



## Review article

## The search for the number form area: A functional neuroimaging meta-analysis

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## ABSTRACT

Recent studies report a putative “number form area” (NFA) in the inferior temporal gyrus (ITG) suggested to be specialized for Arabic numeral processing. However, a number of earlier studies report no such NFA. The reasons for such discrepancies across studies are unclear. To examine evidence for a convergent NFA across studies, we conducted two activation likelihood estimation meta-analyses on 31 and a subset of 20 neuroimaging studies that have contrasted digits with other meaningful symbols. Results suggest the potential existence of an NFA in the right ITG, in addition to a ‘symbolic number processing network’ comprising bilateral parietal regions, and right-lateralized superior and inferior frontal regions. Critically, convergent localization for the NFA was only evident when contrasts were appropriately controlled for task demands, and does not appear to depend on employing methods designed to overcome fMRI signal dropout in the ITG. Importantly, only five studies had foci within the identified ITG NFA cluster boundary, indicating that more empirical evidence is necessary to determine the true functional specialization and regional specificity of the putative NFA.

## 1. Introduction

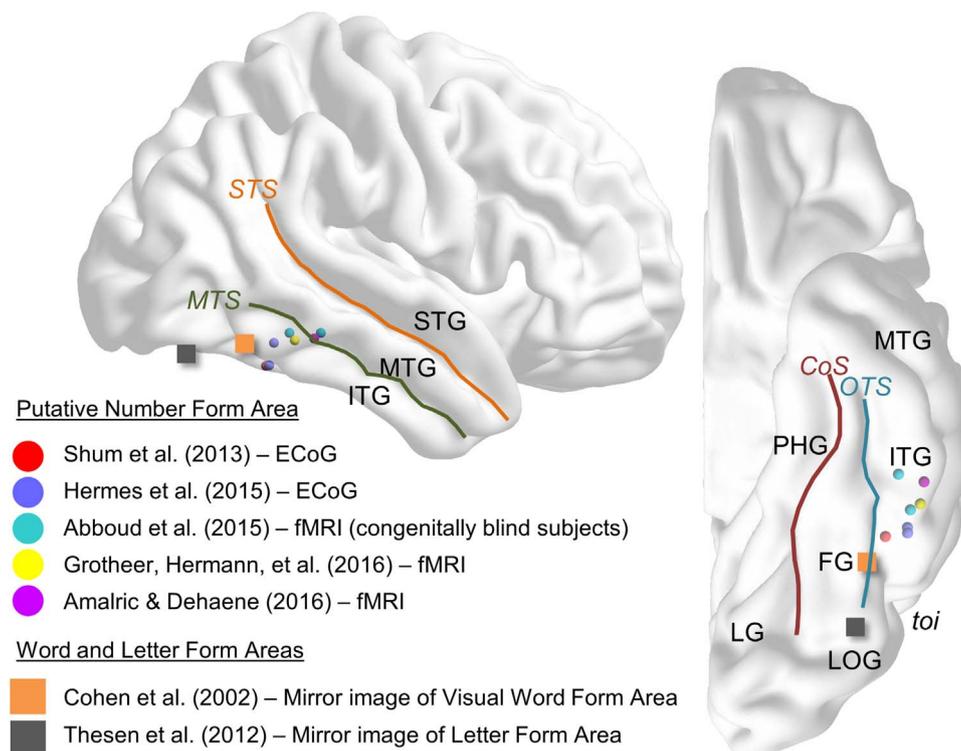
Numbers are one of the most ubiquitous written symbol systems in the modern world. Relative to the 200,000 years of existence of modern humans, the oldest written numeration systems are only approximately 5500 years old (Chrisomalis, 2010). The modern-day digits ‘0’ to ‘9’ of the Hindu-Arabic numeral system are an even more recent invention that were introduced to the Western world as late as the 12th century, and adopted worldwide only several centuries later (Chrisomalis, 2010; Smith and Karpinski, 1911). Despite their relative youth, numbers and the fields of study they enable have allowed the development of astonishing advances in human civilization, from medicine to computing to space travel. The last twenty years have seen a tremendous growth in research on numerical cognition, aimed at understanding how the human brain processes numbers in different formats (i.e., nonsymbolic and symbolic), the quantities they represent, and the mathematical science they support. At the same time, a significant body of research suggests that efficient Arabic numeral processing is an important predictor of children’s mathematical skills (Bugden and Ansari, 2011; Defever et al., 2011; Holloway and Ansari, 2009; Lonnemann et al., 2011; Mundy and Gilmore, 2009). However, despite their evident importance, little is known about how the human brain comes to instantiate Arabic numerals as symbols of numerical informa-

tion. While a number of neuroimaging studies have employed Arabic numerals as stimuli, there is little to no consensus regarding the existence of a neural network specific to the processing of symbolic numbers. A deeper understanding of the ‘symbolic number processing network’ in typically developing adults is a crucial first step towards understanding its typical and atypical development, and the role it plays in the development of symbolic mathematical skills. The present meta-analysis therefore investigates whether across studies and task contexts, there exist common neurocognitive mechanisms that are specialized for Arabic numeral processing, and if so, where those mechanisms are located.

Guiding a substantial amount of research in numerical cognition over the past two decades is the Triple-Code Model (Dehaene, 1992; Dehaene and Cohen, 1995). The neuropsychology-based model posits that numbers are processed in three distinct representations. First, a visual “Arabic number form” code that represents numbers visuo-spatially as an ordered string of Arabic digits (e.g., ‘27’ as ‘2’ ‘7’ instead of ‘7’ ‘2’), and is assumed to be subserved by specialized visual object recognition regions in the bilateral ventral occipitotemporal cortex (vOTC; see Fig. 1). Second, a “verbal word frame” code that represents numbers as syntactically structured sequences of words (e.g., ‘twenty-seven’ or ‘2 tens 7 ones’), as well as a verbally learned count sequence and arithmetic facts. The verbal code is assumed to be subserved by the

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**Fig. 1.** Anatomy of the lateral temporal and ventral occipitotemporal cortices in the right hemisphere, and illustrations of the putative number form area, as well as mirrored locations of the left-hemispheric visual word form and letter form areas. STG: Superior temporal gyrus. MTG: Middle temporal gyrus. ITG: Inferior temporal gyrus. STS: Superior temporal sulcus. MTS: Middle temporal sulcus. OTS: Occipitotemporal sulcus. CoS: Collateral sulcus. *toi*: Temporo-occipital incisure. FG: Fusiform gyrus. PHG: Parahippocampal gyrus. LG: Lingual gyrus. LOG: Lateral occipital gyrus. ECoG: Electrocochography. fMRI: Functional magnetic resonance imaging. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

left-hemispheric perisylvian language regions extending to the temporoparietal junction, comprising the angular and supramarginal gyri (Dehaene, 1992; Dehaene and Cohen, 1995; Dehaene et al., 2003). Third, an “analogue magnitude” code that allows us to represent, estimate, compare, and manipulate nonsymbolic numerical magnitudes, is assumed to be subserved by the bilateral intraparietal sulci (Dehaene, 1992; Dehaene and Cohen, 1995; Dehaene et al., 2003).

A considerable proportion of numerical cognition research has focused on the magnitude and verbal codes, finding consistent empirical support for neural circuits underlying those two representational codes (for reviews and meta-analyses, see Ansari, 2008; Arsalidou and Taylor, 2011; Cohen Kadosh et al., 2008; Dehaene et al., 2003; Houdé et al., 2010; Kaufmann et al., 2011; Moeller et al., 2015; Sokolowski et al., 2017; Zamarian et al., 2009). In contrast, there has been a paucity of research investigating the visual “Arabic number form” code. Hence, little is currently known about the neural mechanisms that enable the processing of Arabic numerals as visual objects and symbols of numerical magnitude that we use effortlessly to compare and order quantities, and perform arithmetic with.

The proposition of an “Arabic number form” code suggests the existence of a putative ‘number form area’ (NFA) in a region of the vOTC that is specialized for the processing of Arabic numerals (i.e., it is engaged by Arabic numerals more than other learned written symbols and novel written characters). Such localization for an NFA would be logical, given that there are regions in the human vOTC thought to have evolved for the processing of highly frequent visual stimuli, such as faces and body parts (Kanwisher, 2010). Indeed, there is a large body of evidence for category specificity in the vOTC for visual categories such as faces (Kanwisher et al., 1997) and body parts (Downing et al., 2001), and such functionally specialized regions have also been observed in non-human primates (Tsao et al., 2003; Yovel and Freiwald, 2013). In contrast, relative to the pace of neural evolution in hominids, the ‘recent’ cultural invention of writing and reading provides insufficient

time for specific brain regions to become specialized for visual symbol recognition through the process of natural selection. Nonetheless, the discovery of a putative “visual word form area” (VWFA; see Fig. 1) in the left mid-fusiform gyrus (FG), which has a preferential response to visually presented words versus pseudowords (Cohen et al., 2000, 2002; McCandliss et al., 2003; for a review, see Dehaene and Cohen, 2011) – as well as a less-discussed, and more posteriorly localized “letter form area” (Thesen et al., 2012) – suggests that ontogenetic experience is sufficient to drive specific brain regions to become progressively specialized for processing visual symbols (Dehaene and Cohen, 2007; Kanwisher, 2010). Apart from the broader question of modularity in the brain (Karmiloff-Smith, 2015), the existence of the VWFA has been controversial (see Cohen and Dehaene, 2004; Dehaene and Cohen, 2011; Price and Devlin, 2003, 2011; for the discussion). Moreover, there is increasing evidence that orthographic processing subserved by the VWFA is dependent on higher-level language representations based in left-hemispheric perisylvian language regions (Bouhali et al., 2014; Saygin et al., 2016). This suggests that the VWFA may not be as functionally independent as other category-specific vOTC regions such as the “fusiform face area”. As Arabic numerals are also a recent invention relative to the evolution of the human brain, the possibility of an NFA, and its role as an independent functional module ought to be questioned (for a recent discussion see Merkle et al., 2016).

If an NFA does exist, to what extent is the NFA spatially distinct from the VWFA? Neuropsychological evidence thus far has been mixed in its support for distinct visual symbol processing regions. Starrfelt and Behrmann (2011) reviewed neuropsychological studies conducted on pure alexia (i.e., an impaired ability to read but not write) since 1892, and found no consistent evidence for a strong dissociation between number- and letter-reading impairment due to temporal lobe (mainly left) lesions. However, they noted that it could be due to a lack of detailed reporting of assessment methods and findings in many studies,

and that by and large, patients with impaired letter or word identification almost always show impaired digit identification, albeit often less severely. Starrfelt and Behrmann (2011) then hypothesized that numbers are inherently easier to identify than letters even in typically developing individuals, which might underlie the differential numeral and letter processing performance observed in the patients with alexia. In a follow-up empirical investigation, they found that that was indeed the case. Nonetheless, their findings do not preclude the possibility of spatially distinct NFA and VWFA that are close in proximity within a lesion site, or the possibility that there is more than one site of each form area. Neither do their findings preclude the possibility that each symbol form area functions interactively with other cortical regions within a processing circuit that takes into account both bottom-up visual and top-down semantic inputs (Plaut and Behrmann, 2011; Price and Devlin, 2011). For instance, stimulation-induced impairments to regions other than the vOTC, such as left supramarginal gyrus and left inferior frontal gyrus, may also selectively impair processing of Arabic numerals, but not words (Roux et al., 2008). In other words, the vOTC may be critical for visual symbol processing, but it is not the only cortical region involved. Given the apparent existence of a VWFA, and neuropsychological findings revealing a trend of dissociation in processing Arabic numerals and letters/words (Starrfelt and Behrmann, 2011), it is therefore reasonable to hypothesize that an NFA may exist, and if it does exist, that it would be located in the vOTC.

fMRI has been an effective and widely-used method for revealing regions in the vOTC that are thought to be functionally specialized in the identification of faces, body parts, places, and words (Kanwisher, 2010) due to its combination of non-invasive, whole-brain spatial coverage, and spatial resolution. Given that the VWFA can easily be localized using fMRI, and that numerical symbols are at least as ubiquitous as letters, it is reasonable to assume that the NFA can also be detected using the same method. However, while some studies report evidence for an NFA, many fMRI studies have failed to find such a functionally specialized region for Arabic digits in the vOTC (see Table 1), despite many of them having sufficient sensitivity to localize other visually-selective object processing regions, such as the VWFA, within the same sample. Thus, the question of whether a specialized NFA exists in the vOTC remains open.

The role of the vOTC in Arabic numeral processing may also be revealed by methods other than fMRI. In an intracranial electrostimulation study with 53 brain-lesion or epileptic patients, Roux et al. (2008) demonstrated that stimulation of a region in the left posterior inferior temporal gyrus (ITG) impaired Arabic numeral recognition, but not naming and reading of number words and sentences. More recently, using intracranial electrophysiological recordings in seven epileptic patients, Shum et al. (2013) identified a spatially consistent region in the right – and, to a lesser extent, left – posterior ITG (see Fig. 1), that demonstrated a preferential response to Arabic numerals compared with control stimuli that are morphologically, semantically, and phonologically similar. In a follow-up fMRI experiment with healthy subjects, the authors found that the NFA falls close to, or within a region that is highly prone to fMRI signal dropout, due to air-tissue boundary artifacts from the auditory canal and venous sinus. This led Shum et al. (2013) to suggest that previous fMRI studies had failed to observe an NFA in the vOTC because of a methodological limitation specific to fMRI, namely, signal dropout. The signal-dropout hypothesis was further supported by subsequent fMRI studies that found a numeral-selective region in the ITG after attempting to overcome low signal-to-noise ratio in the region with advanced imaging and data preprocessing techniques (Abboud et al., 2015; Amalric and Dehaene, 2016; Grotheer et al., 2016b; see Fig. 1 for other localizations of the NFA). However, several prior fMRI studies have found preferential activation for Arabic numerals in the vOTC, or even specifically within the ITG, without the use of advanced imaging and data preprocessing methods (see Table 1). Therefore, while signal dropout may account for some prior null findings, it does not necessarily account for all null

Table 1

fMRI and PET studies that contrasted Arabic numerals with other meaningful written symbols.

| Excluded from current meta-analyses                        | Included in current meta-analyses                             |   |
|--|---|---|
| No numeral-specific activation found anywhere in the brain | Numeral-specific activation within the vOTC                   | Numeral-specific activation only outside the vOTC |
| 1. Anderson et al. (2015)                                  | 1. Amalric and Dehaene (2016) – Bilateral ITG                 | 1. Andres et al. (2012)                           |
| 2. Baker et al. (2007)                                     | 2. Basso et al. (2003) – Bilateral FG                         | 2. Andres et al. (2011)                           |
| 3. Canton et al. (2011)                                    | 3. Coderre et al. (2009) – Left FG                            | 3. Attout et al. (2014)                           |
| 4. Cohen Kadosh et al. (2007a)                             | 4. Cui et al. (2013) – Right ITG                              | 4. Cappelletti et al. (2010)                      |
| 5. Fulbright et al. (2003)                                 | 5. Cummine et al. (2015) – Right ITG                          | 5. Carreiras et al. (2015)                        |
| 6. James et al. (2005)                                     | 6. Fernandes et al. (2005) – Left FG                          | 6. Chochoy et al. (1999)                          |
| 7. Koul et al. (2014)                                      | 7. Fias et al. (2007) – Left FG                               | 7. Cummine et al. (2014)                          |
| 8. Polk and Farah (1998)                                   | 8. Grotheer et al. (2016a,b) – Bilateral ITG and bilateral FG | 8. Holloway et al. (2015)                         |
| 9. Polk et al. (2002)                                      | 9. Gullick and Temple (2011) – Right ITG                      | 9. Libertus et al. (2009)                         |
| 10. Reinke et al., 2008                                    | 10. Knops et al. (2006) <sup>a</sup> – Right FG               | 10. Park et al. (2012)                            |
| 11. van der Ven et al. (2016)                              | 11. Pinel et al. (2001) – Right FG                            | 11. Peters et al. (2015)                          |
|  | 12. Pinel et al. (1999) – Right ITG                           | 12. Pinel et al. (2004)                           |
|  |   | 13. Price and Ansari (2011)                       |
|  |   | 14. Stanesco-Cosson et al. (2000)                 |
|  |   | 15. Wu et al. (2009)                              |
|  |   | 16. Yin et al. (2015)                             |
|  |   | 17. Zago et al. (2008)                            |
|  |   | 18. Zarnhofer et al. (2012)                       |
|  |   | 19. Zhang et al. (2012)                           |

Note. fMRI: functional magnetic resonance imaging. PET: positron emission tomography. vOTC: ventral occipitotemporal cortex. FG: fusiform gyrus. ITG: inferior temporal gyrus.

