

Neural foundations and functional specificity of number representations

Manuela Piazza a,b,c,d,n, Evelyn Eger b,c,d

a Center for Mind/Brain Sciences, University of Trento, Italy

b Cognitive Neuroimaging Unit, INSERM, Gif sur Yvette, France

c NeuroSpin Center, DSV, I2BM, CEA, Gif sur Yvette, France

d University of Paris 11, Orsay, France

ABSTRACT

Number is a complex category, as with the word “number” we may refer to different entities. First, it is a perceptual property that characterizes any set of individual items, namely its cardinality. The ability to extract the (approximate) cardinality of sets is almost universal in the animal domain and present in humans since birth. In primates, posterior parietal cortex seems to be a crucial site for this ability, even if the degree of selectivity of numerical representations in parietal cortex reported to date appears much lower compared to that of other semantic categories in the ventral stream. Number can also be intended as a mathematical object, which we humans use to count, measure, and order: a (verbal or visual) symbol that stands for the cardinality of a set, the intensity of a continuous quantity or the position of an item on a list. Evidence points to a convergence towards parietal cortex for the semantic coding of numerical symbols and to the bilateral occipitotemporal cortex for the shape coding of Arabic digits and other number symbols.

1. Introduction

Consider a child estimating the relative number of candies on different bowls in order to decide which one to get, and a broker pondering upon the numbers in time series describing the latest development of the stock market in order to decide his next move. The word “number” in these two cases refers to extremely different entities. First, it is a property that characterizes any set of concrete individual items, namely its cardinality. In this sense, even if cardinality is not bound to any specific sensory system (a basket of three cherries, the notes of a triadic accord, the beats of the basic rhythm of a Waltz dance, all are universally perceived as sharing a common property of “threeness”), it is part of the realm of percepts. On the other hand, number can also be intended as a more abstract entity: the mathematical object which we use to count, measure, and label: a (verbal or visual) symbol that stands for the cardinality of a set, the intensity of a continuous quantity, and/or the position of an item in a list (order). Number as a percept is automatically and preverbally extracted by humans since the youngest age and also by several non-human species. On the contrary, number in the mathematical sense is a purely cultural object, not part of the evolutionary toolkit of the homo sapiens mind, but invented the first time in its most rudimentary form

around 5000 years ago by the Babylonians, and still nowadays not universal across the human cultures (Gordon, 2004; Pica et al., 2004). It is a question of interest how we humans, through learning and education make sense of numerical symbols and thus construct a mental representation of the mathematical object “number”. Surely perceptually, concrete collections and numerical symbols are extremely different in their surface form, and the brain must follow separate and specific processing pathways to process them. However, one hypothesis is that we make sense of numerical symbols by connecting the sensory representations of the symbols' shapes to a pre-existing representation of the corresponding cardinalities. In this paper we review the scientific literature investigating the neurocognitive underpinnings of these different forms of numerical representations that emerge when we either process concrete quantities or interpret numerical symbols. For each, we review the existing behavioural, neurophysiological and functional imaging data. Then, we put these findings in the context of the broader literature concerning the functional role of

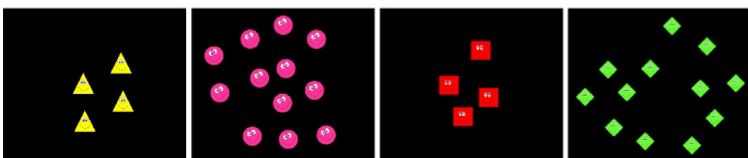
a

Familiarisation



... « tu-tu-tu-tu-tu-tu-tu-tu-tu-tu » ... « ra-ra-ra-ra-ra-ra-ra-ra-ra-ra » ...
 or
 ... « tuuuuu-tuuuuu-tuuuuu-tuuuuu » ... « raaaaa-raaaaa-raaaaa-raaaaa » ...

Test



b

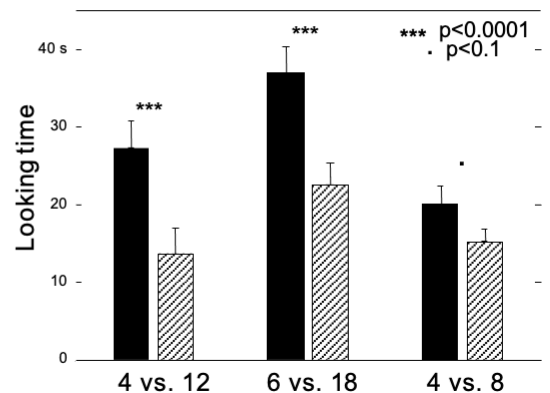


Fig. 1. Spontaneous cross-modal numerical matching in newborns: Left panel: schematic example of stimuli from a cross-modal adaptation paradigm (Coubart et al., 2014; Izard et al., 2009), where newborns were familiarised with syllable sequences of a fixed number (e.g., 12 vs. 4, across subjects), for two minutes. After this phase they were also presented with test images, which depicted either the same (congruent) or a different (incongruent) number of shapes as the number of syllables heard. Three groups of infants were tested, for which different numerosities were contrasted: 4 vs. 12; 6 vs. 18 (1:3 ratio), or 4 vs. 8 (1:2 ratio). Right panel: The looking time indicates that newborns spontaneously match number across the auditory and visual modalities, but appear to be only sensitive to large changes (larger than twofold). Adapted from Izard et al. (2009).

the brain regions identified as important for numerical representations, and approach the question of whether the current evidence allows us to claim that there are specific brain circuits dedicated to number or not.

1.1. Number as the cardinality of a set

1.1.1. Behaviour

Human infants, as most non-human animals, appear, since the youngest age, wired up to extract the property “number” when presented with sets of objects: they spontaneously compare sets and mentally combine them through proto-arithmetical computations (McCrink and Wynn, 2004). This ability is not restricted to small collections of only few items, nor to a single sensory modality: newborns for example spontaneously match the number of sounds in a sequence with the number of shapes in an image even in sets of 10 or more items (see Fig. 1) (Coubart et al., 2014; Izard et al., 2009; McCrink and Wynn, 2004). One key feature of this rather abstract sense of number (also referred to in the literature as “approximate number system”, or ANS) is that it is not precise but approximate, and becomes less precise as the magnitude increases, such that discriminability across sets is a function of their numerical ratio (Buckley and Gillman, 1974; Piazza et al., 2004), as captured by Weber's law. The precision of this system (which can be inferred from classical psychophysical tests, and captured by the Weber fraction, or the “just noticeable difference”), is initially very low, and then progressively refines during the lifespan: at birth newborns seem to discriminate between sets only when their number differs by a 1:3 ratio, while adults are sensitive to much smaller differences, possibly due to combined maturation and educational factors (see Piazza, 2010, for a review). For the case of small sets of 1–3 items it seems that the approximate number system can be supplemented by a mechanism relying on object-based attention which keeps track of multiple individual items and thus can be used to perform exact comparisons and additions/subtractions (Wynn, 1992). However, this system (also referred to in the literature as the “object tracking system”) which is limited to small sets, appears different in nature from the approximate sense of number which operates on the entire range of magnitudes (Anobile et al., 2012; D. Burr et al., 2010; Piazza et al., 2011).

