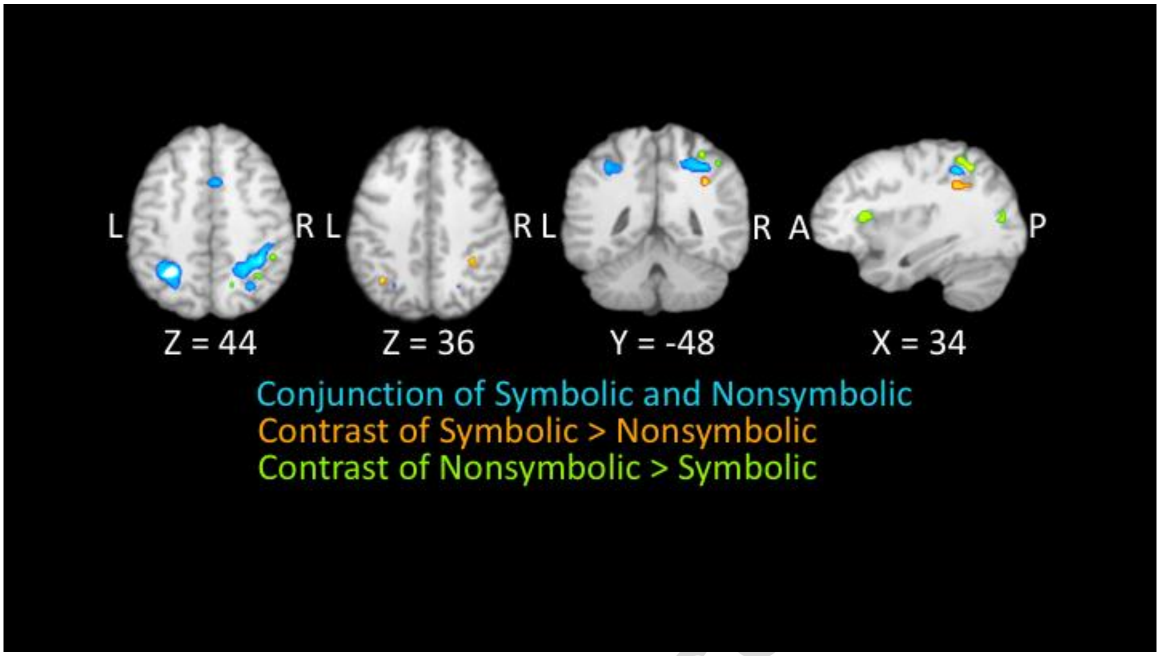
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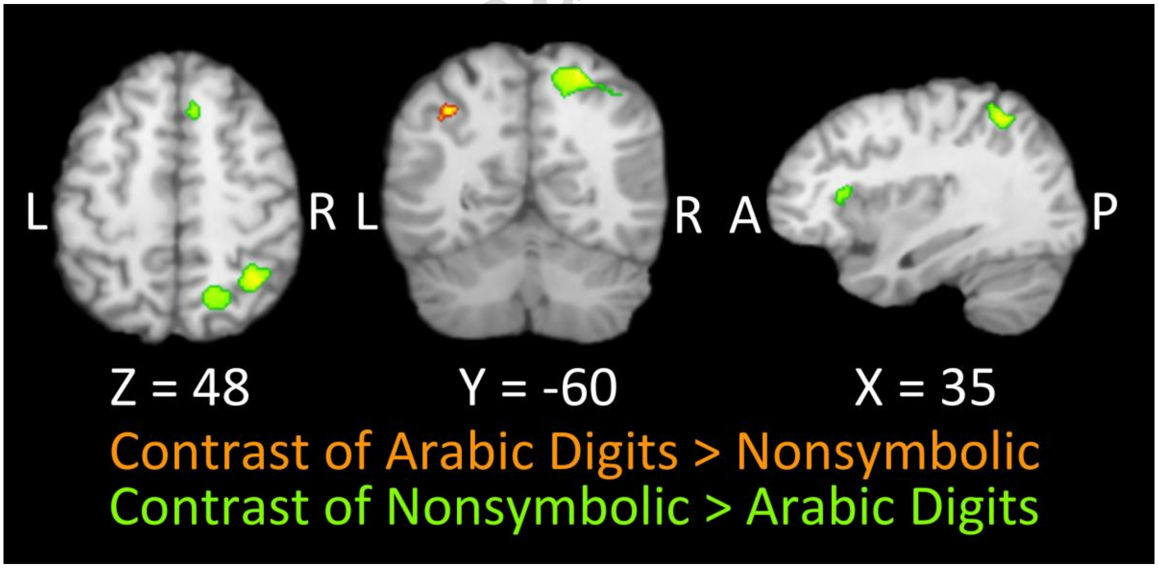
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