<sup>a</sup> Excluded from the meta-analyses as stereotaxic coordinates were not provided for the contrast of interest.

findings related to the NFA. The inconsistent evidence for an NFA across prior studies thus requires further investigation and explanation.

Previous coordinate-based meta-analyses of neuroimaging studies of numerical processing have revealed convergence of functional activation in the vOTC (Arsalidou and Taylor, 2011; Kaufmann et al., 2011; Sokolowski et al., 2017). However, several of those meta-analyses grouped both symbolic and nonsymbolic numerical stimuli under an umbrella term “numbers”, rendering it impossible to claim that vOTC convergence was specific in any way to numerical symbols. Furthermore, the convergence reported in those analyses was more medial than the NFA location reported by Shum et al. (2013), centering on the FG as opposed to the ITG. Sokolowski et al. (2017) were the first to examine symbolic and nonsymbolic number processing independently in a meta-analysis. Specifically, their goal was to reveal concordant activation related to explicit and automatic magnitude processing that is either format-dependent or format-independent. That study did not find evidence for an NFA in the ITG when contrasts using Arabic numerals only were analyzed. However, this may be due to the fact that the authors considered a range of contrasts with varying degrees of control stimuli and also with varying task demands relative to the tasks involving Arabic numerals, such as “numbers > body parts/shapes/letters/scrambled numbers”, “symbolic number comparison > nonsymbolic number comparison”, “symbolic magnitude comparison > letter/digit naming”, and “small number comparison > large number comparison”. Of concern in any investigation of functional specialization in processing a particular visual stimulus category is the extent to which the manipulation of the numerical and non-numerical control tasks (e.g., symbolic number comparison > letter naming) reflects the difference in stimulus category (hereafter referred to as ‘contrast specificity’). Low contrast specificity may include unnecessary noise

(i.e., activations of non-interest) in a meta-analytical procedure and decrease its sensitivity. For instance, in an object-naming meta-analysis, Price et al. (2005) found enhanced sensitivity to activation in regions associated with semantic processing, visual-speech integration, and response selection with high-level baseline conditions (e.g., object naming > face orientation) that controlled for speech and perceptual processing than with low-level baseline conditions that did not control for those (e.g., object naming > fixation). It is thus unclear if there exists a convergence in the vOTC during number processing when Arabic numerals are contrasted only with other meaningful written symbols and with comparable task demands. If an NFA exists, and is specific to Arabic numerals rather than written symbols in general, it should evidence functional specialization by activating more strongly for Arabic numerals than other meaningful written symbols, across a range of task contexts. Alternatively, the engagement of an NFA may be highly task-dependent and a convergence in the vOTC may be attenuated by task demands, which will be further addressed in the discussion.

It is clear, therefore, that evidence for an NFA is inconsistent at present. However, based on some of these most recent positive findings, qualitative reviews have made affirmative statements regarding the reproducible localization of an NFA in the vOTC (Hannagan et al., 2015; Piazza and Eger, 2016). Whether or not the extant body of functional neuroimaging literature does in fact support the existence of an NFA requires further quantitative investigation.

## 2. Current study

To investigate whether the extant literature supports a reproducible localization of an NFA that is functionally specialized for the visual processing of Arabic numerals we conducted two activation likelihood estimation (ALE) meta-analyses of the existing body of neuroimaging studies that contrasted the visual presentation of Arabic numerals with other meaningful written symbols across a variety of tasks in healthy individuals. As both maturation and learning experience are critical for shaping visual category-selective processing over development (Cantlon et al., 2011; Libertus et al., 2009; Polk and Farah, 1998; Schlaggar and McCandliss, 2007), the current study focused on adults, for whom the degree of category-selective neural activity in the vOTC should be well established.

To be maximally inclusive in our analysis, we adopted liberal inclusion criteria with varying degrees of contrast specificity as long as Arabic numerals were contrasted with at least one other symbolic category (e.g., number comparison > letter naming). We predicted that a more liberal set of contrasts would increase the chances of revealing a convergence of activation in an NFA, especially if evidence of its activation is weak due to signal loss complications. It is also possible, however, that the inclusion of less specific contrasts in the meta-analysis may lead to 'noisy' results (Price et al., 2005), potentially masking or washing out convergence in an NFA (see Section 3.2.3 for an explanation). The inclusion of less specific contrasts may also reveal brain regions other than the NFA related to differential task demands between the numerical and non-numerical tasks, but not to the stimulus properties per se. Therefore, we conducted a second meta-analysis using more stringent criteria to include only contrasts that have equivalent task demands between the numerical and non-numerical conditions (e.g., digit matching versus letter matching). Moreover, by controlling for task demands, the second meta-analysis also aimed to increase the specificity of brain regions that are unique to Arabic numeral processing, over and above differences in general cognitive processes such as attention and working memory (i.e., a 'symbolic number processing network').

## 3. Methods

### 3.1. Literature search and article selection

We used a multi-step approach to identify relevant articles. First, a literature search was made in the following databases: PsycINFO (1806–2016), PubMed (1950–2016), Web of Science (1965–2016), ScienceDirect (1823–2016), and Google Scholar until October 2016. To identify journal articles and book chapters that have empirically examined symbolic number processing relative to other meaningful symbols, or have reviewed the empirical evidence for visual number form processing, search terms included (“number form” OR “visual Arabic” OR “visual number” OR “numeral” OR “digit” OR “symbolic number” OR “number symbol” OR “Arabic digit”) AND (“fMRI” OR “functional magnetic resonance imaging” OR “PET” OR “positron emission tomography”).

A study was included if it met the following criteria: (1) published in English language peer-reviewed journals, (2) sample comprised healthy human adults, (3) conducted whole-brain, within-group analyses using fMRI or PET to minimize any bias towards predefined regions of interest, (4) employed tasks that contrasted the visual processing of Arabic numerals with at least one other category of written symbols that are orthographically and semantically familiar to the participants (e.g., letters of the Roman alphabet for English speakers, including Roman numerals, scripts of foreign languages such as Chinese and Japanese characters for Chinese or Japanese speakers respectively, and presumably universally known non-alphanumeric symbols such as \$, %, &, etc.), and (5) reported the coordinates of activation maxima in standardized stereotaxic space such as the Talairach (Talairach and Tournoux, 1988) or Montreal Neurological Institute (MNI) templates. For criterion (4), the control categories against which Arabic numerals were compared to may also include nonsymbolic categories (e.g., false fonts and objects), as long as response profiles were provided to illustrate significantly greater activation of the regions of interest to Arabic numerals than to all other symbolic and nonsymbolic control stimuli (e.g., Amalric and Dehaene, 2016; Grotheer et al., 2016b). In other words, the control conditions could include nonsymbolic stimuli, but they could not be the only control in the contrast. Moreover, to be as comprehensive as possible, identifying an NFA did not have to be the primary theoretical focus of a study to be included in the meta-analyses. As a main goal of this study is to search for a convergence of studies on an NFA, we were liberal in selecting studies that had a non-numerical control task with cognitive demands different than the numerical tasks, as long as the control stimuli used were meaningful written symbols.

Another goal of this study was to investigate the category specificity of an NFA, that is, its preferential response to Arabic numerals relative to other meaningful written symbols. Therefore, for both meta-analyses in this study, we excluded studies that contrasted Arabic numerals with *only* false fonts, nonsymbolic dot arrays, shapes, body parts, or fixation/rest. Studies in which no supra-threshold activation was found for Arabic numerals relative to other meaningful symbols were excluded, as the ALE approach assesses spatial convergence across studies given that there is *some* supra-threshold activation somewhere in the brain (see Table 1). For studies in which the relevant contrasts were performed, but did not report the full list of coordinates, attempts were made to obtain the necessary data, if available; otherwise, they were excluded. We also excluded reviews, meta-analyses, case studies, studies that only presented auditory stimuli (e.g., Abboud et al., 2015, which also used Roman numerals instead of Arabic numerals), and studies that presented auditory and visual stimuli separately, but reported only supramodal contrasts for digits versus letters (e.g., Eger et al., 2003). An exception were studies that presented auditory and visual stimuli simultaneously, and required conscious processing of the visual symbols presented (Fernandes et al., 2005; Holloway et al., 2015).

Secondly, we crosschecked the reference lists of all the relevant

**Table 2**  
Participant demographics, tasks, contrasts, foci of interest, and statistical threshold for the fMRI studies included in meta-analyses I and II.

| Study                                 | Reference                          | N               | Task(s)   | Selected contrast(s)   | Foci                                    | Statistical Threshold  |
|---------------------------------------|------------------------------------|-----------------|---|--|---|--|
| <b>Included in both meta-analyses</b> |                                    |                 |   |  |   |  |
| 1                                     | Amalric and Dehaene (2016)         | 30              | 1-back same/different judgment  | Decimals > Checkers, faces, bodies, tools, houses, mathematical formulas, and words  | 16 <sup>a</sup>                         | $p < 0.001$ uncorrected and $p < 0.05$ cluster-corrected   |
| 2                                     | Cappelletti et al. (2010)          | 22              | Conceptual judgment (quantity and non-quantity related) vs. Perceptual color judgment | Decimals > Object names (conceptual)<br>Decimals > Object names (conceptual)<br>Decimals > Object names (quantity only)<br>Decimals > Object names (non-quantity only)<br>Decimals (Conceptual–Perceptual) > Object names (Conceptual–Perceptual) <sup>#</sup><br>Digit strings > Consonant strings <sup>c</sup> | 14<br>12 <sup>b</sup><br>14<br>14<br>13 | $p < 0.05$ FWE corrected, or $p < 0.001$ uncorrected   |
| 3                                     | Carreiras et al. (2015)            | 21              | 1-back same/different judgment  | Digit strings > Nonalphanumeric symbol strings <sup>c</sup><br>(Arabic > Japanese Kana) and (Arabic > Japanese Kanji)  | 7                                       | $p < 0.001$ uncorrected, or $p < 0.05$ peak/cluster-level FWE/FDR corrected                                |
| 4                                     | Coderre et al. (2009)              | 9               | Number identification   | Arabic > Japanese Kanji  | 2<br>3<br>4                             | $p < 0.03$ uncorrected and $p < 0.05$ cluster-corrected  |
| 5                                     | Chochon et al. (1999) <sup>e</sup> | 8               | Digit naming/Magnitude comparison/Multiplication/Subtraction vs. Letter naming        | Digit naming > Letter naming   | 2                                       | $p < 0.001$ uncorrected and extent threshold, $k = 16$ voxels (432 mm <sup>3</sup> , $p < 0.05$ corrected) |
| 6                                     | Cui et al. (2013)                  | 18              | Semantic distance judgment  | Magnitude comparison > Letter naming*<br>Multiplication > Letter naming*<br>Subtraction > Letter naming*<br>Numerical tasks > Letter naming*<br>Digits > Chinese characters (Numerical classifiers)  | 13<br>12<br>12<br>14<br>14              | $p < 0.001$ uncorrected and $k = 10$ voxels (270 mm <sup>3</sup> )   |
| 7                                     | Cummine et al. (2015)              | 15              | Rapid automatized naming  | Digits > Words   | 18                                      | $p < .001$ uncorrected and $p < 0.05$ cluster-corrected  |
| 8                                     | Cummine et al. (2014)              | 15              | Rapid automatized naming  | Digits > Nonwords<br>Digits > Letters  | 5<br>2<br>9                             | $p < 0.001$ uncorrected and $p < 0.05$ cluster-corrected   |
| 9                                     | Grotheer et al. (2016b)            | 22              | 1-back same/different judgment  | Digits > False digits, noise digits, letters, false letters, and objects   | 6                                       | $p < 0.05$ FWE corrected and $k = 20$ voxels (20 mm <sup>3</sup> )   |
| 10                                    | Holloway et al. (2015)             | 18              | Passive simultaneous viewing and listening  | Visual digits and audio number word > Visual letters and audio letter sounds/names   | 1                                       | $p < 0.005$ uncorrected and $p < 0.05$ cluster-corrected   |
| 11                                    | Libertus et al. (2009)             | 14 <sup>d</sup> | 2-back same/different judgment  | Digits > Letters and faces   | 6                                       | $p < 0.01$ uncorrected, $p < 0.05$ cluster-corrected, and $k = 8$ voxels (64 mm <sup>3</sup> )             |
| 12                                    | Park et al. (2012)                 | 20              | Simultaneous same/different judgment task   | Digit strings > Consonant strings  | 1                                       | $p < 0.005$ uncorrected and $k = 20$ voxels (540 mm <sup>3</sup> , $p = 0.01$ cluster-corrected)           |
| 13                                    | Peters et al. (2015)               | 12              | Subtraction   | Digits > Number words  | 2                                       | $p < 0.05$ FDR-corrected   |
| 14                                    | Pinel et al. (2001)                | 9               | Magnitude comparison  | Digit strings > Number words   | 6                                       | $p < 0.05$ corrected   |
| 15                                    | Pinel et al. (1999)                | 11              | Magnitude comparison  | Digits > Number words  | 1                                       | $p < 0.001$ uncorrected  |
| 16                                    | Pinel et al. (2004)                | 15              | Physical size comparison  | Digits > Letters   | 1                                       | $p < 0.01$ uncorrected and $p < 0.05$ cluster-corrected  |
| 17                                    | Price and Ansari (2011)            | 19              | Oddball target detection (passive viewing)  | (Digits > Letters) and (Digits > False digits)   | 1                                       | $p < 0.005$ uncorrected and $p < 0.05$ cluster-corrected   |
| 18                                    | Yin et al. (2015)                  | 11 <sup>f</sup> | Memory (ordinality)   | Digit/digit strings > Letters (encoding)   | 1                                       | $p < 0.001$ uncorrected and $k = 100$ voxels (normalized voxel size not reported)                          |
| 19                                    | Zarnhofer et al. (2012)            | 42              | Arithmetic verification   | Digit/digit strings > Letters (recall)   | 3                                       | $p < 0.001$ uncorrected and $p < 0.05$ FWE cluster-corrected   |
| 20                                    | Zhang et al. (2012)                | 20              | Semantic distance judgment  | Digits > Number words<br>Numerals > Chinese characters   | 5<br>22                                 | $p < 0.008$ uncorrected and $k = 50$ voxels (1350 mm <sup>3</sup> )  |
| <b>Excluded from Meta-analysis II</b> |                                    |                 |   |  |   |  |
| 21                                    | Andres et al. (2012)               | 18              | Arithmetic vs. Letter naming  | Arithmetic > Letter naming*  | 5                                       | $p < .05$ FDR-corrected and $k = 100$ voxels (800 mm <sup>3</sup> )  |
| 22                                    | Andres et al. (2011)               | 10              | Arithmetic vs. Letter naming  | (Subtraction > Letter naming) and (Multiplication > Letter naming)*  | 8                                       | $p < 0.001$ uncorrected, or $p < 0.05$ FWE cluster-corrected, $k = 150$ voxels (1200 mm <sup>3</sup> )     |
| 23                                    | Attout et al. (2014)               | 26              | Numerical order judgment vs. Letter luminance judgment                                | Numerical order > Letter luminance*  | 5                                       | $p < 0.05$ FWE-corrected   |
| 24                                    | Basso et al. (2003)                | 5               | Digit verification (working memory and temporal production) vs. Letter verification   | Number working memory > Letter verification*   | 5                                       | $p < 0.0001$ uncorrected, $k = 10$ voxels (360 mm <sup>3</sup> ), and peak-level corrected at $p = 0.01$   |