In adults, the sense of approximate number is universal and also present in cultures with no counting system and limited words for numbers (Gordon, 2004; Pica et al., 2004). Moreover, like other fundamental perceptual properties such as motion, colour, or size, it is subject to adaptation and thus produces robust after-effects: we tend to overestimate visual sets of a given number of dots if we are previously exposed to smaller sets, and we underestimate them if previously adapted to larger sets (Burr and Ross, 2008). Importantly, number adaptation is not restricted to visual items but also occurs across sensory modalities (audio-visual) and presentation modes (simultaneous-sequential) (Arrighi et al., 2014). This supports the idea that at a certain representational level sensory-specific number representations are brought together and feed into one common modality and mode-invariant representation, as also previously suggested by reports of no behavioural cost in performing numerical operations across sensory modalities compared to within modality conditions (Barth et al., 2005).

How the brain converts sensory stimulation into such rather abstract representation of numerosity is however still an open question. There are two broad views on the issue: one assumes that the numerosity extraction is an object-based mechanism, whereby scenes are first parsed into individual objects, of which the mental representation is then passed on to some form of numerosity estimation systems (Dehaene and Changeux, 1993; Verguts and Fias, 2004), while the others consider that number is the output on mechanism for extracting ensemble statistics, which operates at the level of the scene, and does not rely on object individuation (Dakin et al., 2011; Durgin, 2008). Representative of the first view, for example, Dehaene's model postulates that number is extracted through a dedicated multiple-staged system that first segments the visual input into discrete objects, then discards their non-numerical sensory features (such as the shape, colour, size, density, which are irrelevant as for the property "number"), and extracts number through an accumulator-type of mechanism. As the final step, this model postulates that the output of the accumulator mechanism is fed into "numerosity detector cells", each representing a given numerosity (Dehaene and Changeux, 1993). This class of models, still unspecified in physiological terms especially for what concerns the early extraction stages, relies on the implicit assumption that the visual (and auditory) system is able to individuate an arbitrarily large number of objects while at the same time discarding their associated features, a hypothesis that needs to be reconciled with the current knowledge of the limitations of the object individuation system to 3–4 items at a time (Piazza et al., 2011; Pylyshyn, 2001).

An alternative view considers that number is estimated through a mechanism more similar to those underlying the computations of ensemble statistics (such as average size or orientation; e.g., Ariely (2001)), subtending perception of global patterns in scenes (as opposed to individual item processing). One group of researchers, for example, has suggested that the early extraction stages of visual numerosity consist in a combination of spatial frequency filters, plausibly implemented in low-level visual cortex, related to those involved in estimating texture density (Dakin et al., 2011; Durgin, 2008; Morgan et al., 2014). As a rebuttal to this position, however, Burr and collaborators (Anobile et al., 2014) have recently shown that the psychophysical laws governing numerosity judgements are different from those of density judgements, at least for not too dense displays (< 10 dots per degree). This indicates that extraction of number does not proceed via density estimation, at least not in all circumstances. Developmental studies also

support the view that number can hardly be reduced to a simple combination of low-level stimuli properties: while infants are quite sensitive to changes in the size or brightness of a single item, when presented with sets of multiple items they are more sensitive to changes in number than they are to changes in the items' size (Cordes and Brannon, 2011) or total occupied area (Cordes and Brannon, 2008), suggesting that number is not derived from explicit estimates of these other properties but rather relies on its own dedicated extraction processes in the visual system. In sum, number and other low-level perceptual features, such as average size and/or density are likely to be coded by separate "channels", the detailed characteristics and implementation of which have still to be understood in more detail. The fact that number might be extracted by separate channels from the other physical properties of the stimuli, however, does not exclude that numerical and other physical properties may interfere at some level in the brain. Indeed, it is now well demonstrated that numerical judgements (i.e., deciding which of two sets contain more or less dots) can be heavily influenced by other physical properties of the sets such as item size and density, resulting in sometimes strong congruity effects. For example, subjects instructed to choose the numerically larger of two sets are less accurate when the size of the items or the inter-item distance is incongruent with number (e.g., Gebuis and Reynvoet, 2012). Reciprocally, judgements over the continuous properties of sets, such as cumulative area occupied by the dots, are shown to be influenced by congruency with numerosity, in both adults (Nys and Content, 2012) and children from the age of 3 (Rousselle and Noel, 2008). These reciprocal interferences are also observed in sequential presentation paradigms, where the estimation of the temporal duration of a given sequence of dots is influenced by the number of dots (Dormal et al., 2006; Droit-Volet et al., 2003). Interestingly, some researchers reported that the strength of such interferences correlates with generic inhibition skills (measured, for example, through Stroop-like paradigms) (Cappelletti et al., 2014; Gilmore et al., 2013) suggesting that the representation of number and the non-numerical parameters interfere at the level of the response selection, when subjects need to produce an explicit comparative decision. It remains possible, however, that number and other quantitative properties of scene also interfere earlier than the response selection stage, during the extraction of the information: this could occur, for example, if number and other physical parameters are estimated through the combination of partly overlapping spatial (or temporal) filters.

In sum, despite disagreements on the precise mechanisms subtending the early stages of extraction of the property "number", there is a large consensus that numerosity is automatically extracted from sets, as it is the case for other quantitative information, such as the average size, density, or orientation. Behavioural evidence also suggests that we automatically access a rather abstract representation of number, which is invariant from the sensory modality of stimuli. This high-level representation could be achieved either by highly connected sensory-specific number systems or by the convergence of sensory-specific systems to a common representation. Behavioural data is unable to decide between these two different possibilities.

1.1.2. Neurophysiology

Neurophysiological recordings in animals have identified single neurons with differential responses to different

numerosities in different subregions of the parietal and prefrontal cortex, under different stimuli and task conditions: in the association cortex of the anaesthetised cat, presumably homologous to the posterior parietal cortex of primates, during sequential presentations of visual and auditory items (Thompson et al., 1970); in posterior parietal cortex and lateral prefrontal cortex of the macaque during an active numerical matching task on visual sets of items (Nieder, 2005); and in area 5 and 2 of the superior parietal cortex of the macaque during the execution of sequences of actions (Sawamura et al., 2002). Most of these findings were obtained with small numerosities (e.g., 1–5 dots; 1–5 sounds; 1–5 movements), but for prefrontal cortex selective responses to (visual) numerosity have been confirmed across a larger (1–30) range (Nieder and Merten, 2007). The tuning functions of these neurons resemble bell-shaped functions with an asymmetric profile (Fig. 2 A and B), indicating approximate coding with decreased discriminability as the numerosity increases, consistent with Weber's law, which also underlies the animals' behavioural performance in numerosity tasks.