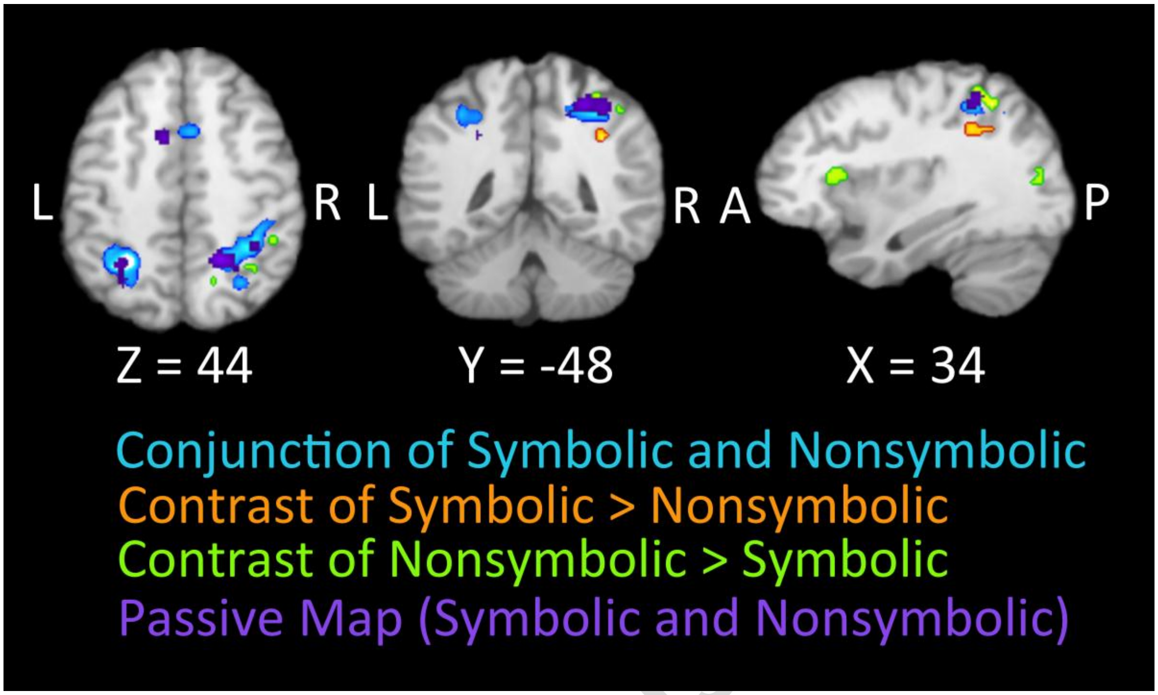
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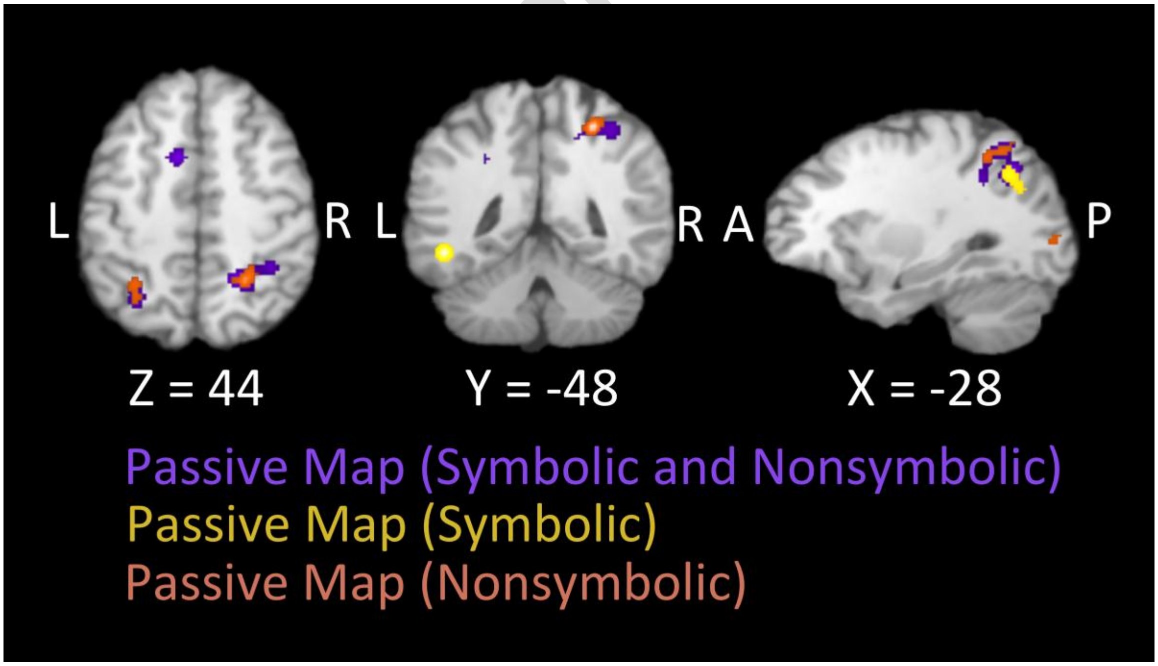
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