(continued on next page)

Table 2 (continued)

| Study | Reference                                  | N  | Task(s)   | Selected contrast(s)   | Foci | Statistical Threshold   |
|-------|--|----|---|--|------|---|
| 25    | Fernandes et al. (2005)                    | 12 | Parity judgement vs. Animacy judgement [Divided attention (DA) with auditory word list recognition]<br>Full attention (FA) auditory word list recognition/visual number parity/visual animacy judgement | Number temporal production > Letter verification*<br>(DA digits-FA auditory recognition) > (DA animacy-FA auditory recognition)*   | 8    | $p < 0.005$ uncorrected and $k = 50 \text{ mm}^3$   |
| 26    | Fias et al. (2007)                         | 17 | Comparison (number magnitude vs. letter ordinality) vs. Dimming detection   | (DA digits-FA digits) > (DA animacy-FA animacy) **<br>(DA digits-Auditory baseline) > (DA Animacy-Auditory baseline)* <sup>c</sup><br>(Number comparison-Number dimming) > (Letter comparison-Letter dimming) ** | 3    | $p < 0.005$ uncorrected, masked with main effect results at $p < 0.05$ uncorrected, and $k = 5 \text{ voxels}$ ( $135 \text{ mm}^3$ ) |
| 27    | Gullick and Temple (2011)*                 | 16 | Ordinality comparison vs. passive viewing of nonalphanumeric symbols/nonwords   | (Years as events-Symbols) > (Event Words-Nonwords)*<br>Years as events > Symbols* <sup>c</sup>   | 1    | $p < 0.001$ uncorrected, $p < .05$ FDR cluster-corrected, and $k = 20 \text{ voxels}$ ( $540 \text{ mm}^3$ )                          |
| 28    | Gullick and Temple (2011)*                 | 16 | Magnitude comparison vs. passive viewing of nonalphanumeric symbols   | Numbers > Symbols* <sup>c</sup>  | 23   | $p < 0.0001$ uncorrected, $p < 0.05$ FDR cluster-corrected, and $k = 10 \text{ voxels}$ ( $270 \text{ mm}^3$ )                        |
| 29    | Stanescu-Cosson et al. (2000) <sup>c</sup> | 7  | Exact and approximate calculation vs. Letter-matching   | Years as numbers > Symbols* <sup>c</sup><br>Digits (1-9) > Letters* <sup>a</sup>   | 10   | $p < 0.001$ uncorrected, and $p < 0.05$ cluster-corrected   |
| 30    | Wu et al. (2009)                           | 18 | Arithmetic verification vs. Symbol identification (contained both numerals and nonalphanumeric symbols)   | Small digits (1-5) > Letters*<br>(Arabic Calculation-Arabic Identification) > (Roman Calculation-Roman Identification) #   | 7    | $p < 0.01$ uncorrected and $p < 0.01$ extent threshold  |
| 31    | Zago et al. (2008)                         | 14 | Manipulation (addition vs. noun generation) vs. Memory task   | (Numbers Manipulation-Maintenance) > (Syllables Manipulation-Maintenance) **   | 1    | $p < 0.001$ uncorrected and $p < 0.05$ cluster-corrected  |

Note. FWE: Familywise Error. FDR: False Discovery Rate. Unless otherwise stated, the statistical threshold reported was applied to all contrasts within a study. In some cases, a mixture of uncorrected and corrected findings may be reported for a particular contrast (e.g.,  $p < 0.05$  FWE corrected, or  $p < 0.001$  uncorrected). \*These contrasts were excluded from Meta-Analysis II to control for the influence of overly-specific contrasts. \*\*These contrasts were excluded from Meta-Analysis II to control for the influence of differential task demands between the numerical and non-numerical tasks.

<sup>a</sup> Includes unpublished foci provided by Amalric and Dehaene (2016).

<sup>b</sup> Response times modeled over both number and object names were factored out from the main effect of stimulus for this specific contrast. All other contrasts had response times modeled separately for numbers and object names.

<sup>c</sup> From supplementary data.

<sup>d</sup> Child sample in this study was excluded from the meta-analysis.

<sup>e</sup> Original coordinates were believed to be in MNI (SPM) space instead of the reported Talairach space.

<sup>f</sup> A superior memorist as a case study subject ( $n = 1$ ) was excluded from the meta-analysis.

<sup>g</sup> This study is split into two independent samples as a between-subject design was used.

empirical papers, review articles, meta-analyses, and book chapters, to identify additional studies that were not captured by the database searches. Thirdly, we performed forward citation searches on the relevant studies that cited Shum et al. (2013), and studies that those articles cited in relation to an NFA. Finally, to be as inclusive as possible, and to avoid further subjective thresholding, all reported activation foci were included, regardless of whether they were global peaks or subpeaks (i.e. local peaks within an activation cluster), and corrected or uncorrected for multiple comparisons. A final set of 30 fMRI studies (from Table 1) met the inclusion-exclusion criteria. The sample in Gullick and Temple (2011) was split into two independent studies or subject groups as a between-subjects design was used, resulting in a total of 31 studies with 50 contrasts, 388 foci, and 510 subjects. Details of those studies are presented in Table 2. All meta-analyses conducted in the current study met the recommended minimum number of studies (i.e., 20) necessary to avoid results that are strongly influenced by individual studies and for sufficient power to detect moderate effects (Eickhoff et al., 2016).

### 3.2. Data analyses

Two separate meta-analyses were conducted with different inclusion criteria based on contrast specificity. Contrast specificity was defined by the extent to which the contrast has the potential to reveal activation specific to Arabic numerals after controlling for task demands. Hence, all the relevant contrasts were categorized into three groups: (1) less specific contrasts, in which the numerical tasks had different cognitive demands than the non-numerical control tasks (e.g., multiplication > letter naming) (47.9% of foci), (2) suitably specific contrasts, in which the numerical tasks and non-numerical control tasks had equivalent or closely-matched task demands (e.g., digit naming > letter naming) and the main difference lies in the visual stimulus (48.2% of foci), and (3) overly specific contrasts that controlled for all neural activations related to visual perceptual processes pertaining to number form, leaving only the higher-order effect of interaction between stimulus category and task demands (e.g., [Arabic digit calculation – Arabic digit identification] > [Roman numeral calculation – Roman numeral identification]) (5.7% of foci). A small number of contrasts were simultaneously less specific and overly specific, such as [Number magnitude comparison – Number dimming detection] > [Letter ordinal comparison – Letter dimming detection] (1.8% of foci).

#### 3.2.1. Meta-analysis I: all relevant contrasts

In the first meta-analysis, all 31 studies with 50 contrasts, 388 foci, and 510 subjects were included as we wanted to be liberal as possible in our search for an NFA. The bulk of the less specific contrasts had more cognitively demanding numerical tasks than non-numerical ones. Their inclusion should therefore potentially increase the probability of finding greater convergence of an NFA during Arabic numeral processing.

#### 3.2.2. Meta-analysis II: suitably specific contrasts only

In the second meta-analysis, a subset comprising 20 studies with 28 contrasts, 187 foci, and 351 subjects was analyzed to control for task demands by excluding ‘less specific’ contrasts, and degree of contrast specificity by excluding ‘overly specific’ contrasts. Thus, only ‘suitably specific’ contrasts were included.

#### 3.2.3. Activation likelihood estimation procedure

Before analyzing the data, all foci were converted into a common stereotaxic space. Due to the variability in the templates used by various software (e.g., SPM, FSL, etc.) for spatial normalization to MNI space, and that there is no reason to favor one algorithm over another, we opted to transform all foci reported in MNI space to Talairach space using the various best-fit Lancaster transformation options (i.e.,

“icbm2tal”; Laird et al., 2010; Lancaster et al., 2007) implemented for different software. Studies that performed spatial normalization in MNI space in SPM99, SPM96, and SPM2, and reported those coordinates in Talairach space are assumed to have applied the Brett transformation (i.e., “mni2tal”; Brett et al., 2002). An exception were studies by Stanesco-Cosson et al. (2000) and Chochon et al. (1999), in which the published coordinates are believed to be in MNI (SPM) space instead of Talairach space as reported (verified with BrainMap’s Sleuth 2.4 database; Laird et al., 2005). For those studies that applied the Brett transformation, we adopted the recommended approach to “un-Brett” the coordinates using the “Brett: Talairach to MNI” transform followed by the Lancaster “MNI (SPM) to Talairach” transform (Fox et al., 2013; Laird et al., 2010). After the transformations, only 3 foci (0.89%) in the dorsal, middle frontal region fell outside of the smaller, more conservative mask, which is typically used for meta-analyses of functional imaging studies (Fox et al., 2013). Typically, one would expect less than 3% of the foci to fall outside of the mask, and outlying foci that are close enough to foci within the mask still contribute to the ALE calculations (Fox et al., 2013).

To quantitatively assess the concordance of brain regions that support the functional specialization of visual processing of Arabic numerals across different tasks and subject groups, coordinate-based meta-analyses were conducted using the ALE approach with GingerALE version 2.3.6 (Eickhoff et al., 2009, 2012, 2017; Turkeltaub et al., 2012; <http://brainmap.org/ale>). The ALE algorithm first models foci from contrasts within each study as centers of three-dimensional Gaussian probability distributions. Taking into consideration between-template variances, and the relationship between study sample size and inter-subject localization uncertainty, studies with larger sample sizes are weighted such that they have a narrower full width at half maximum and higher peaks (Eickhoff et al., 2009).

Prior to the modification of the ALE algorithm by Turkeltaub et al. (2012), the union of probability distributions at a given voxel was used to generate a probabilistic map of modeled activation (MA) for each contrast (i.e., an MA value represents the probability of an activation in a particular voxel). This had resulted in contrasts with multiple *within-contrast* foci in close proximity contributing more to the MA values. To address this within-contrast influence, the revised non-additive algorithm by Turkeltaub et al. (2012) now takes the *maximum* probability associated with any one Gaussian distribution from a contrast (see Turkeltaub et al., 2012 for a schematic explanation). Lastly, an ALE map is then computed as the voxel-wise union of the MA maps from the meta-analysis dataset. The ALE values thus represent the likelihood that at least one study activated a given voxel.

In addition, the previous algorithm required foci to be organized by contrast, such that studies with multiple non-independent contrasts will have greater influence than studies with a single contrast. Due to this limitation in the algorithm, prior relevant meta-analyses (Arsalidou and Taylor, 2011; Houdé et al., 2010; Kaufmann et al., 2009) had selected only one contrast per study to ensure statistical independence between sets of foci. In the revised algorithm, sets of foci can now optionally be organized by study or subject group, such that multiple contrasts within a study can be included in conjunction with the mitigation of within-contrast influences described above (see Turkeltaub et al., 2012 for a schematic explanation). This mitigates within-study influences, and avoids selection bias and the exclusion of potentially informative findings by limiting to a single contrast per study.

In summary, this updated approach minimizes both within-contrast and within-study effects by preventing multiple foci within a contrast from jointly impacting the MA value of a single voxel, and also by preventing multiple non-independent contrasts within a study from jointly impacting the ALE values (Turkeltaub et al., 2012). Therefore the ALE approach determines an above-chance convergence of activation probabilities between *studies*, rather than between *foci* (Eickhoff et al., 2012). In light of this non-additive modification to the ALE algorithm, we included the foci from all relevant contrasts reported in a

study, and organized the foci by study. Hence, multiple contrasts within each study are considered together.

GingerALE then performs a random-effects significance test on the ALE scores against an ALE-null distribution that is conceptually akin to randomly distributed activation foci across the whole brain, except that it is derived from MA-histogram permutations instead of individual voxels (see Eickhoff et al., 2012; for detailed descriptions of the concept and algorithm). It is noteworthy that a larger number of studies included in a meta-analysis is likely to result in higher  $p$ -values for the same ALE scores (Eickhoff et al., 2016), and may account for differences in findings between the two meta-analyses conducted in this current study. The parametric map with associated  $p$ -values obtained from the significance test is then subjected to the recommended cluster-level family-wise error (FWE) correction for multiple comparisons, which was found to provide optimal compromise between sensitivity and specificity (Eickhoff et al., 2016). Using the Monte-Carlo based approach with 1000 permutations, the cluster-level FWE thresholding was performed with an uncorrected, cluster-forming threshold of  $p < 0.001$ , followed by a cluster-level threshold of  $p < 0.05$ . Crucially, this cluster-thresholding step is dependent on a random distribution of all the foci in the dataset, which potentially influences the ultimate cluster size threshold, and the findings between the two meta-analyses conducted. Other than the ALE global peaks within each cluster, local peaks were provided to illustrate the spatial extent of each cluster. To be consistent with previous meta-analysis, anatomical labels were assigned to the ALE peak locations within each cluster using the Talairach Daemon (talairach.org) that is native to GingerALE. Supplementary anatomical labels were also assigned using cytoarchitectonic maximum probability maps in the Anatomy Toolbox v2.2c (Eickhoff et al., 2005) after transforming the Talairach peak coordinates were transformed to MNI (SPM) space. Besides providing sulci labels, which Talairach Daemon does not, the Anatomy Toolbox also provides additional anatomical specificity, such as gyri and sulci subdivisions.

## 4. Results

### 4.1. Meta-analysis I: all relevant contrasts

The all-inclusive meta-analysis revealed two regions in the bilateral parietal lobes and one region in the right frontal lobe that appear to be functionally specialized for symbolic number processing (Table 3 and Fig. 2). The right parietal cluster comprised the intraparietal sulcus extending to the inferior parietal lobule, precuneus, and posterior superior parietal lobule. The left parietal cluster comprised the intraparietal sulcus extending to the inferior parietal lobule, specifically the supramarginal gyrus. The right frontal cluster comprised the

**Table 3**

Activation likelihood estimation results for functional specialization of symbolic number processing in studies with all relevant contrasts (Meta-analysis I).

| Anatomical labels                          | Talairach coordinates | Talairach coordinates |            |           | ALE value<br>( $\times 10^{-3}$ ) | Volume (mm <sup>3</sup> ) | Studies with foci within the cluster <sup>a</sup>           |
|--|-----------------------|-----------------------|------------|-----------|-----------------------------------|---------------------------|---|
|  |                       | x                     | y          | z         |                                   |                           |   |
| Talairach Daemon                           | Anatomy Toolbox       |                       |            |           |                                   |                           |   |
| <b>R. inferior parietal lobule (BA 40)</b> | <b>hIP2</b>           | <b>40</b>             | <b>-48</b> | <b>44</b> | <b>32.75</b>                      | <b>7680</b>               | <b>1, 2, 3, 5, 6, 8, 10, 11, 20, 21, 22, 24, 25, 28, 29</b> |
| R. inferior parietal lobule (BA 40)        | hIP3                  | 34                    | -46        | 38        | 31.33                             |                           |   |
| R. precuneus (BA 7)                        | -                     | 28                    | -64        | 38        | 25.46                             |                           |   |
| R. precuneus (BA 7)                        | Area 7P               | 14                    | -74        | 48        | 23.33                             |                           |   |
| R. precuneus (BA 19)                       | hIP3                  | 28                    | -58        | 38        | 22.26                             |                           |   |
| <b>L. supramarginal gyrus (BA 40)</b>      | <b>hIP1</b>           | <b>-40</b>            | <b>-44</b> | <b>36</b> | <b>34.44</b>                      | <b>3832</b>               | <b>1, 2, 5, 6, 11, 22, 23, 24, 25, 28, 29, 31</b>           |
| L. inferior parietal lobule (BA 40)        | hIP1                  | -36                   | -54        | 42        | 23.61                             |                           |   |
| <b>R. anterior cingulate (BA 24)</b>       | <b>-</b>              | <b>18</b>             | <b>6</b>   | <b>46</b> | <b>16.91</b>                      | <b>744</b>                | <b>1, 6, 7, 8, 18</b>                                       |
| R. superior frontal gyrus/premotor (BA 6)  | -                     | 22                    | 6          | 60        | 0.01637                           |                           |   |

Note. BA: Brodmann Area. ALE: Activation likelihood estimation. R: Right. L: Left. hIP: Horizontal segment of the intraparietal sulcus (with subdivisions 1, 2, and 3). Area 7P: Posterior subdivision of BA7. Global peak of each cluster is in bold, and local peaks are not in bold.