When compared within the same animals and the same paradigm, posterior parietal cortex neurons respond with shorter latencies to visual numerosity than prefrontal ones, suggesting that visual numerosity might be initially extracted in the dorsal visual stream, and later amplified in prefrontal cortex for task purposes (Nieder and Miller, 2004). In addition to the initial findings of numerical responses in posterior parietal cortex localised in the functionally defined ventral intraparietal area (VIP), responses to the numerosity of visual sets have also been recorded in the neighbouring lateral intraparietal area (LIP) (Roitman et al., 2007). In both cases, neuronal responses reflected number of dots across changes in low-level parameters (such as overall number of pixels, item size, or density). Differences, however, were found in the exact neuronal response profiles observed in the different studies, which have been interpreted as being indicative of a summation code (firing rate increases or decreases monotonically with number, indicating number selectivity) in area LIP, and a place code (firing rate peaks at a certain number and continuously decreases for neighbouring numbers, indicating number sensitivity) in area VIP (Fig. 2 C). Number selective neurons made up to around 20% of the neurons tested in functionally defined VIP (Nieder and Miller, 2004), and around 34% in the superior parietal cortex (histologically, not functionally defined (Sawamura et al., 2002)), while number sensitive neurons (Roitman et al. 2007) represented 61% of the tested neurons in LIP. A further study compared selectivity for numerosity and continuous magnitude (line length) and found that while most neurons were selective for either one or the other kind of magnitude, neurons responding to both types (although not necessarily with a corresponding relative preference) did also exist (Tudusciuc and Nieder, 2007). Neurophysiological responses to number at stages earlier than LIP/VIP (i.e., in the earlier visual cortices) have not been reported so far, but the extent to which this might reflect true absence, or has simply not received much attention due to the lack of hypotheses motivating related experiments, is hard to determine.

In how far can neurophysiological findings regarding number selectivity be explained by explicit numerical training? While many of the initial studies were carried out using either a delayed

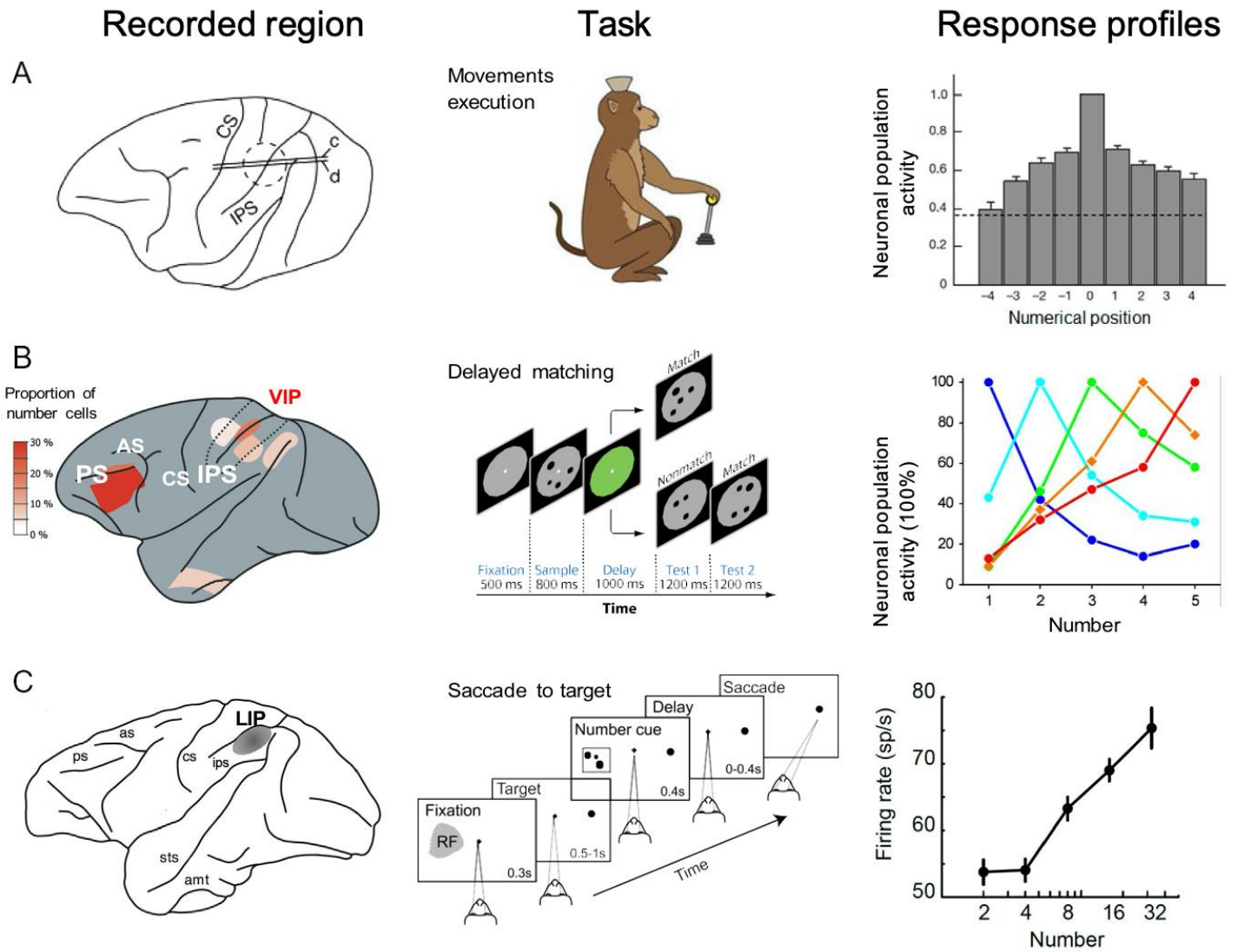


Fig. 2. Neurophysiological evidence for a neural code for number in the macaque monkey's brain: A) In the study by Sawamura et al. (2002) neuronal activity was recorded around the IPS (Brodmann areas 5 and 2, represented in the highlighted region on a later view of the macaque brain (left panel) during a sequential movement task consisting in alternating blocks of sequences of 5 "push" and 5 "turn" movements (middle panel). Many of the recorded neurons presented a preferential response for a given numerical position in the sequence. The normalised population tuning profile was an asymmetric bell-shaped curve indicating larger confusion between numerical positions as the number increases, consistent with an approximate and compressed code (right panel). Reproduced from Sawamura et al. (2002). B) In the study by Nieder and Miller (2004), many neurons in posterior parietal (mostly in the VIP region) and prefrontal cortex (left panel) were selective for number during a delayed match-to-sample task with small sets of dots (middle panel). Tuning functions of neurons with numerical preferences were bell-shaped curves with increasing width as the number increases, in line with Weber's law. Adapted from Nieder and Miller, 2004. C) In the experiment of Roitman et al. (2007), Neurons were recorded in the LIP region of the macaque superior parietal cortex during a non-numerical saccade to target task. Sets of dots were presented in the neurons' receptive fields and their response as a function of their number investigated. Number was task-irrelevant, as monkeys were rewarded to

saccade to a target located outside the receptive field. Tuning profiles were not bell shaped as in other studies, but instead positively (right panel) or negatively (not shown) proportional to number. Reproduced from Roitman et al. (2007).

match-to-numerosity task or a motor sequence execution task involving extensive prior training, the mentioned findings for LIP (Roitman et al., 2007) were obtained without prior numerical training in a task where number was not explicitly relevant (although indicative of the reward the monkey was going to receive, nevertheless, neurons responded to numerosity irrespective of reward status). Recently, numerical responses were also confirmed in VIP (13% of the neurons, 10% “pure” numerosity selective, without an effect of low-level stimulus factors) and PFC (14% of all neurons, 10% “pure” numerosity selective) in not numerically trained monkeys during a delayed match-to-sample task where colour instead of number was the task-relevant parameter (Viswanathan and Nieder, 2013). This indicates that the parietal cortex code for number may be underlying not only a highly trained skill, but also the spontaneous extraction of number that is observed in primates.