<sup>a</sup> Although studies with foci that fall within the boundary of each cluster are listed, it is important to note that studies not listed could also contribute to the ALE scores if they lie on or close to the cluster boundary (Fox et al., 2013).

anterior cingulate and superior frontal gyrus, specifically, the premotor region.

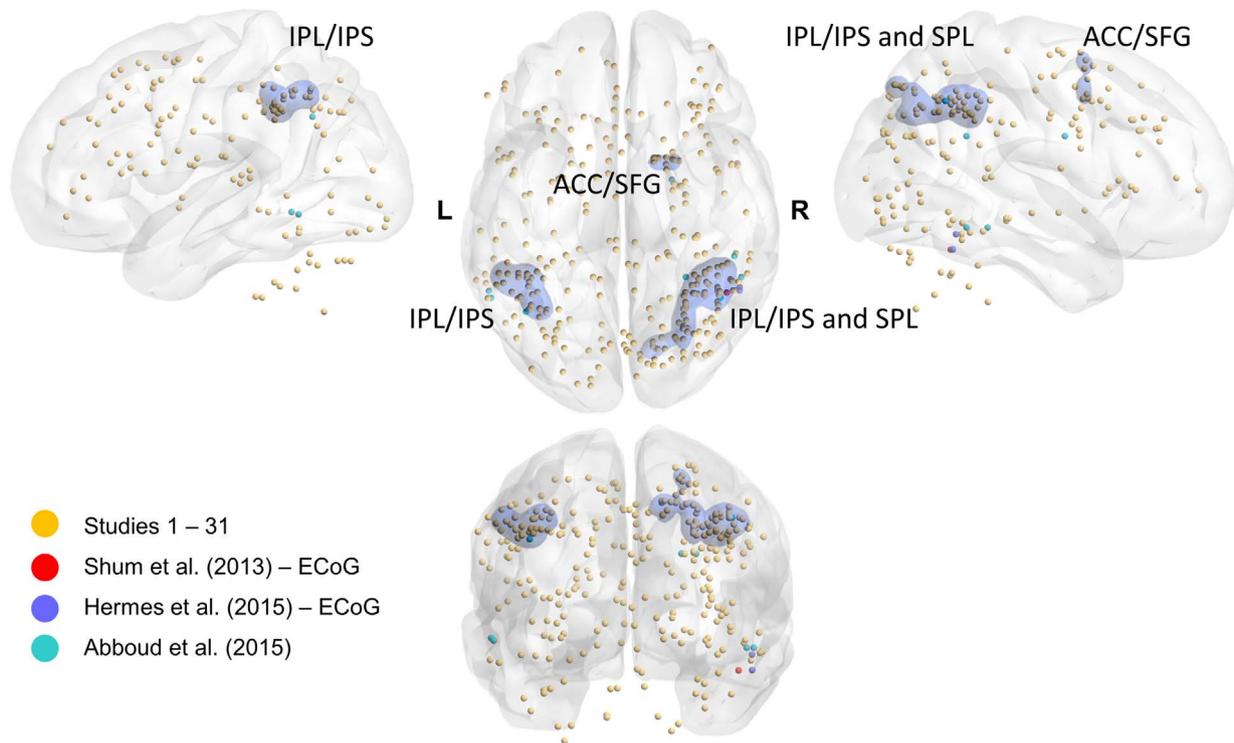
### 4.2. Meta-analysis II: suitably specific contrasts only

The second, more stringent meta-analysis that controlled for task demands and contrast specificity revealed a right lateral prefrontal cluster at the intersection of the precentral and inferior frontal gyri, specifically, the pars opercularis, and a right temporal cluster comprising the inferior and middle temporal gyri (Table 4 and Fig. 3, red blobs). The peak of the inferior temporal cluster is slightly superior relative to the NFA locations reported by Shum et al. (2013) (Talairach (TAL) coordinates: 47, -51, -21), and Hermes et al. (2015) (TAL: 52, -48, -15, and 52, -50, -21), but extremely close to those foci (at most 3 mm) along the  $x$  (left-right)- and  $y$  (anterior-posterior)-axes. However, the peak of our cluster is as superior to those found by Abboud et al. (2015) (TAL: 53, -44, -12, and 50, -35, -12).

In addition, this meta-analysis revealed a frontoparietal network overlapping that observed in Meta-analysis I (Fig. 3, blue blobs). The right parietal cluster comprised the precuneus, anterior superior parietal lobule, and intraparietal sulcus extending to the inferior parietal lobule. A smaller left parietal cluster comprised the intraparietal sulcus extending to the inferior parietal lobule, specifically the supramarginal gyrus. A right frontal cluster included the superior frontal (specifically, the premotor region) and anterior cingulate gyri.

## 5. Discussion

The current study examined whether the extant literature supports the existence of a reproducibly localized 'number form area' (NFA) in the ventral occipitotemporal cortex (vOTC). By being maximally inclusive in Meta-analysis I, we predicted that we would find a convergence of activation in an NFA. In Meta-analysis II, we tested the hypothesis that the exclusion of less specific and overly specific contrasts in the meta-analysis may increase the sensitivity of the convergence in an NFA, especially if its activation is weak due to signal loss complications. Only after controlling for task demands and contrast specificity by increasing the specificity of our exclusion criteria in Meta-analysis II did we observe such a numeral-specialized region in the right inferior temporal gyrus (ITG). In addition to an NFA in the right ITG, the bilateral inferior parietal regions, and a right-lateralized network of superior parietal, and superior and inferior frontal regions also appear to be functionally specialized for processing visually presented Arabic numerals. This 'symbolic number processing network' possibly supports cognitive processes engaged specifically by Arabic numeral processing, over and above any differences in task demands



**Fig. 2.** ALE concordant clusters (blue blobs) and foci (dots) from all relevant contrasts in meta-analysis I (cf. Table 3), and from relevant studies excluded from the meta-analysis, overlaid on the Colin27 brain template. Top panel: left lateral hemispheric, ventral axial, and right lateral hemispheric views. Bottom panel: posterior coronal view. L: Left. R: Right. IPL: Inferior parietal lobule. IPS: Intraparietal sulcus. SPL: Superior parietal lobule. ACC: Anterior cingulate cortex. SFG: Superior frontal gyrus. ECoG: ElectroCorticography. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) *Note.* BrainNet Viewer (Xia et al., 2013) was used to visualize the clusters and foci. While some foci appeared to fall outside the template used above, all but 3 foci in the middle frontal region were within the boundaries of the mask used in the meta-analysis.

**Table 4**  
Activation likelihood estimation results for functional specialization of symbolic number processing in studies with suitably specific contrasts only (Meta-analysis II).

| Anatomical labels                                |                            | Talairach coordinates |            |            | ALE value ( $\times 10^{-3}$ ) | Volume (mm <sup>3</sup> ) | Studies with foci within the cluster <sup>a</sup> |
|--|----------------------------|-----------------------|------------|------------|--------------------------------|---------------------------|---|
| Talairach Daemon                                 | Anatomy Toolbox            | x                     | y          | z          |                                |                           |   |
| R. precuneus (BA 7)                              | –                          | <b>16</b>             | <b>–74</b> | <b>48</b>  | <b>22.23</b>                   | <b>5536</b>               | <b>1, 2, 3, 6, 8, 10, 11, 14, 20</b>              |
| R. inferior parietal lobule (BA 40)              | hIP3                       | 34                    | –46        | 38         | 21.63                          |                           |   |
| R. inferior parietal lobule (BA 40)              | hIP2                       | 40                    | –50        | 44         | 21.58                          |                           |   |
| R. superior parietal lobule (BA 7)               | Area 7A                    | 28                    | –68        | 46         | 18.20                          |                           |   |
| R. inferior parietal lobule (BA 40)              | hIP2                       | 46                    | –40        | 40         | 17.05                          |                           |   |
| R. inferior parietal lobule (BA 39)              | hIP3                       | 28                    | –56        | 38         | 16.15                          |                           |   |
| <b>L. supramarginal gyrus (BA 40)</b>            | <b>hIP3</b>                | <b>–38</b>            | <b>–44</b> | <b>36</b>  | <b>22.93</b>                   | <b>1400</b>               | <b>1, 2, 6, 11</b>                                |
| L. inferior parietal lobule (BA 40)              | hIP3                       | –36                   | –50        | 42         | 15.21                          |                           |   |
| L. inferior parietal lobule (BA 40)              | hIP2                       | –48                   | –48        | 42         | 13.04                          |                           |   |
| L. inferior parietal lobule (BA 40)              | hIP2                       | –50                   | –44        | 42         | 11.94                          |                           |   |
| <b>R. superior frontal gyrus/premotor (BA 6)</b> | –                          | <b>22</b>             | <b>6</b>   | <b>60</b>  | <b>16.13</b>                   | <b>1104</b>               | <b>1, 6, 7, 8, 18</b>                             |
| R. anterior cingulate (BA 24)                    | –                          | 16                    | 6          | 44         | 14.84                          |                           |   |
| <b>R. inferior temporal gyrus (BA 37)</b>        | –                          | <b>50</b>             | <b>–48</b> | <b>–10</b> | <b>13.95</b>                   | <b>728</b>                | <b>1, 6, 7, 9, 15</b>                             |
| R. middle temporal gyrus (BA 20)                 | –                          | 56                    | –40        | –14        | 13.86                          |                           |   |
| <b>R. precentral gyrus (BA 6)</b>                | –                          | <b>42</b>             | <b>2</b>   | <b>34</b>  | <b>16.07</b>                   | <b>696</b>                | <b>1, 6, 20</b>                                   |
| R. inferior frontal gyrus (BA 9)                 | pars opercularis (Area 44) | 50                    | 4          | 28         | 14.70                          |                           |   |
| R. inferior frontal gyrus (BA 9)                 | pars opercularis (Area 44) | 48                    | 4          | 24         | 12.75                          |                           |   |

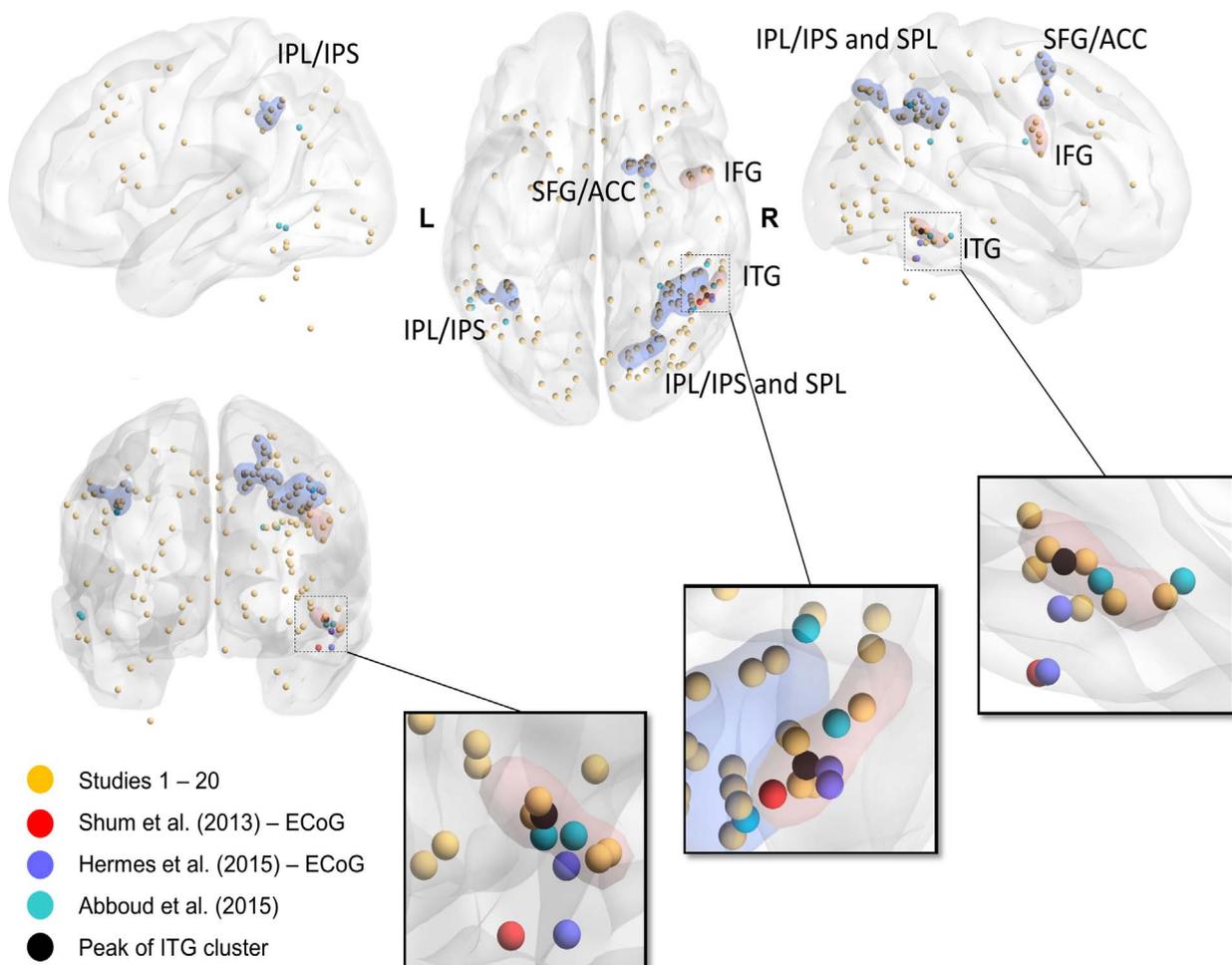
*Note.* BA: Brodmann Area. ALE: Activation likelihood estimation. R: Right. L: Left. hIP: Horizontal segment of the intraparietal sulcus (with subdivisions 1, 2, and 3). Area 7A: Anterior subdivision of BA7. Global peak of each cluster is in bold, and local peaks are not in bold.

<sup>a</sup> Although studies with foci that fall within the boundary of each cluster are listed, it is important to note that studies not listed could also contribute to the ALE scores if they lie on or close to the cluster boundary (Fox et al., 2013).

between the numerical and non-numerical conditions unrelated to processing of numerical information or of visual number symbols. To our knowledge, this is the first meta-analysis to quantitatively review the existence of a reproducibly localized NFA, and its associated network.