Very few neurophysiological experiments have also been conducted to test for selectivity to numerosity in VIP and/or prefrontal neurons across stimulus modality and mode. Nieder et al. (2006) investigated responses to small numbers of visually presented dots for either simultaneous or sequential presentation using a delayed match-to-sample task. During stimulus presentation, the responses of most VIP neurons with numerical selectivity were specific to one or the other mode of presentation. However, during the delay period, when number had to be kept in working memory, most number selective neurons were tuned to number irrespective of presentations mode (19% of all neurons tested). The extraction of numerosity and the final storage of cardinality were carried out by largely non-overlapping populations of neurons within the same area (thus many neurons were number-selective during the sample but not the delay period and vice versa). In another experiment with sequential presentation of dots in either the visual or auditory modality, numerical responses specific for each modality were found in both PCC and PFC (Nieder, 2012). Identical numerical preferences across modalities during the sample phase were found in 11% percent of prefrontal neurons, but only 3% of VIP neurons. During the later delay period, some neurons with bimodal numerical preferences were found (13% in PFC, 10% in VIP). Since bi-modal responses were already present during the sample phase in prefrontal but hardly in parietal cortex, monkey parietal cortex does not seem a likely substrate for the initial extraction of a supra-modal numerosity representation, unless only very few neurons would be needed to establish the link across modalities, and assuming that due to limited sampling the recordings might not have been able to detect them efficiently.

Regarding the role of prefrontal cortex, it has to be noted that these experiments were carried out in trained monkeys during an explicit numerosity matching task, and we still do not know in how far supra-modal selectivity arises spontaneously.

To summarise, a relatively large body of neurophysiological work has implicated macaque posterior parietal as well as pre-frontal cortices in the representation of visual numerosity. These

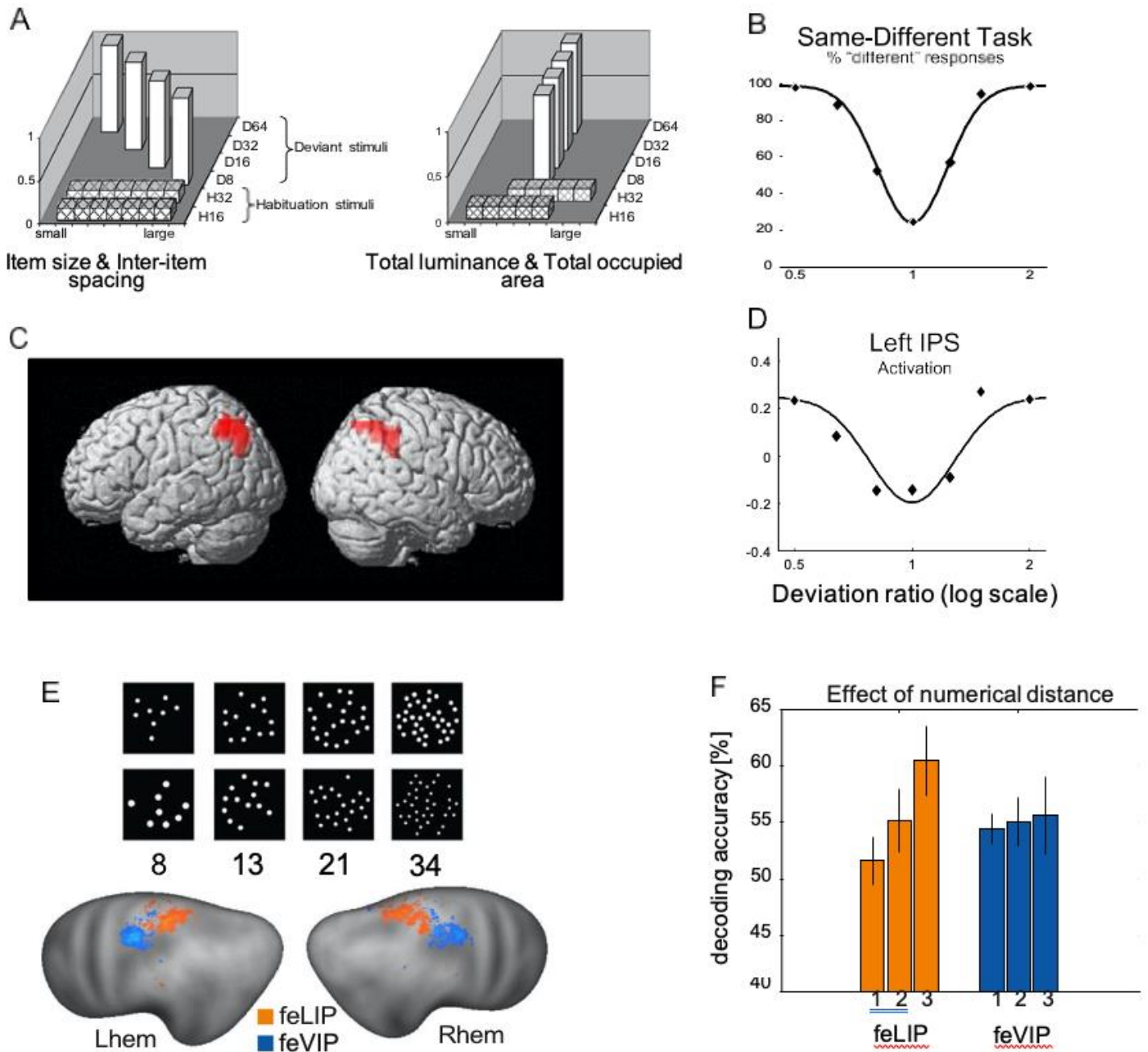


Fig. 3. Neuroimaging evidence for a neural code for number in the human brain. A) Using an adaptation paradigm, Piazza et al. (2004) repeatedly presented visual sets of a fixed number of items (e.g., 16) which, from trial to trial, varied randomly in position and in two physical parameters: size and density (defined as average inter-item spacing). Occasionally, sets with a different number of items, spanning from half (e.g., 8) to double (e.g., 32) the adaptation value, were presented. The deviant

stimuli were generated such that item size and inter-item spacing were inversely correlated with number (and this because the resulting extensive parameters of total luminance and total occupied area were controlled across numbers), and spanned the same range of values as those of the adaptation stimuli. As a consequence, deviant stimuli were all equally novel compared to adaptation stimuli along all physical parameters. This control was used to ensure that a response to numerical novelty could not be attributed to a response in novelty of the physical stimuli parameters. Adapted and reproduced from Piazza et al. (2004). B) Using the same stimuli adult subjects were asked to perform a matching task using a “reminder” paradigm, where three reference stimuli (drawn from the set of adaptation stimuli) are presented in temporal order and followed by a target stimulus (drawn from the set of deviant stimuli). Subjects decided if the target did (or not) match the previous ones. Performance is extremely well fitted by a Gaussian on a log scale, in line with Weber law. During fMRI, subjects passively looked at the stimuli. C) The bilateral mid-posterior parietal cortex was activated by the presentation of numerical deviants, in a way that was proportional to the ratio between the deviant and adaptation numerosity, again confirming a Weberian code (D). E) In an fMRI study using a multivariate decoding approach, subjects were presented with sets of between 8 and 34 dots, for which they carried out a delayed number comparison task. The study focussed on different subregions of human intraparietal cortex functionally equivalent to those where numerical responses had been observed by different groups in macaque monkeys, and used neurophysiologically motivated localiser paradigms to define them: feLIP - functional equivalent of macaque areas LIP, feVIP - functional equivalent of macaque area VIP (Eger et al., 2015). F) Activation patterns evoked by different individual numbers could be discriminated in both subregions in humans. In feLIP this decoding was more accurate the larger the numerical distance between two given sample numbers, while such a distance effect was not detected in feVIP. Adapted from Eger et al. (2015).

data support the notion that visual numerosity is first extracted in the dorsal visual stream/posterior parietal cortex and later amplified in prefrontal cortex for task purposes. Some numerical selectivity in both areas is found even in the absence of explicit numerical training. Comparably fewer studies exist so far regarding the perceptual representation of numerosity with sequential presentation and in modalities other than the visual one, such as auditory or haptic. Those who directly compared numerical responses in the same neurons across modes and modalities indicate some degree of convergence onto a common modality and mode invariant representation of number in fronto-parietal areas when explicitly task relevant.

1.1.3. Neuroimaging

fMRI activation studies in humans point to an important role for posterior parietal cortex in the processing of visual numerosity, (e.g., Ansari and Dhital, 2006; Castelli et al., 2006). For small numerosities, activity has been shown to monotonically increase with the number of items presented in regions of the superior parietal lobule (e.g., Santens et al., 2010). Furthermore, mapping studies based on more sophisticated encoding models have recently provided

evidence for a systematic spatial layout of responses to small numbers of dots in superior parietal areas (Harvey et al., 2013) (Fig. 4 A). However, beyond the range of small numbers, direct mapping methods do hardly allow to distinguish between numbers, and more precise evidence concerning numerical representation within the larger number range has been obtained with techniques that go beyond mere large-scale activation differences, such as fMRI adaptation and multivariate decoding.

fMRI adaptation was first used by Piazza et al. (2004) to investigate the representation of visual numerosity. After a habituation period to a given numerosity with a constant large number of elements (16 or 32) but highly variable associated low-level-

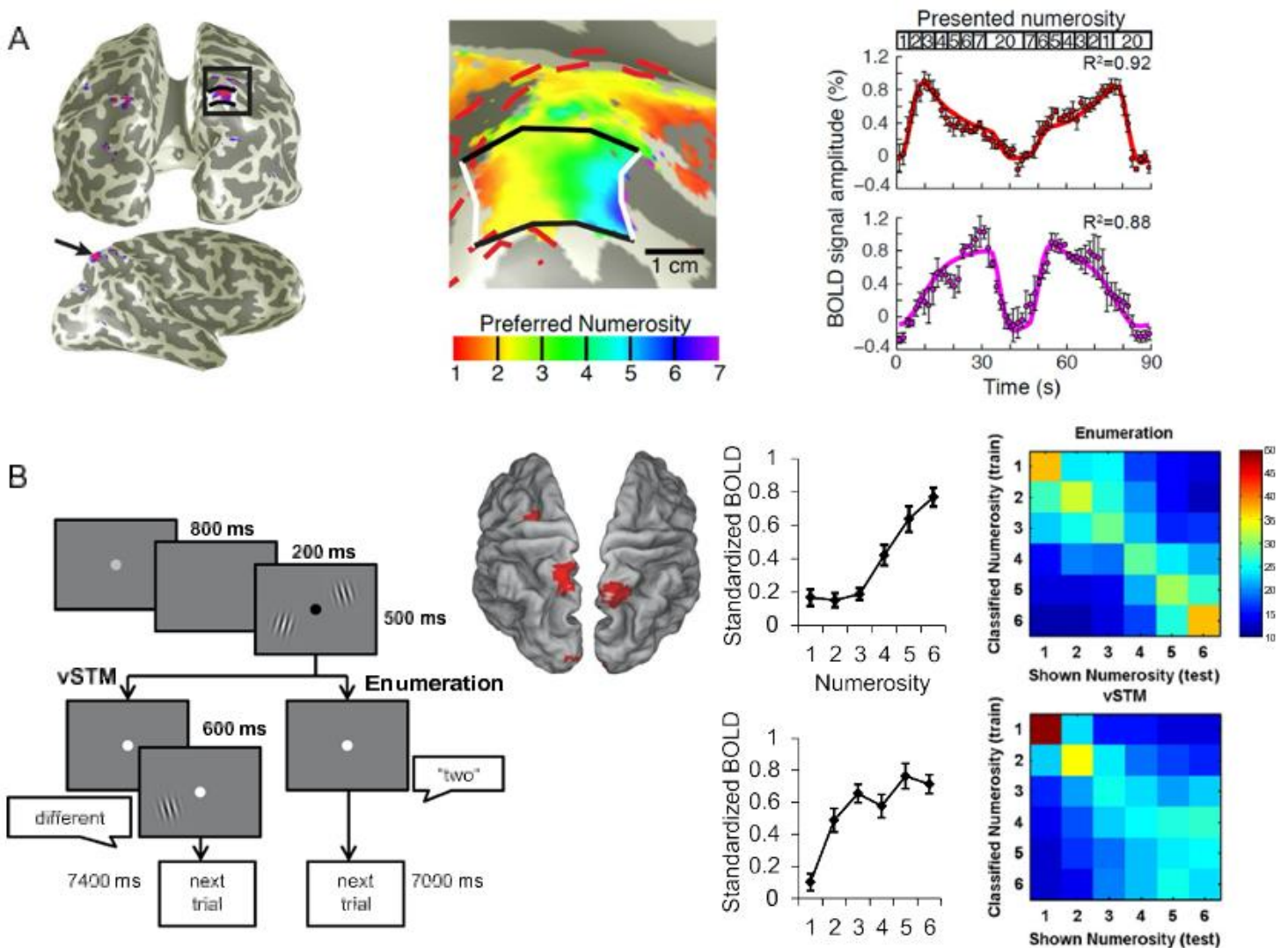


Fig. 4. Specific neuroimaging findings for small numerosities in the human brain: A) Human adult subjects were scanned with high-field fMRI while passively looking at dot patterns that increase and decrease in numerosity over time (spanning 1–7, and,

as a control 20 dots) (Harvey et al., 2013). A group of voxels, consistently located in the right posterior superior parietal cortex across subjects (left panel, the activation spots in one representative subject), show preference for specific small numerosities, especially marked for those in the 1–4 range. These number-tuned voxels are spatially organised and form a “numerotopically” organised continuum, oriented medio-laterally, where the cortical space dedicated to each number is inversely related to number (mid panel). Right panel: Exemplar time course of two voxels in the PPC: top, a voxel responding preferentially to 3 dots; bottom, a voxel responding preferentially to 7 dots. No spatial layout was observed in that study for symbolic or larger non-symbolic numbers. Reproduced from Harvey et al. (2013). B) In a single fMRI experiment subjects were engaged, in different blocks, in two different tasks, both involving the processing of multiple stimuli (1–6 Gabors), but with different attentional requirements: in one they were asked to enumerate the objects, and in the other to keep in short term memory the orientation of the objects (Knops et al., 2014). A common set of voxel in the PPC, independently chosen for their involvement in saccades (second panel from left), where activated in both tasks, and differentially modulated by number across tasks (third panel from left). These activation profiles could be explained by a model of a saliency map architecture, using different amounts of lateral inhibition. Confusion matrices from multivariate decoding of a activation patterns evoked by the different numerosities (right panel) indicate that while in the enumeration task the number of items could be accurately decoded across the entire range, during the visual working memory task only the lowest numbers of items could be decoded while for higher numbers information was progressively lost, indicating different capacity limits during the two tasks. These results are compatible with the notion of a saliency map architecture (with different amounts of lateral inhibition, leading to different capacity limits) underlying both visual object working memory and enumeration of small numbers in PPC (area LIP). Adapted from Knops et al., 2014.