### 5.1. NFA in the inferior temporal gyrus

Our findings provide some degree of support for the existence of an NFA in the ITG, and are consistent with a series of recent intracranial electrophysiological (Daitch et al., 2016; Hermes et al., 2015; Roux et al., 2008; Shum et al., 2013) and fMRI (Abboud et al., 2015; Amalric and Dehaene, 2016; Grotheer et al., 2016b) studies supporting its existence and spatial localization as distinct from other category-



**Fig. 3.** ALE concordant clusters (blue and red blobs) and foci (dots) from suitably specific contrasts in meta-*meta*-analysis II (cf. Table 4), and from relevant studies excluded from the meta-analysis, overlaid on the Colin27 brain template. The blue clusters overlapped with those observed in Meta-analysis I, and the red clusters are unique to Meta-analysis II. Top panel: left lateral hemispheric, ventral axial, and right lateral hemispheric views. Bottom panel: posterior coronal view. Inserts (left to right): Magnified coronal, axial, and sagittal views of the right inferior temporal cluster. L: Left. R: Right. IPL: Inferior parietal lobule. IPS: Intraparietal sulcus. SPL: Superior parietal lobule. ACC: Anterior cingulate cortex. SFG: Superior frontal gyrus. IFG: Inferior frontal gyrus. ITG: Inferior temporal gyrus. ECoG: Electrocorticography. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

selective object processing regions, such as the visual word form area (VWFA). The fact that we observed a convergence of activation in the right ITG only after controlling for task demands and contrast specificity suggests that the cognitive demands of the control tasks, as well as the contrasts that researchers chose to analyze, may mask or wash out any possible convergence in an NFA, especially if its activation is susceptible to signal attenuation. Although it has been suggested that fMRI cannot reliably detect the NFA due to signal dropout (Shum et al., 2013), only two (Amalric and Dehaene, 2016; Grotheer et al., 2016b) out of the five studies with foci within the right ITG cluster boundary employed advanced imaging and data preprocessing techniques designed to overcome signal loss. Our findings suggest, therefore, that while signal dropout in fMRI may have contributed to some previous null findings, it is clearly not the only factor influencing a study's ability to detect the NFA. Moreover, only a quarter of the 20 studies contributed to the ITG cluster (we omitted each of the seven studies that had numeral-specific activation in the vOTC in Meta-analysis II (cf. Tables 1 and 2), re-ran the analyses, and confirmed that the five studies listed in Table 4 were the only contributors), which further suggests that its activation may be highly dependent on task contexts. Alternatively, the statistical thresholding criteria used could also partly account for the mixed findings of an NFA. Specifically, we also observed that among the 12 studies in Table 1 that observed numeral-specific activity in the vOTC (either ITG and/or fusiform gyri), an equal

proportion of studies did not employ correction for multiple comparisons or apply an arbitrary spatial extent threshold (33.3%), employed voxelwise familywise error (FWE) or false discovery rate (FDR) correction (33.3%), or employed cluster-level correction (33.3%). However, among 19 studies that did not observe an NFA in Table 1, there is a trend that more stringent cluster-level correction (52.6%) and voxelwise FWE/FDR correction (31.6%) were employed.

It is important to note that concordant activation in the right ITG in the present work is still insufficient evidence to demonstrate that it is truly an NFA. 'Functional specialization (or specificity)' of a cortical region has been commonly defined in neuroscience and neuropsychology only *quantitatively*, either as being "exclusively engaged in a single mental function", or as being "slightly more engaged in one mental function than another" (Kanwisher, 2010, p. 11163), without specifying the aspects of a stimulus category that a region is attuned to. During the initial and recent debates on the existence of the VWFA, Cohen and Dehaene (2004) put forth three independent criteria to provide a framework by which to evaluate the specialization of the VWFA both *qualitatively* and *quantitatively*: (i) functional specialization, which refers to the hypothesis that "the visual system has become, at least in part, attuned to the requirements [e.g., abstract case invariance such as identical neuronal responses to 'A' and 'a'] of reading in a given script" (p. 467), and ascribed the quantitative aspects of the definition to (ii) regional selectivity, which they refer to as the hypothesis that there are

cortical patches “at a suitably small scale (e.g., 1 or 2 mm)” that “respond exclusively to letters or words, and do not respond at all to stimuli such as faces or objects that do not contain features of letters or words” (p. 468), and (iii) reproducible localization. However, [Cohen and Dehaene \(2004\)](#) [[Dehaene and Cohen, 2011](#)][2011] acknowledged that neuroimaging techniques, especially functional magnetic resonance imaging (fMRI), currently only have the spatial resolution to determine if a region is *partially* selective (i.e., the region may also be responsive to other stimulus categories, but more for one category than others). Henceforth, the present consensus of the quantitative aspects is a matter of degree rather than an exclusive all-or-nothing one ([Kanwisher, 2010](#)).

Given the analogous nature of the debates surrounding the VWFA and the NFA as symbol form areas, we believe these same three criteria and more nuanced definitions can be effectively applied to the evaluation of evidence relating to the existence of an NFA. Additionally, based on the contrasting findings between the two meta-analyses – before and after controlling for task demands and contrast specificity, we propose that the existence of an NFA should instead be task-independent.

#### 5.1.1. Functional specialization

An NFA should first be attuned to the orthographic computational requirements in the Hindu-Arabic numeral script. For example, familiarity with the Hindu-Arabic numeral system should allow one to easily distinguish between (i) digits and letters (e.g., ‘5’ from ‘S’, ‘9’ from ‘g’), (ii) individual digits (e.g., ‘6’ from ‘9’ and ‘0’), and (iii) digit strings (e.g., ‘23’ from ‘32’). Several behavioral studies have demonstrated some degree of functional independence and specialization in digit and letter recognition mechanisms. For instance, after controlling for physical attributes, a letter is typically detected faster when it is presented in an array of digits than in an array of other letters, and the same is true for digit search among letters or digits (e.g., [Hamilton et al., 2006](#)). Most importantly, it should be noted that the ‘Arabic number form’ was originally conceived as an analogue to the ‘visual word form’, detecting digit strings rather than single symbol representations ([Cohen and Dehaene, 1991, 1995](#)). In other words, just as differential activation patterns have been found for single letters and letter strings ([James et al., 2005](#)), it is crucial for studies to distinguish single digit and multi-digit encoding processes. To date, existing studies have contrasted symbol categories using a mixture of single and multi-digit numerals and letters rendering comparison across studies a challenge. Taken together, a complete characterization of the different levels of functional specialization for Arabic numerals has not been systematically investigated.

#### 5.1.2. Regional selectivity

According to the regional selectivity criterion by [Cohen and Dehaene \(2004\)](#), the NFA should respond exclusively to Arabic numerals, but not at all to perceptually dissimilar stimuli, such as faces or cars, at a scale of a couple of millimeters in a given region. Regional selectivity can therefore only be demonstrated using imaging methods with high spatial resolution, such as intracranial recordings (e.g., [Daitch et al., 2016](#); [Hermes et al., 2015](#); [Roux et al., 2008](#); [Shum et al., 2013](#)) and high-resolution fMRI-adaptation protocols, which allows the activation of specific neuronal populations within a region to be examined rather than the averaged activation of heterogeneous neuronal populations ([Avidan et al., 2002](#); [Cohen Kadosh et al., 2007a](#); [Grill-Spector and Malach, 2001](#)). No study has employed an fMRI-adaptation paradigm to examine the regional specificity of an NFA. Moreover, to rule out the possibility of differential physical attributes and the possibility that the NFA is merely a ‘non-letter/word form area’, the NFA should show preferential response to Arabic numerals over other meaningful written symbols (e.g., letters and logographic non-alphanumeric symbols such as @, \$, or%), and non-meaningful, but visually matched characters (e.g., scrambled numerals), with no

difference in activation between the control stimuli. Most of the fMRI studies to date have not employed a full range of control stimuli (but see [Reinke et al., 2008](#); who did not find any numeral-specific activation relative to words, nonalphanumeric symbols, and Hebrew characters). It is therefore difficult to assess if the NFA shows preferential response to numerals only over the specific subset of control stimuli chosen. For instance, some studies showed that a right inferior temporal ([Carreiras et al., 2015](#)) or lateral occipital region ([Park et al., 2012](#)) with preferential response to Arabic numerals over letters was in fact more responsive to nonalphanumeric symbols and false fonts than to numerals respectively. The possibility that the NFA could be a general symbol form area is also supported by a recent transcranial magnetic stimulation study by [Grotheer et al. \(2016a\)](#) that found the stimulation of the right NFA observed in [Grotheer et al. \(2016b\)](#) impaired the identification of both numerals and letters, but not false numerals and false letters. This led the authors to suggest that while the NFA plays a causal role in numeral processing, it might be more of “a flexible processing module for the early visual encoding of learned characters” than a numeral-specific one ([Grotheer et al., 2016a, p. 317](#)). Given the limited range of control stimuli considered within each study, and that four of five studies contributing to ITG cluster only included letters as the sole symbol control category, we believe that regional selectivity has not been adequately demonstrated across existing fMRI studies.

#### 5.1.3. Reproducible localization

Lastly, the location of an NFA should be reproducible across individuals and tasks involving Arabic numerals ([Cohen and Dehaene, 2004](#)). The present work does provide some degree of evidence for the reproducibility criterion, but its validity hinges on the fulfilment of the criteria of functional specialization and regional specificity. Furthermore, it is important to note that only five out of 20 studies contributed directly to the NFA observed in our analysis (or five out of 41 studies, including those with no numeral-specific activity anywhere in the brain ([Table 1](#))), suggesting that it is highly task-dependent. All in all, further research is necessary to fully characterize the functional specialization and regional selectivity of an NFA, and its relation to other regions.

#### 5.1.4. Task-independence

Another issue which requires further empirical investigation is the role of task-dependent, top-down, goal-directed processes in the activation of the NFA. [Price and Devlin \(2003, 2011\)](#) proposed that the bottom-up sensory processing function of regions within the vOTC changes as it interacts with top-down predictions from other cortical regions based on prior experience with the stimuli. Using intracranial electrophysiology, [Hermes et al. \(2015\)](#) found that responses in the ITG were heightened by increased cognitive demands during active calculation relative to numeral reading and an oddball color detection task involving Arabic digits in the background. Interestingly, the modulation of the NFA responses was not numeral-specific, but extended to calculation using number words, suggesting that cognitive demands of calculation, rather than visual perception alone, influenced the NFA activity ([Hermes et al., 2015](#)). More recently, [Daitch et al. \(2016\)](#) found strong feedback-based functional coupling between the posterior ITG and the anterior IPS. Specifically, the NFA was involved in bottom-up coupling with the IPS during passive processing of Arabic numerals, and the IPS was involved in top-down coupling with the NFA during arithmetic ([Daitch et al., 2016](#)). Furthermore, the study by [Price and Ansari \(2011\)](#) employed a passive viewing paradigm, which revealed no preferential activation for Arabic numerals in the vOTC, relative to letters and novel characters, suggesting that perhaps active stimulus processing is required to reveal NFA activity. Evidence for this hypothesis is provided by [Polk et al. \(2002\)](#) who found a lack of preferential ITG responses to digits in most of their participants in a passive viewing task, but found that the active string-matching task elicited greater digit responses in the ITG relative to the passive viewing

task in some of their participants, albeit still not significant at the group level. In a similar vein, Peters et al. (2015) found a numeral-specialized region in the lateral occipital cortex with a subtraction task that contrasted digits and number words, but failed to replicate the findings after controlling for string length and switching to an order judgment task in a follow-up experiment. The authors proposed that the initial findings could be dependent on either task (i.e., relevance of numerosity) or stimulus characteristics (i.e., string length). Taken together, these findings suggest that the bottom-up, sensory processes of the NFA may be highly modulated by top-down, semantically related processes specific to the tasks.

## 5.2. The ‘symbolic number processing network’

In addition to an NFA in the ITG, other brain regions also appear to be specialized for Arabic numeral processing, including the bilateral inferior parietal lobules (IPL) and intraparietal sulci (IPS), a right-lateralized collection of regions in the precuneus, the superior parietal lobule (SPL), the premotor region of the superior frontal gyrus (SFG) and anterior cingulate, and the inferior frontal gyrus (IFG). Given that we controlled for task demands in Meta-analysis II, and that digits are inherently easier to identify than letters even when perceptual information is limited (Starrfelt and Behrmann, 2011), our findings suggest that the extensive frontoparietal network is possibly involved in additional semantic, syntactic, and lexical processing that Arabic numerals may require beyond what other symbol sets do. In other words, this network supports cognitive processes engaged by the processing of Arabic digits more than other symbols, as opposed to being domain-specific to Arabic digits.

As noted by Price and Ansari (2011), and Starrfelt and Behrmann (2011), single Arabic digits contain richer semantic associations than most other single symbols do. For example, most syllabic symbols are only meaningful in strings. Not only do single digits carry information about identity (e.g., ‘7’ is ‘seven’ or a jersey number), they are also associated with magnitude (e.g., ‘4’ implies [·]), and ordinality (e.g., ‘2’ can imply the second number on a ‘mental number line’). Furthermore, processing multi-digit Arabic numerals may involve a higher-order interaction of syntactic or ordinal, semantic, and lexical processing, possibly accounting for the greater activation of a frontoparietal network specific to Arabic numerals. For instance, as noted by Pinel et al. (2001), the place-value rules of the base-10 decimal system render the order of digits in a digit string to be particularly important for the extraction of its semantic and lexical content (e.g., the digit ‘2’ in ‘2’, ‘12’, ‘20’, and ‘200’ require mappings onto different number words [‘two’, ‘twelve’, or ‘twenty’] and magnitude representations [two ones, two tens, or two hundreds]). Although alphabetic/syllabic *number words* (e.g., English and Japanese Kana), and logographic *number symbols* (e.g., Chinese and Japanese Kanji), may seem similar to Arabic numerals in their semantic, syntactic, and lexical content, each number word or number symbol is less conceptually rich than Arabic digits. For instance, ‘23’ is written in Chinese as ‘二十三’, which is ‘two-ten-three’. Hence, ‘二’ is always associated with just ‘two’ regardless of its place value. Likewise, the word ‘twenty’ is also always associated with only ‘two tens’. Moreover, recent behavioral findings by Hurst et al. (2017) suggest that preschool children may first map verbal number words onto nonsymbolic quantities, then map Arabic numerals onto verbal number words, such that the association between Arabic numerals and nonsymbolic quantities may be indirect. Such indirect mappings may inevitably require greater cognitive processing. Taken together, Arabic numerals may possibly require a greater degree of syntactic, semantic, and lexical processing than do most other non-numerical symbols, and in doing so recruit an extensive frontoparietal network collectively recruited by various domain-specific and domain-general cognitive processes.

### 5.2.1. Parietal regions

The localization of an NFA in the ITG has been hypothesized to be a result of biased intrinsic structural and functional connectivity between the bilateral NFAs and magnitude processing regions in the bilateral IPS (Abboud et al., 2015; Hannagan et al., 2015). As more than half of the studies that contributed to each IPS/IPL cluster involved numerical tasks did not require explicit magnitude processing, the convergence of activation in the bilateral IPS may reflect the possibility that Arabic numerals automatically activate magnitude representations more than most non-numerical symbols do (Cohen Kadosh et al., 2007b; Girelli et al., 2000; Henik and Tzelgov, 1982; Rubinsten et al., 2002; although see Cohen, 2009; Naparstek and Henik, 2010; Price and Ansari, 2011 for caveats).