features such as dot size, overall luminance and density, a change in numerosity lead to a release from adaptation in bilateral in- traparietal cortex, the size of which reflected the ratio between adaptation and deviant number, in agreement with Weber's law (Fig. 3 A–D). Intraparietal cortex did not simply respond to de- tection of any change in the stimulus: shape deviants were ac- companied by a release from adaptation that was more pro- nounced in ventral visual than in parietal cortex. This dissociation between greater sensitivity for number deviants in parietal cortex, and greater sensitivity for shape deviants in ventral visual cortex has later been confirmed with fMRI in 4 year old children (Cantlon et al., 2006), in 6 months olds (Hyde et al., 2010) using near infra- red spectroscopy (NIRS), and even in 3 months olds using elec- troencephalography (EEG) (Izard et al., 2008). This suggests that parietal adaptation is specific to visual numerosity compared to the visual items' shape, and reflective of a very primordial pro- cessing capacity preceding language and explicit learning.

As an alternative to the adaptation approach, Eger et al. (2009) used multivariate pattern recognition to test for discriminability of direct evoked activity patterns between different visually pre- sented sample numerosities that the subject was seeing and holding in mind (during a delayed numerosity comparison task). In a multivariate

searchlight analysis, discrimination of number- evoked activity patterns was most significant in bilateral intraparietal cortex. Individual numerosities could be accurately decoded across changes in low-level stimulus properties (overall number of pixels or dot size equated between numerosities. A later study (Eger et al., 2015) tested for numerosity information in specific intraparietal subregions functionally equivalent to those (areas LIP and VIP) where number-selective neurons have been observed by neurophysiology and confirmed discrimination between individual numbers in both regions in humans. Multivariate decoding also provided evidence for the graded nature of the numerical representation in PPC: Numerical distance effects on classification of sample numbers (separated from behavioural decision difficulty) were observed for both small (2–8 dots, Eger et al., 2009), and large numerosities (8–34 dots, Eger et al., 2015) (Fig. 3E and F). In the latter case the distance effect was arising mainly in the functional equivalent of area LIP but not VIP, suggesting a coarser representation of numerosity in the aforementioned area, which could be either due to broader tuning or a summation code as has been suggested by neurophysiological studies (Roitman et al., 2007).

Multivariate discrimination of patterns evoked by small numerosities has been recently confirmed by other studies using slightly different task contexts: numerosity comparison (Bulthé et al., 2014, 2015), and also simple viewing (Damarla and Just, 2015). Numerosity also could be decoded in regions beyond parietal and frontal cortex such as occipital (Bulthé et al., 2014, 2015; Eger et al., 2015) and ventral visual cortex (Bulthé et al., 2014). While these studies did not exhaustively control low-level features between the different numerosities, it is interesting to note that a recent EEG study (Park et al., 2015) observed stronger modulation of visual responses at a very early latency (75 ms) for changes in numerosity than two other dimensions (spacing and size) varying orthogonally between stimuli in their design. This is supporting the notion that the visual system is not relying on explicit representations of these other features to compute numerosity, but instead may be wired up to extract numerosity from the information available in sensory cortices starting extremely early, which warrants further research also from the side of functional imaging.

For what concerns the processing of numerosity invariant of presentation mode (sequential vs. simultaneous) or input modality (auditory vs. visual), overall activations during number discrimination with either sequentially or simultaneously presented numerosities have been found to be partially overlapping and partially distinct in the right intraparietal sulcus (Dormal et al., 2010). Likewise, enumeration in both the visual and auditory modality recruited right fronto-parietal regions to a similar extent (Piazza et al., 2006). However, no data are available so far addressing more directly the coding of individual numerosities within each presentation mode/modality and their extent of representational overlap by adaptation methods. Only one recent study, using multivariate decoding, investigated responses to serially presented numerosity in either the visual or the auditory modality (Cavdaroglu et al., 2015), and failed to find generalisation across modalities. However, even within the same modality, patterns for sample numbers were not discriminable above chance in that study, suggesting a potentially weaker representation of sequentially presented numerosity in the areas in question, although the null result could also reflect a limitation of sensitivity due to the use of mostly large numbers separated by a smaller ratio than in

previous studies.

Neuroimaging studies did more easily detect differences between small than large numerosities, which warrants the question of whether the processing of small numerosities might involve additional mechanisms to those operating across the entire range. Although decisive data are still missing in this regard, one idea which was tested in an fMRI study by Knops et al. (2014) is that a saliency map architecture (Koch and Ullman, 1985) in parietal cortex (area LIP) could underlie the representation of multiple visual items and thus be crucially involved in tasks requiring numerosity estimation, precise enumeration, and also multiple objects' features tracking (as in visual working memory tasks). Models of "saliency maps" have been proposed in the form of artificial neural networks composed of a number of nodes exhibiting both self-excitation and mutual inhibition (Itti and Koch, 2001; Roggeman et al., 2010). One critical parameter of these models is the amount of mutual inhibition: as the inhibition decreases, a larger number of items/locations can be represented, albeit with decreasing precision. With a higher inhibition, locations can be represented with a high precision at the cost of being restricted to very few of them (lower capacity limit). In the study of Knops et al. (2014) subjects were presented visually with small numbers of Gabor patches under two task conditions: enumeration, which does not require precise encoding of features of the items or their location and can thus be thought of as a low/medium inhibition setting in the context of the mentioned model, or a visual working memory task for Gabor orientation which can be thought of as a high inhibition setting (because both the specific location and orientation of the items has to be encoded for the task). An identical set of voxels in the human equivalent of area LIP dynamically adapted its overall response profile to number as a function of the task, and showed different set size limits: smaller for the short term memory and larger for the enumeration, precisely mirroring behavioural set size limits. These response profiles were well simulated by a saliency map model with either medium or high later inhibition between nodes representing item locations. Finally, to provide evidence beyond overall activation profiles in favour of different capacity limits, multivariate decoding was applied during the different tasks. During enumeration, the number of items could be decoded across the complete range (1–6 items), and discrimination performance showed the typical effect of numerical distance which had already been found in previous multivariate decoding studies of number (Eger et al., 2009, 2015). During the working memory task, however, only the lowest numbers of items could be precisely decoded, whereas for larger sets the numerical information was progressively lost (Fig. 4B). This study involved no explicit comparison between small and large numerosity estimation. Saliency maps could either provide an additional mechanism for the enumeration of small numbers of items, compatible with the fact that the behavioural precision of discrimination of small but not larger numbers depends on attention (Burr et al., 2010), and this could explain why smaller numbers appeared better discriminable in fMRI studies. On the other hand, it is also possible (as speculated by Roggeman et al., 2010) that at even lower levels of lateral inhibition (as it could be the case when the task is an approximation instead of precise enumeration) saliency map architectures may provide a basis for the estimation of larger sets as well.