Moreover, the bilateral IPS, particularly the anterior portion, may be involved in ordinal processing that is co-recruited with magnitude processing (Ansari, 2008). While magnitude and ordinal processing are highly related for nonsymbolic stimuli, they are dissociable processes with distinct neural bases for Arabic digits (Lyons and Beilock, 2013; see Lyons et al., 2016, for review). In fact, the other parietal and frontal regions in the ‘symbolic number processing network’ have been implicated in ordinal processing of Arabic digits (Fias et al., 2007; Fulbright et al., 2003; Ischebeck et al., 2008; see Lyons et al., 2016, for a review).

The left IPL, specifically the supramarginal gyrus, supports a myriad of cognitive processes such as orthographic-to-phonological conversion (Price, 1998), phonological working memory (Church et al., 2011; Paulesu et al., 1993), symbol-referent semantic associations (Grabner et al., 2013; Kim et al., 2011), as well as temporal order processing (Ortuño et al., 2002; Wiener et al., 2010a,b). The adjacent left angular gyrus is also often implicated in verbal and semantic processing of symbolic numbers (Dehaene et al., 2003; Price and Ansari, 2011; Seghier, 2012). All in all, the concordant activation in the IPL in the current study may reflect a confluence of lexical, semantic, and ordinal processing of Arabic numerals.

The bilateral posterior SPL, including the precuneus, are possibly involved in attention and visuo-spatial orientation on an abstract ‘mental number line’ (i.e., relative order of numbers) (Cavanna and Trimble, 2006; Dehaene et al., 2003; Hubbard et al., 2005; Lyons and Ansari, 2009). It is conceivable that similar mechanisms are involved in attending to the length of a digit string to extract the syntactic verbal frame, and then to the specific order of digits to fill the verbal frame (e.g., ‘243’ → ‘two hundred, forty, three’). Hence, the convergence of activation in the right superior parietal regions may reflect visuo-spatial attention mechanisms related to ordinal and syntactic processing of Arabic numerals.

### 5.2.2. Frontal regions

Along with the superior parietal regions, the SFG and IFG may also play a role in selective visuo-spatial attention (Anderson et al., 2007). The convergence of activation in the frontal regions may thus also reflect visuo-spatial attention mechanisms related to ordinal and syntactic processing of Arabic numerals.

Recently, converging evidence from human and non-human primate studies, has led to the proposal that the IFG may not only be involved in general language processing. For instance, Diester and Nieder (2007) found that neurons in BA 44/45 in non-human primates were tuned to both symbolic and non-symbolic numerical magnitudes after learning to associate Arabic digits with their corresponding nonsymbolic numerosities. These findings led the authors to suggest that the IFG may facilitate the associations between arbitrary shapes (i.e., Arabic digits, Roman numerals, and number words) and nonsymbolic numerosities. Findings that the IFG is activated to a greater extent in children than in adults during notation-independent numerical magnitude processing also support its role during the formative stage of the symbol-referent associations (Ansari et al., 2005; Cantlon et al., 2009; Kaufmann et al., 2006; Rivera et al., 2005). There is also growing evidence that the IFG

may also play a more fundamental role in magnitude processing (Damarla et al., 2016; Sokolowski et al., 2017; Tang et al., 2006). For instance, using a multi-voxel pattern analysis, Damarla et al. (2016) demonstrated that several parietal and frontal regions, including the right IFG, support cross-modality (visual and auditory) classification of magnitude representations, which suggest the role of the IFG in an abstract code for magnitude. Tang et al. (2006) found greater activation in the bilateral IFG when processing numerical distance than physical size of Arabic digits in a numerical stroop task, suggesting its role in magnitude processing. Additionally, the IFG, or prefrontal cortex more generally, may be critical for establishing syntactic representations in human symbol systems, such as grammar, ordinality, and place-value notational rules (Friederici et al., 2006; Meyer et al., 2012 see Nieder, 2009; for a review). Therefore, in the current study, the observed convergence in the IFG may reflect its multiple roles in magnitude processing, mapping and processing of Arabic digits, and higher-order integration of the semantic, syntactic and lexical information.

In summary, in combination with the extant literature, our current findings suggest that the bilateral parietal regions (IPS and IPL), and a right-lateralized collection of regions comprising the SFG, IFG, and ITG form a potential ‘symbolic number processing network’. The ITG may be involved in asemantic shape processing of visual symbols; the bilateral IPS and IFG in magnitude processing; bilateral IPL in lexical, semantic, and ordinal processing; right SPL and SFG in visuo-spatial processing of the perceptual syntactic and abstract ordinal relations among the symbols; and the right IFG in higher-order integration of all task-relevant information. Further empirical investigations are necessary to systematically dissociate the specific cognitive processes involved, their underlying mechanisms, the neural subdivisions supporting each function, and their interaction.

Finally, although we use the term ‘symbolic number processing network’ here, the extent to which this collection of regions constitutes a true interdependent *network*, as opposed to simply a group of simultaneously activated but functionally independent regions, is yet to be determined. Thus far, some degree of temporoparietal (Daitch et al., 2016; Park et al., 2012) and frontoparietal coupling have been demonstrated during numerical symbol processing (Abboud et al., 2015; Diester and Nieder, 2007). However, it is still unclear how independent or interdependent those two networks are. Moreover, as shown in Table 1, the findings for functional specialization for Arabic numerals at large have been very inconsistent, and it is unclear why many studies did not find a single region that is numeral-selective. In summary, given the hypothesized complex interaction of semantic, syntactic, and lexical processing engaged by Arabic numerals, the choice of numerical and non-numerical tasks is critical for characterizing the interdependent functional mechanisms underlying the different nodes of the ‘symbolic number processing network’.

### 5.3. Limitations

Common to other ALE meta-analyses, the current study lacked the means to statistically control for differences in statistical thresholding methods across studies, spatial extent and magnitude of the activation foci, or confounding variables such as age. It is also important to note that unlike a conventional behavioral meta-analysis that addresses the question of whether there is an effect at all, the ALE approach addresses the question of whether there is convergence across studies given the premise that there is some stimulus- or task-specific activation somewhere in the brain. Hence, studies that did not find any numeral-specific activity anywhere in the brain (11 studies in Table 1) had to be excluded. This bias therefore warrants caution in interpreting our findings as definitive about the existence of an NFA.

One limitation specific to this study is the liberal inclusion of uncorrected foci (16% of total foci). However, this was deliberate as the primary goal of the study was to detect an NFA, which has supposedly been plagued by signal loss complications. With signal loss, any

activation may be less likely to survive correction for multiple comparisons, and so liberal inclusion criteria were essential.

## 6. Conclusions

The present findings suggest that if an NFA does exist, the most reproducible localization is in the right ITG, but that such convergent localization is only evident when tasks are appropriately controlled. Several of the studies contributing to this region did not employ methods designed to overcome signal dropout, suggesting that signal dropout is not the only factor underlying previous null fMRI findings. However, given that only five studies contributed directly to this region (i.e., have foci within the ITG cluster boundary), more evidence is necessary to characterize the functional specialization and regional specificity of the NFA. In addition to an NFA, the current study revealed a candidate ‘symbolic number processing network’ consistent with the body of extant literature. It comprises the bilateral parietal regions, and right-lateralized superior and inferior frontal regions. While they may be involved in numerical magnitude processing, and domain-general processes related to ordinality, syntax, lexicon, and symbol-referent associations, their roles specific to Arabic numeral processing require further empirical investigation. The present work thus provides insights for understanding the neurocognitive mechanisms that support the processing of symbolic numbers. Such insights are critical for future research as we seek to understand how such systems develop, and the role they play in the typical and atypical development of mathematical skills.

### Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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## References

- Abboud, S., Maidenbaum, S., Dehaene, S., Amedi, A., 2015. A number-form area in the blind. *Nat. Commun.* 6, 6026. <http://dx.doi.org/10.1038/ncomms7026>.
- Amalric, M., Dehaene, S., 2016. Origins of the brain networks for advanced mathematics in expert mathematicians. *Proc. Natl. Acad. Sci. U. S. A.* 113 (18), 4909–4917. <http://dx.doi.org/10.1073/pnas.1603205113>.
- Anderson, E.J., Mannan, S.K., Husain, M., Rees, G., Sumner, P., Mort, D.J., et al., 2007. Involvement of prefrontal cortex in visual search. *Exp. Brain Res.* 180 (2), 289–302. <http://dx.doi.org/10.1007/s00221-007-0860-0>.
- Anderson, B., Soliman, S., O'Malley, S., Danckert, J., Besner, D., O'Malley, S., et al., 2015. Control over the strength of connections between modules: a double dissociation between stimulus format and task revealed by Granger causality mapping in fMRI. *Front. Psychol.* 6 (March), 1–10. <http://dx.doi.org/10.3389/fpsyg.2015.00321>.
- Andres, M., Pelgrims, B., Michaux, N., Olivier, E., Pesenti, M., 2011. Role of distinct parietal areas in arithmetic: an fMRI-guided TMS study. *NeuroImage* 54 (4), 3048–3056. <http://dx.doi.org/10.1016/j.neuroimage.2010.11.009>.
- Andres, M., Michaux, N., Pesenti, M., 2012. Common substrate for mental arithmetic and finger representation in the parietal cortex. *NeuroImage* 62 (3), 1520–1528. <http://dx.doi.org/10.1016/j.neuroimage.2012.05.047>.
- Ansari, D., Garcia, N., Lucas, E., Hamon, K., Dhital, B., 2005. Neural correlates of