To summarise, functional imaging studies in humans, based on approaches sensitive to within-category discrimination, have underlined a critical role of posterior parietal cortex for the representation of individual

visual numerosities. Visual numerosities are discriminable in equivalent regions to those where numerical responses were observed in the monkey, thus establishing a close parallel between neurophysiology and human functional imaging. More work is needed in humans regarding the mechanisms by which numerosity is initially extracted along the cortical hierarchy and in the different sensory modalities, and on how numerosity information from the different modalities is brought together.

1.2. Number as a mathematical object: semantic representation of numerical symbols

1.2.1. Behaviour

Numerical symbols (e.g., Arabic digits, number words) are the mathematical objects that stand for cardinality, measurement, or order. While one may think that the cultural ability to understand and mentally combine numerical symbols may emerge from purely abstract thinking, several lines of behavioural evidence suggest that, at least some important components of their mental representation are grounded on the pre-existing system for representing and mentally manipulating concrete numerosities (see review in Piazza (2010)). First, the metric characterizing the mental representation of numerical symbols (as inferred through similarity judgements or comparison tasks) shares some key properties with the one governing approximate quantity: in both cases, response times and error rates are captured by Weber's law in that they increase when the numerical distance between two values decreases, and when their absolute magnitude increases (Buckley and Gillman, 1974; Dehaene et al., 1990; Koechlin et al., 1999). Second, the variability in the precision of numerosity discrimination (even when measured in children at a very young age) is not only correlated, but longitudinally (and rather selectively) predictive of the subsequent success in symbolic number skills such as number comparison and arithmetical calculation (e.g., Gilmore et al., 2007; Halberda et al., 2008). At one extreme of variability, some children suffer from dyscalculia, a disproportionate impairment in learning arithmetic that cannot be imputed to general intelligence, sensorimotor deficit, or deficient social or educational background. The non-verbal sense of number is indeed impaired in dyscalculic compared to age and intelligence matched control children (Mazzocco et al., 2011; Mussolin et al., 2010; Piazza et al., 2010). Third, training studies indicate that exercises aimed at improving approximate additions/subtractions of concrete numerosities (compared to training visuo-spatial short-term memory) have a positive transfer effect to symbolic (and not to reading) (Park and Brannon, 2013, 2014). Reciprocally, learning symbols for number and learning to count have a positive impact on the perception of concrete numerosities (Piazza et al., 2013). Fourth, brain lesioned patients with deficit in the semantic representation of numerical symbols (e.g., impaired in exact and approximate calculation but not in the retrieval of arithmetical tables) can also be impaired in numerosity estimation, comparison, and approximate calculation with sets of dots (Lemer et al., 2003). Furthermore, temporary deactivation of the IPS similarly affects symbolic and non-symbolic number comparison tasks (Cappelletti et al., 2007). Finally, the study of semantic impairments in neuro-degenerative diseases indicate that semantic representations of number dissociate from semantic representation of other semantic categories of

objects (such as animals, tools, fruits, vegetables, etc.): patients with semantic dementia or grossly deteriorated semantic processing, with functional and structural alterations at the level of the anterior temporo-frontal lobe may be entirely spared in number comprehension and calculation (Thioux, Pillon, Samson, De Partz, Noel, & Seron, 1998; Butterworth, Cappelletti, & Kopelman, 2001; Cappelletti, Butterworth, & Kopelman, 2001). On the other side, a few cases of impaired semantic processing of numbers following focal parietal lesions may show largely preserved language and semantic functions Cipelotti et al. (1991). This suggests that the temporal lobe does not play a key role in semantic number representations, while the parietal lobe does.

Taken together, these behavioural data support the idea that during the course of learning numerical symbols get their meaning by mapping their superficial forms (Arabic digits, number words) onto a pre-existing representation of cardinality in parietal cortex, and that, throughout the entire lifespan there is a profound and bidirectional causality link between formal and informal numerical skills. From a neural point of view, this link may result into a convergence onto a common format invariant representation of numerical quantity in parietal cortex. However, it is also compatible with the existence of two separate but highly interconnected notation-specific cortical systems. In what follows, we review the literature investigating the neurophysiological underpinning of the semantic representation of numerical symbols and the relation with that underlying the representation of cardinality as evoked by the presentation of sets.

1.2.2. Neurophysiology

When investigating high-level symbolic abilities it is difficult to use animal models to study their neuronal underpinnings. In the case of numerical cognition, some studies on monkeys have indicated that at least for a limited range of numbers, monkeys are able to successfully use numerical symbols by linking them to specific (although approximate) cardinalities (Livingstone et al., 2010; Matsuzawa, 2009). One major difference, however, exists between animals and humans: humans understand the generative aspect of enumeration, which is intrinsic in the notion of “counting”. Young children, in fact, learn the meaning of symbols for number through an associative mapping for the numbers 1–4 (usually between age 2–4) but then by abstraction they understand the counting principles and therefore grasp the meaning of any arbitrarily large symbol, provided that they know its position in the counting sequence. The understanding of the counting principles has never been demonstrated in animals other than humans. In this sense neurophysiological reports of the neural underpinning of the representation of numerical symbols in non-human primates may be little informative as to that in humans, as the nature of symbolic representations in the two species may be rather different.

One study so far has performed electrophysiological recordings in macaques trained to associate small numbers of dots (1–4) with the corresponding Arabic number symbols (Diester and Nieder, 2007). While numerical selectivities specific to either the non-symbolic or the symbolic format could be found in both posterior parietal (PPC) and prefrontal cortex (PFC), “association neurons” which had similar tuning functions across stimulus formats were largely restricted to PFC (23% of the neurons in that area), and very rare in PPC (only 2% of the neurons which was

just above chance level). Thus, it appears that in the macaque, prefrontal cortex is the area where associations between numerosities and the corresponding symbols are formed. Because the monkeys were trained for only two months (contrary to humans who, through the use of language, receive a life-long training in this sort of associations), the question remains whether longer training, possibly associated with higher behavioural proficiency with symbolic number, such abstract representations could be found in parietal cortex as well.

In humans, a recent electrophysiological study in epilepsy patients has been able to identify electrodes in the human intraparietal sulcus which were preferentially activated when the subjects referred to numerical concepts in several contexts (Dastjerdi et al., 2013). It would be interesting to see in the future whether, through this method, it will be possible to discriminate individual numbers and systematically test the response tuning, as well as the level of invariance to input format (symbolic vs. non-symbolic), in order to allow for comparison with the macaque findings.