- symbolic number processing in children and adults. *Neuroreport* 16 (16), 1769–1773. <http://dx.doi.org/10.1097/01.wnr.0000183905.23396.f1>.
- Ansari, D., 2008. Effects of development and enculturation on number representation in the brain. *Nat. Rev. Neurosci.* 9 (4), 278–291. <http://dx.doi.org/10.1038/nrn2334>.
- Arsalidou, M., Taylor, M.J., 2011. Is  $2 + 2 = 4$ ? Meta-analyses of brain areas needed for numbers and calculations. *NeuroImage* 54 (3), 2382–2393. <http://dx.doi.org/10.1016/j.neuroimage.2010.10.009>.
- Attout, L., Fias, W., Salmon, E., Majerus, S., 2014. Common neural substrates for ordinal representation in short-term memory, numerical and alphabetical cognition. *PLoS One* 9 (3). <http://dx.doi.org/10.1371/journal.pone.0092049>.
- Avidan, G., Hasson, U., Hendler, T., Zohary, E., Malach, R., 2002. Analysis of the neuronal selectivity underlying low fMRI signals. *Curr. Biol.* 12 (12), 964–972. [http://dx.doi.org/10.1016/S0960-9822\(02\)00872-2](http://dx.doi.org/10.1016/S0960-9822(02)00872-2).
- Baker, C.I., Liu, J., Wald, L.L., Kwong, K.K., Benner, T., Kanwisher, N., 2007. Visual word processing and experiential origins of functional selectivity in human extrastriate cortex. *Proc. Natl. Acad. Sci. U. S. A.* 104 (21), 9087–9092. <http://dx.doi.org/10.1073/pnas.0703300104>.
- Basso, G., Nichelli, P., Wharton, C.M., Peterson, M., Grafman, J., 2003. Distributed neural systems for temporal production: a functional MRI study. *Brain Res. Bull.* 59 (5), 405–411. [http://dx.doi.org/10.1016/S0361-9230\(02\)00941-3](http://dx.doi.org/10.1016/S0361-9230(02)00941-3).
- Bouhali, F., Thiebaut de Schotten, M., Pinel, P., Poupon, C., Mangin, J.-F., Dehaene, S., Cohen, L., 2014. Anatomical connections of the visual word form area. *J. Neurosci.* 34 (46), 15402–15414. <http://dx.doi.org/10.1523/JNEUROSCI.4918-13.2014>.
- Brett, M., Johnsrude, I.S., Owen, A.M., 2002. The problem of functional localization in the human brain. *Nat. Rev. Neurosci.* 3 (3), 243–249. <http://dx.doi.org/10.1038/nrn756>.
- Bugden, S., Ansari, D., 2011. Individual differences in children's mathematical competence are related to the intentional but not automatic processing of Arabic numerals. *Cognition* 118 (1), 35–47. <http://dx.doi.org/10.1016/j.cognition.2010.09.005>.
- Cantlon, J.F., Libertus, M.E., Pinel, P., Dehaene, S., Brannon, E.M., Pelphey, K.A., 2009. The neural development of an abstract concept of number. *J. Cogn. Neurosci.* 21 (11), 2217–2229. <http://dx.doi.org/10.1162/jocn.2008.211159>.
- Cantlon, J.F., Pinel, P., Dehaene, S., Pelphey, K.A., 2011. Cortical representations of symbols, objects, and faces are pruned back during early childhood. *Cereb. Cortex* 21 (1), 191–199. <http://dx.doi.org/10.1093/cercor/bhq078>.
- Cappelletti, M., Lee, H.L., Freeman, E.D., Price, C.J., 2010. The role of right and left parietal lobes in the conceptual processing of numbers. *J. Cogn. Neurosci.* 22 (2), 331–346. <http://dx.doi.org/10.1162/jocn.2009.21246>.
- Carreiras, M., Quiñones, I., Hernández-Cabrera, J.A., Duñabeitia, J.A., 2015. Orthographic coding: brain activation for letters, symbols, and digits. *Cereb. Cortex* 25 (12), 4748–4760. <http://dx.doi.org/10.1093/cercor/bhu163>.
- Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129 (3), 564–583. <http://dx.doi.org/10.1093/brain/awl004>.
- Chochon, F., Cohen, L., van de Moortele, P.F., Dehaene, S., 1999. Differential contributions of the left and right inferior parietal lobules to number processing. *J. Cogn. Neurosci.* 11 (6), 617–630. <http://dx.doi.org/10.1162/089892999563689>.
- Chrisomalis, S., 2010. *Numerical Notation: A Comparative History*, 1st ed. Cambridge University Press, New York, NY.
- Church, J.A., Balota, D.A., Petersen, S.E., Schlaggar, B.L., 2011. Manipulation of length and lexicality localizes the functional neuroanatomy of phonological processing in adult readers. *J. Cogn. Neurosci.* 23 (6), 1475–1493. <http://dx.doi.org/10.1162/jocn.2010.21515>.
- Coderre, E.L., Filippini, C.G., Newhouse, P.A., Dumas, J.A., 2009. Ichi, ni, 3, 4: neural representation of kana, kanji, and Arabic numbers in native Japanese speakers. *Brain Cogn.* 70 (3), 289–296. <http://dx.doi.org/10.1016/j.bandc.2009.03.002>.
- Cohen Kadosh, R., Cohen Kadosh, K., Kaas, A., Henik, A., Goebel, R., 2007a. Notation-dependent and -independent representations of numbers in the parietal lobes. *Neuron* 53 (2), 307–314. <http://dx.doi.org/10.1016/j.neuron.2006.12.025>.
- Cohen Kadosh, R., Cohen Kadosh, K., Schuhmann, T., Kaas, A., Goebel, R., Henik, A., Sack, A.T., 2007b. Virtual dyscalculia induced by parietal-lobe TMS impairs automatic magnitude processing. *Curr. Biol.* 17 (8), 689–693. <http://dx.doi.org/10.1016/j.cub.2007.02.056>.
- Cohen Kadosh, R., Lammertyn, J., Izard, V., 2008. Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. *Prog. Neurobiol.* 84 (2), 132–147. <http://dx.doi.org/10.1016/j.pneurobio.2007.11.001>.
- Cohen, L., Dehaene, S., 1991. Neglect dyslexia for numbers? A case report. *Cogn. Neuropsychol.* 8 (April), 39–58. <http://dx.doi.org/10.1080/02643299108253366>.
- Cohen, L., Dehaene, S., 1995. Number processing in pure alexia: the effect of hemispheric asymmetries and task demands. *Neurocase* 1 (2), 121–137. <http://dx.doi.org/10.1080/13554799508402356>.
- Cohen, L., Dehaene, S., 2004. Specialization within the ventral stream: the case for the visual word form area. *NeuroImage* 22 (1), 466–476. <http://dx.doi.org/10.1016/j.neuroimage.2003.12.049>.
- Cohen, L., Dehaene, S., Naccache, L., Lehéry, S., Dehaene-Lambertz, G., Hénaff, M.A., Michel, F., 2000. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain* 123, 291–307. <http://dx.doi.org/10.1093/brain/123.2.291>.
- Cohen, L., Lehéry, S., Chochon, F., Lemer, C., Rivaud, S., Dehaene, S., 2002. Language-specific tuning of visual cortex? Functional properties of the visual word form area. *Brain* 125 (5), 1054–1069. <http://dx.doi.org/10.1093/brain/awf094>.
- Cohen, D.J., 2009. Integers do not automatically activate their quantity representation. *Psychon. Bull. Rev.* 16 (2), 332–336. <http://dx.doi.org/10.3758/PBR.16.2.332>.
- Cui, J., Yu, X., Yang, H., Chen, C., Liang, P., Zhou, X., 2013. Neural correlates of quantity processing of numeral classifiers. *Neuropsychology* 27 (5), 583–594. <http://dx.doi.org/10.1037/a0033630>.
- Cummine, J., Szepesvári, E., Chouinard, B., Hanif, W., Georgiou, G.K., 2014. A functional investigation of RAN letters, digits, and objects: how similar are they? *Behav. Brain Res.* 275, 157–165. <http://dx.doi.org/10.1016/j.bbr.2014.08.038>.
- Cummine, J., Chouinard, B., Szepesvári, E., Georgiou, G.K., 2015. An examination of the rapid automatized naming-reading relationship using functional magnetic resonance imaging. *Neuroscience* 305, 49–66. <http://dx.doi.org/10.1016/j.neuroscience.2015.07.071>.
- Daitch, A.L., Foster, B.L., Schrouff, J., Rangarajan, V., Kaşıkçı, I., Gattas, S., Parvizi, J., 2016. Mapping human temporal and parietal neuronal population activity and functional coupling during mathematical cognition. *Proc. Natl. Acad. Sci. U. S. A.* 113 (46), E7277–E7286. <http://dx.doi.org/10.1073/pnas.1608434113>.
- Damarla, S.R., Cherkassky, V.L., Just, M.A., 2016. Modality-independent representations of small quantities based on brain activation patterns. *Hum. Brain Mapp.* 37 (4), 1296–1307. <http://dx.doi.org/10.1002/hbm.23102>.
- Defever, E., Sasanguie, D., Gebuis, T., Reynvoet, B., 2011. Children's representation of symbolic and nonsymbolic magnitude examined with the priming paradigm. *J. Exp. Child Psychol.* 109 (2), 174–186. <http://dx.doi.org/10.1016/j.jecp.2011.01.002>.
- Dehaene, S., Cohen, L., 1995. Towards an anatomical and functional model of number processing. *Math. Cogn.* 1 (1), 83–120.
- Dehaene, S., Cohen, L., 2007. Cultural recycling of cortical maps. *Neuron* 56 (2), 384–398. <http://dx.doi.org/10.1016/j.neuron.2007.10.004>.
- Dehaene, S., Cohen, L., 2011. The unique role of the visual word form area in reading. *Trends Cogn. Sci.* 15 (6), 254–262. <http://dx.doi.org/10.1016/j.tics.2011.04.003>.
- Dehaene, S., Piazza, M., Pinel, P., Cohen, L., 2003. Three parietal circuits for number processing. *Cogn. Neuropsychol.* 20 (3–6), 487–506. <http://dx.doi.org/10.1080/02643290244000239>.
- Dehaene, S., 1992. Varieties of numerical abilities. *Cognition* 44 (1–2), 1–42. [http://dx.doi.org/10.1016/0010-0277\(92\)90049-N](http://dx.doi.org/10.1016/0010-0277(92)90049-N).
- Diester, I., Nieder, A., 2007. Semantic associations between signs and numerical categories in the prefrontal cortex. *PLoS Biol.* 5 (11), 2684–2695. <http://dx.doi.org/10.1371/journal.pbio.0050294>.
- Downing, P.E., Jiang, Y.H., Shuman, M., Kanwisher, N., 2001. A cortical area selective for visual processing of the human body. *Science* 293 (5539), 2470–2473. <http://dx.doi.org/10.1126/science.1063414>.
- Eger, E., Sterzer, P., Russ, M.O., Giraud, A.-L., Kleinschmidt, A., 2003. A supramodal number representation in human intraparietal cortex. *Neuron* 37 (4), 719–726. [http://dx.doi.org/10.1016/S0896-6273\(03\)00036-9](http://dx.doi.org/10.1016/S0896-6273(03)00036-9).
- Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage* 25 (4), 1325–1335. <http://dx.doi.org/10.1016/j.neuroimage.2004.12.034>.
- Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum. Brain Mapp.* 30 (9), 2907–2926. <http://dx.doi.org/10.1002/hbm.20718>.
- Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Fox, P.T., 2012. Activation likelihood estimation meta-analysis revisited. *NeuroImage* 59 (3), 2349–2361. <http://dx.doi.org/10.1016/j.neuroimage.2011.09.017>.
- Eickhoff, S.B., Nichols, T.E., Laird, A.R., Hoffstaedter, F., Amunts, K., Fox, P.T., et al., 2016. Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. *NeuroImage* 137, 70–85. <http://dx.doi.org/10.1016/j.neuroimage.2016.04.072>.
- Eickhoff, S.B., Laird, A.R., Fox, P.M., Lancaster, J.L., Fox, P.T., 2017. Implementation errors in the GingerALE Software: Description and recommendations. *Hum. Brain Mapp.* 38 (1), 7–11. <http://dx.doi.org/10.1002/hbm.23342>.
- Fernandes, M.A., Moscovitch, M., Ziegler, M., Grady, C., 2005. Brain regions associated with successful and unsuccessful retrieval of verbal episodic memory as revealed by divided attention. *Neuropsychologia* 43 (8), 1115–1127. <http://dx.doi.org/10.1016/j.neuropsychologia.2004.11.026>.
- Fias, W., Lammertyn, J., Caessens, B., Orban, G.A., 2007. Processing of abstract ordinal knowledge in the horizontal segment of the intraparietal sulcus. *J. Neurosci.* 27 (33), 8952–8956. <http://dx.doi.org/10.1523/jneurosci.2076-07.2007>.
- Fox, P.T., Laird, A.R., Eickhoff, S.B., Lancaster, J.L., Fox, M., Uecker, A.M., et al., 2013. *User Manual for GingerALE 2.3*. Research Imaging Institute, UT Health Science Center, San Antonio, TX.
- Friederici, A.D., Bahlmann, J., Heim, S., Schubotz, R.I., Anwander, A., 2006. The brain differentiates human and non-human grammars: functional localization and structural connectivity. *Proc. Natl. Acad. Sci. U. S. A.* 103 (7), 2458–2463. <http://dx.doi.org/10.1073/pnas.0509389103>.
- Fulbright, R.K., Manson, S.C., Skudlarski, P., Lacadie, C.M., Gore, J.C., 2003. Quantity determination and the distance effect with letters, numbers, and shapes: a functional MR imaging study of number processing. *Am. J. Neuroradiol.* 24 (2), 193–200.
- Girelli, L., Lucangeli, D., Butterworth, B., 2000. The development of automaticity in accessing number magnitude. *J. Exp. Child Psychol.* 76 (2), 104–122. <http://dx.doi.org/10.1006/jecp.2000.2564>.
- Grabner, R.H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., 2013. The function of the left angular gyrus in mental arithmetic: evidence from the associative confusion effect. *Hum. Brain Mapp.* 34 (5), 1013–1024. <http://dx.doi.org/10.1002/hbm.21489>.
- Grill-Spector, K., Malach, R., 2001. fMRI-adaptation: a tool for studying the functional properties of human cortical neurons. *Acta Psychol.* 107 (1–3), 293–321. [http://dx.doi.org/10.1016/S0001-6918\(01\)00019-1](http://dx.doi.org/10.1016/S0001-6918(01)00019-1).
- Grotheer, M., Ambrus, G.G., Kovács, G., 2016a. Causal evidence of the involvement of the number form area in the visual detection of numbers and letters. *NeuroImage* 132,

- 314–319. <http://dx.doi.org/10.1016/j.neuroimage.2016.02.069>.
- Grotheer, M., Herrmann, K.-H., Kovács, G., 2016b. Neuroimaging evidence of a bilateral representation for visually presented numbers. *J. Neurosci.* 36 (1), 88–97. <http://dx.doi.org/10.1523/JNEUROSCI.2129-15.2016>.
- Gullick, M.M., Temple, E., 2011. Are historic years understood as numbers or events? An fMRI study of numbers with semantic associations. *Brain Cogn.* 77 (3), 356–364. <http://dx.doi.org/10.1016/j.bandc.2011.09.004>.
- Hamilton, J.P., Mirhin, M., Polk, T.A., Mirkin, M., 2006. Category-level contributions to the alphanumeric category effect in visual search. *Psychon. Bull. Rev.* 13 (6), 1074–1077. <http://dx.doi.org/10.3758/BF03213928>.
- Hannagan, T., Amedi, A., Cohen, L., Dehaene-Lambertz, G., Dehaene, S., 2015. Origins of the specialization for letters and numbers in ventral occipitotemporal cortex. *Trends Cogn. Sci.* 19 (7), 374–382. <http://dx.doi.org/10.1016/j.tics.2015.05.006>.
- Henik, A., Tzelgov, J., 1982. Is three greater than five: the relation between physical and semantic size in comparison tasks. *Mem. Cogn.* 10 (4), 389–395. <http://dx.doi.org/10.3758/BF03202431>.
- Hermes, D., Rangarajan, V., Foster, B.L., King, J.-R., Kasikci, I., Miller, K.J., Parvizi, J., 2015. Electrophysiological responses in the ventral temporal cortex during reading of numerals and calculation. *Cereb. Cortex* (2011) bhv250. <http://dx.doi.org/10.1093/cercor/bhv250>.
- Holloway, I.D., Ansari, D., 2009. Mapping numerical magnitudes onto symbols: the numerical distance effect and individual differences in children's mathematics achievement. *J. Exp. Child Psychol.* 103 (1), 17–29. <http://dx.doi.org/10.1016/j.jecp.2008.04.001>.
- Holloway, I.D., van Atteveldt, N., Blomert, L., Ansari, D., 2015. Orthographic dependency in the neural correlates of reading: evidence from audiovisual integration in English readers. *Cereb. Cortex* 25 (6), 1544–1553. <http://dx.doi.org/10.1093/cercor/bht347>.
- Houdé, O., Rossi, S., Lubin, A., Joliot, M., 2010. Mapping numerical processing, reading, and executive functions in the developing brain: an fMRI meta-analysis of 52 studies including 842 children. *Dev. Sci.* 13 (6), 876–885. <http://dx.doi.org/10.1111/j.1467-7687.2009.00938.x>.
- Hubbard, E.M., Piazza, M., Pinel, P., Dehaene, S., 2005. Interactions between number and space in parietal cortex. *Nat. Rev. Neurosci.* 6 (6), 435–448. <http://dx.doi.org/10.1038/nrn1684>.
- Hurst, M., Anderson, U., Cordes, S., 2017. Mapping among number words, numerals, and nonsymbolic quantities in preschoolers. *J. Cog. Dev.* 18 (1), 41–62. <http://dx.doi.org/10.1080/15248372.2016.1228653>.
- Ischebeck, A., Heim, S., Siedentopf, C., Zamarian, L., Schocke, M., Kremser, C., et al., 2008. Are numbers special? Comparing the generation of verbal materials from ordered categories (months) to numbers and other categories (animals) in an fMRI study. *Hum. Brain Mapp.* 29 (8), 894–909. <http://dx.doi.org/10.1002/hbm.20433>.
- James, K.H., James, T.W., Jobard, G., Wong, A.C.N., Gauthier, I., 2005. Letter processing in the visual system: different activation patterns for single letters and strings. *Cogni. Affect. Behav. Neurosci.* 5 (4), 452–466. <http://dx.doi.org/10.3758/CABN.5.4.452>.
- Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.* 17 (11), 4302–4311. <http://dx.doi.org/10.3410/f.717989828.793472998>.
- Kanwisher, N., 2010. Functional specificity in the human brain: a window into the functional architecture of the mind. *Proc. Natl. Acad. Sci. U. S. A.* 107 (25), 11163–11170. <http://dx.doi.org/10.1073/pnas.1005062107>.
- Karmiloff-Smith, A., 2015. An alternative to domain-general or domain-specific frameworks for theorizing about human evolution and ontogenesis. *AIMS Neurosci.* 2 (2), 91–104. <http://dx.doi.org/10.3934/Neuroscience.2015.2.91>.
- Kaufmann, L., Koppeltaetter, F., Siedentopf, C., Haala, I., Haberlandt, E., Zimmerhackl, L.-B., et al., 2006. Neural correlates of the number-size interference task in children. *Neuroreport* 17 (6), 587–591 (Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16603917>).
- Kaufmann, L., Vogel, S.E., Starke, M., Kremser, C., Schocke, M., 2009. Numerical and non-numerical ordinality processing in children with and without developmental dyscalculia: evidence from fMRI. *Cogn. Dev.* 24 (4), 486–494. <http://dx.doi.org/10.1016/j.cogdev.2009.09.001>.
- Kaufmann, L., Wood, G., Rubinsten, O., Henik, A., 2011. Meta-Analyses of developmental fMRI studies investigating typical and atypical trajectories of number processing and calculation. *Dev. Neuropsychol.* 36 (6), 763–787. <http://dx.doi.org/10.1080/87565641.2010.549884>.
- Kim, K.K., Karunanayaka, P., Privitera, M.D., Holland, S.K., Szaflarski, J.P., 2011. Semantic association investigated with functional MRI and independent component analysis. *Epilepsy Behav.* 20 (4), 613–622. <http://dx.doi.org/10.1016/j.yebeh.2010.11.010>.
- Knops, A., Nuerk, H.-C., Fimm, B., Vohn, R., Willmes, K., 2006. A special role for numbers in working memory? An fMRI study. *NeuroImage* 29 (1), 1–14. <http://dx.doi.org/10.1016/j.neuroimage.2005.07.009>.
- Koul, A., Tyagi, V., Singh, N.C., 2014. Notational usage modulates attention networks in binumerates. *Front. Hum. Neurosci.* 8. <http://dx.doi.org/10.3389/fnhum.2014.00326>.
- Laird, A.R., Lancaster, J.L., Fox, P.T., 2005. BrainMap: The Social Evolution of a Human Brain Mapping Database. *Neuroinformatics* 3 (1), 065–078. <http://dx.doi.org/10.1385/Ni:3:1:065>.
- Laird, A.R., Robinson, J.L., McMillan, K.M., Tordesillas-Gutiérrez, D., Moran, S.T., Gonzales, S.M., et al., 2010. Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. *NeuroImage* 51 (2), 677–683. <http://dx.doi.org/10.1016/j.neuroimage.2010.02.048>.
- Lancaster, J.L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., et al., 2007. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Hum. Brain Mapp.* 28 (11), 1194–1205. <http://dx.doi.org/10.1002/hbm.20345>.
- Libertus, M.E., Brannon, E.M., Pelphrey, K.A., 2009. Developmental changes in category-specific brain responses to numbers and letters in a working memory task. *NeuroImage* 44 (4), 1404–1414. <http://dx.doi.org/10.1016/j.neuroimage.2008.10.027>.
- Lonnemann, J., Linkersdörfer, J., Hasselhorn, M., Lindberg, S., 2011. Symbolic and non-symbolic distance effects in children and their connection with arithmetic skills. *J. Neurolinguist.* 24 (5), 583–591.
- Lyons, I.M., Ansari, D., 2009. The cerebral basis of mapping nonsymbolic numerical quantities onto abstract symbols: an fMRI training study. *J. Cogn. Neurosci.* 21 (9), 1720–1735. <http://dx.doi.org/10.1162/jocn.2009.21124>.
- Lyons, I.M., Beilock, S.L., 2013. Ordinality and the nature of symbolic numbers. *J. Neurosci.* 33 (43), 17052–17061. <http://dx.doi.org/10.1523/JNEUROSCI.1775-13.2013>.
- Lyons, I.M., Vogel, S.E., Ansari, D., 2016. On the ordinality of numbers: a review of neural and behavioral studies. *The Mathematical Brain Across the Lifespan*, 1st ed. Elsevier B.V. pp. 187–221. <http://dx.doi.org/10.1016/bs.pbr.2016.04.010>.
- McCandless, B.D., Cohen, L., Dehaene, S., 2003. The visual word form area: expertise for reading in the fusiform gyrus. *Trends Cogn. Sci.* 7 (7), 293–299. [http://dx.doi.org/10.1016/S1364-6613\(03\)00134-7](http://dx.doi.org/10.1016/S1364-6613(03)00134-7).
- Merkley, R., Wilkey, E.D., Matejko, A.A., 2016. Exploring the origins and development of the visual number form area: A functionally specialized and domain-specific region for the processing of number symbols? *J. Neurosci.* 17, 4659–4661. <http://dx.doi.org/10.1523/JNEUROSCI.0710-16.2016>.
- Meyer, L., Obleser, J., Anwender, A., Friederici, A.D., 2012. Linking ordering in Broca's area to storage in left temporo-parietal regions: the case of sentence processing. *NeuroImage* 62 (3), 1987–1998. <http://dx.doi.org/10.1016/j.neuroimage.2012.05.052>.
- Moeller, K., Willmes, K., Klein, E., 2015. A review on functional and structural brain connectivity in numerical cognition. *Front. Hum. Neurosci.* 9 (May), 1–14. <http://dx.doi.org/10.3389/fnhum.2015.00227>.
- Mundy, E., Gilmore, C.K., 2009. Children's mapping between symbolic and nonsymbolic representations of number. *J. Exp. Child Psychol.* 103 (4), 490–502. <http://dx.doi.org/10.1016/j.jecp.2009.02.003>.
- Naparstek, S., Henik, A., 2010. Count me in! On the automaticity of numerosity processing. *J. Exp. Psychol. Learn. Mem. Cogn.* 36 (4), 1053–1059. <http://dx.doi.org/10.1037/a0019766>.
- Nieder, A., 2009. Prefrontal cortex and the evolution of symbolic reference. *Curr. Opin. Neurobiol.* 19 (1), 99–108. <http://dx.doi.org/10.1016/j.conb.2009.04.008>.
- Ortuno, F., Ojeda, N., Arbizu, J., López, P., Martí-Climent, J.M., Peñuelas, I., Cervera, S., 2002. Sustained attention in a counting task: normal performance and functional neuroanatomy. *NeuroImage* 17 (1), 411–420. <http://dx.doi.org/10.1006/nimg.2002.1168>.
- Park, J., Hebrank, A., Polk, T.A., Park, D.C., 2012. Neural dissociation of number from letter recognition and its relationship to parietal numerical processing. *J. Cogn. Neurosci.* 24 (1), 39–50. <http://dx.doi.org/10.1162/jocn.2011.00085>.
- Paulesu, E., Frith, C.D., Frackowiak, R.S.J., 1993. The neural correlates of the verbal component of working memory. *Nature* 362 (6418), 342–345. <http://dx.doi.org/10.1038/362342a0>.
- Peters, L., De Smedt, B., Op de Beeck, H.P., 2015. The neural representation of Arabic digits in visual cortex. *Front. Hum. Neurosci.* 9 (September), 517. <http://dx.doi.org/10.3389/fnhum.2015.00517>.
- Piazza, M., Eger, E., 2016. Neural foundations and functional specificity of number representations. *Neuropsychologia* 83, 257–273. <http://dx.doi.org/10.1016/j.neuropsychologia.2015.09.025>.
- Pinel, P., Le Clec'h, G., van de Moortele, P.-F., Naccache, L., Le Bihan, D., Dehaene, S., 1999. Event-related fMRI analysis of the cerebral circuit for number comparison. *NeuroReport* 10 (7), 1473–1479. <http://dx.doi.org/10.1097/00001756-199905140-00015>.
- Pinel, P., Dehaene, S., Rivière, D., LeBihan, D., 2001. Modulation of parietal activation by semantic distance in a number comparison task. *NeuroImage* 14 (5), 1013–1026. <http://dx.doi.org/10.1006/nimg.2001.0913>.
- Pinel, P., Piazza, M., Le Bihan, D., Dehaene, S., 2004. Distributed and overlapping cerebral representations of number, size, and luminance during comparative judgments. *Neuron* 41 (6), 983–993. [http://dx.doi.org/10.1016/S0896-6273\(04\)00107-2](http://dx.doi.org/10.1016/S0896-6273(04)00107-2).
- Plaut, D.C., Behrmann, M., 2011. Complementary neural representations for faces and words: a computational exploration. *Cogn. Neuropsychol.* 28 (3–4), 251–275. <http://dx.doi.org/10.1080/02643294.2011.609812>.
- Polk, T.A., Farah, M.J., 1998. The neural development and organization of letter recognition: evidence from functional neuroimaging, computational modeling, and behavioral studies. *Proc. Natl. Acad. Sci. U. S. A.* 95 (3), 847–852. <http://dx.doi.org/10.1073/pnas.95.3.847>.
- Polk, T.A., Stalcup, M., Aguirre, G.K., Alsop, D.C., D'Esposito, M., Detre, J.A., Farah, M.J., 2002. Neural specialization for letter recognition. *J. Cogn. Neurosci.* 14 (2), 145–159. <http://dx.doi.org/10.1162/089892902317236803>.
- Price, G.R., Ansari, D., 2011. Symbol processing in the left angular gyrus: evidence from passive perception of digits. *NeuroImage* 57 (3), 1205–1211. <http://dx.doi.org/10.1016/j.neuroimage.2011.05.035>.
- Price, C.J., Devlin, J.T., 2003. The myth of the visual word form area. *NeuroImage* 19 (3), 473–481. [http://dx.doi.org/10.1016/S1053-8119\(03\)00084-3](http://dx.doi.org/10.1016/S1053-8119(03)00084-3).
- Price, C.J., Devlin, J.T., 2011. The interactive account of ventral occipitotemporal contributions to reading. *Trends Cogn. Sci.* 15 (6), 246–253. <http://dx.doi.org/10.1016/j.tics.2011.04.001>.
- Price, C.J., Devlin, J.T., Moore, C.J., Morton, C., Laird, A.R., 2005. Meta-analyses of object naming: effect of baseline. *Hum. Brain Mapp.* 25 (1), 70–82. <http://dx.doi.org/10.1002/hbm.20345>.

- 10.1002/hbm.20132.
- Price, C.J., 1998. The functional anatomy of word comprehension and production. *Trends Cogn. Sci.* 2 (8), 281–288. [http://dx.doi.org/10.1016/S1364-6613\(98\)01201-7](http://dx.doi.org/10.1016/S1364-6613(98)01201-7).
- Reinke, K., Fernandes, M., Schwindt, G., O'Craven, K., Grady, C.L., 2008. Functional specificity of the visual word form area: general activation for words and symbols but specific network activation for words. *Brain Lang.* 104 (2), 180–189. <http://dx.doi.org/10.1016/j.bandl.2007.04.006>.
- Rivera, S.M., Reiss, A.L., Eckert, M.A., Menon, V., 2005. Developmental changes in mental arithmetic: evidence for increased functional specialization in the left inferior parietal cortex. *Cereb. Cortex* 15 (11), 1779–1790. <http://dx.doi.org/10.1093/cercor/bhi055>.
- Roux, F.E., Lubrano, V., Lauwers-Cances, V., Giussani, C., Démonet, J.F., 2008. Cortical areas involved in Arabic number reading. *Neurology* 70 (3), 210–217. <http://dx.doi.org/10.1212/01.wnl.0000297194.14452.a0>.
- Rubinsten, O., Henik, A., Berger, A., Shahar-Shalev, S., 2002. The development of internal representations of magnitude and their association with Arabic numerals. *J. Exp. Child Psychol.* 81 (1), 74–92. <http://dx.doi.org/10.1006/jecp.2001.2645>.
- Saygin, Z.M., Osher, D.E., Norton, E.S., Youssoufian, D.A., Beach, S.D., Feather, J., et al., 2016. Connectivity precedes function in the development of the visual word form area. *Nat. Neurosci.* 19 (9), 1250–1255. <http://dx.doi.org/10.1038/nn.4354>.
- Schlaggar, B.L., McCandliss, B.D., 2007. Development of neural systems for reading. *Annu. Rev. Neurosci.* 30 (1), 475–503. <http://dx.doi.org/10.1146/annurev.neuro.28.061604.135645>.
- Seghier, M., 2012. The angular gyrus: multiple functions and multiple subdivisions. *The Neuroscientist* 19 (1), 43–61. <http://dx.doi.org/10.1177/1073858412440596>.
- Shum, J., Hermes, D., Foster, B.L., Dastjerdi, M., Rangarajan, V., Winawer, J., et al., 2013. A brain area for visual numerals. *J. Neurosci.* 33 (16), 6709–6715. <http://dx.doi.org/10.1523/JNEUROSCI.4558-12.2013>.
- Smith, D.E., Karpinski, L.C., 1911. *The Hindu–Arabic Numerals*. Ginn and Company, Boston and London.
- Sokolowski, H.M., Fias, W., Mousa, A., Ansari, D., 2017. Common and distinct brain regions in both parietal and frontal cortex support symbolic and nonsymbolic number processing in humans: a functional neuroimaging meta-analysis. *NeuroImage* 146 (October), 376–394. <http://dx.doi.org/10.1016/j.neuroimage.2016.10.028>.
- Stanesco-Cosson, R., Pinel, P., van de Moortele, P.F., Le Bihan, D., Cohen, L., Dehaene, S., 2000. Understanding dissociations in dyscalculia: a brain imaging study of the impact of number size on the cerebral networks for exact and approximate calculation. *Brain* 123 (11), 2240–2255. <http://dx.doi.org/10.1093/brain/123.11.2240>.
- Starrfelt, R., Behrmann, M., 2011. Number reading in pure alexia—A review. *Neuropsychologia* 49 (9), 2283–2298. <http://dx.doi.org/10.1016/j.neuropsychologia.2011.04.028>.
- Talairach, J., Tournoux, P., 1988. *Co-Planar stereotaxic atlas of the human brain*. Direct 270.
- Tang, J., Critchley, H.D., Glaser, D.E., Dolan, R.J., Butterworth, B., 2006. Imaging informational conflict: a functional magnetic resonance imaging study of numerical stroop. *J. Cogn. Neurosci.* 18 (12), 2049–2062. <http://dx.doi.org/10.1162/jocn.2006.18.12.2049>.
- Thesen, T., McDonald, C.R., Carlson, C., Doyle, W., Cash, S., Sherfey, J., et al., 2012. Sequential then interactive processing of letters and words in the left fusiform gyrus. *Nat. Commun.* 3, 1284. <http://dx.doi.org/10.1038/ncomms2220>.
- Tsao, D.Y., Freiwald, W.A., Knutsen, T.A., Mandeville, J.B., Tootell, R.B.H., 2003. Faces and objects in macaque cerebral cortex. *Nat. Neurosci.* 6 (9), 989–995. <http://dx.doi.org/10.1038/nn1111>.
- Turkeltaub, P.E., Eickhoff, S.B., Laird, A.R., Fox, M., Wiener, M., Fox, P., 2012. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Hum. Brain Mapp.* 33 (1), 1–13. <http://dx.doi.org/10.1002/hbm.21186>.
- van der Ven, F., Takashima, A., Segers, E., Fernández, G., Verhoeven, L., 2016. Non-symbolic and symbolic notations in simple arithmetic differentially involve intraparietal sulcus and angular gyrus activity. *Brain Res.* 1643, 91–102. <http://dx.doi.org/10.1016/j.brainres.2016.04.050>.
- Wiener, M., Hamilton, R., Turkeltaub, P., Matell, M.S., Coslett, H.B., 2010a. Fast forward: supramarginal gyrus stimulation alters time measurement. *J. Cogn. Neurosci.* 22 (1), 23–31. <http://dx.doi.org/10.1162/jocn.2009.21191>.
- Wiener, M., Turkeltaub, P.E., Coslett, H.B., 2010b. Implicit timing activates the left inferior parietal cortex. *Neuropsychologia* 48 (13), 3967–3971. <http://dx.doi.org/10.1016/j.neuropsychologia.2010.09.014>.
- Wu, S.S., Chang, T.T., Majid, A., Caspers, S., Eickhoff, S.B., Menon, V., 2009. Functional heterogeneity of inferior parietal cortex during mathematical cognition assessed with cytoarchitectonic probability maps. *Cereb. Cortex* 19 (12), 2930–2945. <http://dx.doi.org/10.1093/cercor/bhp063>.
- Xia, M., Wang, J., He, Y., 2013. BrainNet viewer: a network visualization tool for human brain connectomics. *PLoS One* 8 (7). <http://dx.doi.org/10.1371/journal.pone.0068910>.
- Yin, L.-J., Lou, Y.-T., Fan, M.-X., Wang, Z.-X., Hu, Y., 2015. Neural evidence for the use of digit-image mnemonic in a superior memorist: an fMRI study. *Front. Hum. Neurosci.* 9, 109. <http://dx.doi.org/10.3389/fnhum.2015.00109>.
- Yovel, G., Freiwald, W.A., 2013. Face recognition systems in monkey and human: are they the same thing? *F1000Prime Rep.* 5 (April), 10. <http://dx.doi.org/10.12703/p5-10>.
- Zago, L., Petit, L., Turbelin, M.-R., Andersson, F., Vigneau, M., Tzourio-Mazoyer, N., 2008. How verbal and spatial manipulation networks contribute to calculation: an fMRI study. *Neuropsychologia* 46 (9), 2403–2414. <http://dx.doi.org/10.1016/j.neuropsychologia.2008.03.001>.
- Zamarian, L., Ischebeck, A., Delazer, M., 2009. Neuroscience of learning arithmetic—evidence from brain imaging studies. *Neurosci. Biobehav. Rev.* 33 (6), 909–925. <http://dx.doi.org/10.1016/j.neubiorev.2009.03.005>.
- Zarnhofer, S., Braunstein, V., Ebner, F., Koschutnig, K., Neuper, C., Reishofer, G., Ischebeck, A., 2012. The influence of verbalization on the pattern of cortical activation during mental arithmetic. *Behav. Brain Funct.* 8 (1), 13. <http://dx.doi.org/10.1186/1744-9081-8-13>.
- Zhang, H., Chen, C., Zhou, X., 2012. Neural correlates of numbers and mathematical terms. *NeuroImage* 60 (1), 230–240. <http://dx.doi.org/10.1016/j.neuroimage.2011.12.006>.