1.2.3. Neuroimaging

Functional imaging studies have consistently observed activations in human parietal and frontal cortex in a variety of symbolic numerical tasks (different types of mental arithmetics, number comparison, etc.), as has already been reviewed extensively by others (e.g., Ansari, 2008; Dehaene et al., 2003), also see (Arsalidou and Taylor, 2011) for a meta-analysis of fMRI studies related to number processing. Furthermore, hypo-activation or anatomical disorganisation of parietal regions has been reported in dyscalculia, a specific learning disability that affects the representation of number and of mental calculation (Barnea-Goraly et al., 2005; Eliez et al., 2001; Isaacs et al., 2001; Kucian et al., 2006; Molko et al., 2003). These alterations are often due to genetic pre- or perinatal pathologies, suggesting that they may represent plausible causes rather than consequences of dyscalculia. Thus, those results suggest that availability of a functional parietal quantity system is an essential prerequisite for successful learning of numeracy skills.

While traditional functional mapping studies underlined the importance of parietal and frontal areas for symbolic numerical computations, they did not necessarily isolate a mere representation of numbers (as opposed to other processes that might be instrumental to and recruited differentially between complex numerical and control tasks). Attempts at isolating the correlate of a semantic representation of number with more tightly controlled paradigms and a basic subtraction approach have not been successful in many cases: although Eger et al. (2003) observed stronger responses to numerals than letters and colours (in both the visual and auditory modalities), this was not confirmed in slightly different task contexts (e.g., Fias et al., 2007). A first more direct demonstration for a quantity code subtending the cortical representation of symbolic numbers came from an fMRI adaptation study using both non-symbolic (visual numerosities) and symbolic stimuli (Arabic digits), where Piazza et al. (2007) found that that for both formats, parietal and frontal cortex responded more to numerically far deviant stimuli than for numerically close ones. This was the first direct demonstration that in parietal and frontal cortex Arabic digits and dot patterns are both represented according to a quantity metric. A similar distance-dependent recovery from adaptation for

Arabic digits was more recently replicated mainly in the left intra-parietal cortex (Holloway et al., 2012; Notebaert et al., 2010a, 2010b). This ratio-dependent adaptation was also shown to increase with age (6–12 years), presumably reflecting increasing sharpening of the cortical representation of the meaning of the numerals due to experience (Vogel et al., 2014). Numerical repetition effects have also been observed across different symbolic notations: Naccache and Dehaene (2001), using Arabic digits or written number words in a masked priming paradigm, found reduced activation in bi-lateral parietal cortex when prime and target were the same as opposed to different numbers, across changes in symbolic notation. Again, in some cases such adaptation across symbolic notation was only detected in left parietal cortex (Cohen Kadosh et al., 2007). While mere comparisons of same vs different numbers in adaptation paradigms support some common representation across different symbolic formats, more precise evidence for a magnitude basis of these transfer effects comes from studies that manipulated the numerical distance: Notebaert et al. (2010a, 2010b), found that release from adaptation in bilateral parietal cortex followed numerical distance across changes in symbolic notation (written number words and Arabic digits). In this case, however, the ratio-dependent adaptation occurred only when Arabic digits preceded the verbal numeral and not the reverse, suggesting that semantic processing of symbolic numbers might not occur automatically in all task contexts. The question of whether in parietal cortex there are separate representations of quantity for non-symbolic and symbolic inputs has also been the object of several studies. Piazza et al. (2007) used an fMRI adaptation paradigm and reasoned that if a representation of cardinality is commonly accessed by dot patterns and numerical symbols, then this should result in a distance-dependent recovery from adaptation even in the presence of a change in format (symbolic vs. non-symbolic). Results precisely showed a notation invariant distance effect in parietal and frontal areas. This does not mean that parietal areas are entirely insensitive to the format of stimulus presentation: a format change without a change in number could also lead to release from adaptation in the same regions (Cohen Kadosh et al., 2011). Using the multivariate decoding approach to test for generalisation across non-symbolic vs symbolic formats, Eger et al. (2009) trained a multivariate classifier to discriminate number in one given format, and tested in how far the same classifier was able to correctly classify activation patterns from for a given number in the other format. A classifier trained on numbers of dots (which was highly accurate for discrimination of dots themselves) yielded chance performance when tested on digit-related activity patterns. Nevertheless, a classifier trained on digits completely generalised its performance to the corresponding numbers of dots. The fact that generalisation was unidirectional, and that furthermore the two formats could be discriminated for the same number, suggests that the complete pattern within intra-parietal cortex as a whole does not reflect a single or entirely abstract representation. Nevertheless, the generalisation from digits to dots indicates the existence of a format-invariant component which might be intermingled with representations of non-symbolic numerosity, in a way that the methods did not allow to distinguish, either in closely neighbouring subregions, or even within the same area. Others researchers have more recently failed to replicate generalisation of pattern classification from digits to dots (Bulthé et al., 2014, 2015). It is worth noting the slight differences in the paradigms across studies: in the study of Eger et al. (2009), the sample numbers had to be held in mind by the subjects over a delay of several seconds to later

be compared with a second number, thus the (perceptual and working memory) representation of the number itself were separated from the comparison process. This was not the case in the studies of Bulthé et al. where the subject carried out a comparison task at the appearance of each number. Also, there were slight differences in the imaging parameters (spatial resolution) across the studies, although these might not be critical.

One might wonder why correlates of a format-invariant representation might have been so far more consistently picked up by the adaptation than the multivariate decoding approach. Potentially, because adaptation studies rely on a memory

phenomenon between sequentially presented stimuli, they could be more influenced by semantic representations (instead of mere stimulus-evoked activity) in the areas in question. fMRI adaptation may further be more sensitive to neuronal representations intermingled at a very fine spatial scale (i.e., the sub-voxel level) in contrast to multivariate decoding which can be predicted to have best performance when the evoked activity patterns are relatively distributed across many voxels (also see Drucker and Aguirre, 2009). In that context it is also interesting to note that while for small numbers of dots an orderly cortical layout in parietal areas has been discovered recently by advanced fMRI mapping methods (Fig. 4 A), no particular layout could be detected for digits at that coarse resolution (Harvey et al., 2013). If spatial resolution is the decisive factor for the different results between fMRI adaptation and methods comparing direct evoked activity, one would potentially expect to obtain more similar findings between the different approaches at ultra-high resolution, feasible at higher magnetic fields strengths (Figs. 5 and 6).

To summarise, the available results of fMRI adaptation and multivariate decoding studies combined provide some evidence to support a stage of semantic representation of numerical symbols in human intraparietal cortex. Some research supports the notion that this representation is commonly accessed by numbers presented in non-symbolic format. However, intraparietal cortex is not completely insensitive to format, and generalisation across format was not replicated in some studies. These contradictory findings could reflect that different stages of numerical representation coexist in close proximity in intraparietal cortex, an issue which we will come back to in the discussion.

1.3. Number as a mathematical object: visual representation of symbolic number forms

1.3.1. Behaviour

The triple-code model of numerical representation (Dehaene, 1992; Dehaene and Cohen, 1995), based on a synthesis of behavioural and neuropsychological data, first proposed an important node for the processing of Arabic number symbols in ventral visual cortex. According to this model, there are at least three different types of (interconnected)

representations of numbers in the brain: the first one is semantic, and relates to the meaning of numerical symbols, and the other two are pre-semantic, in that they relate to

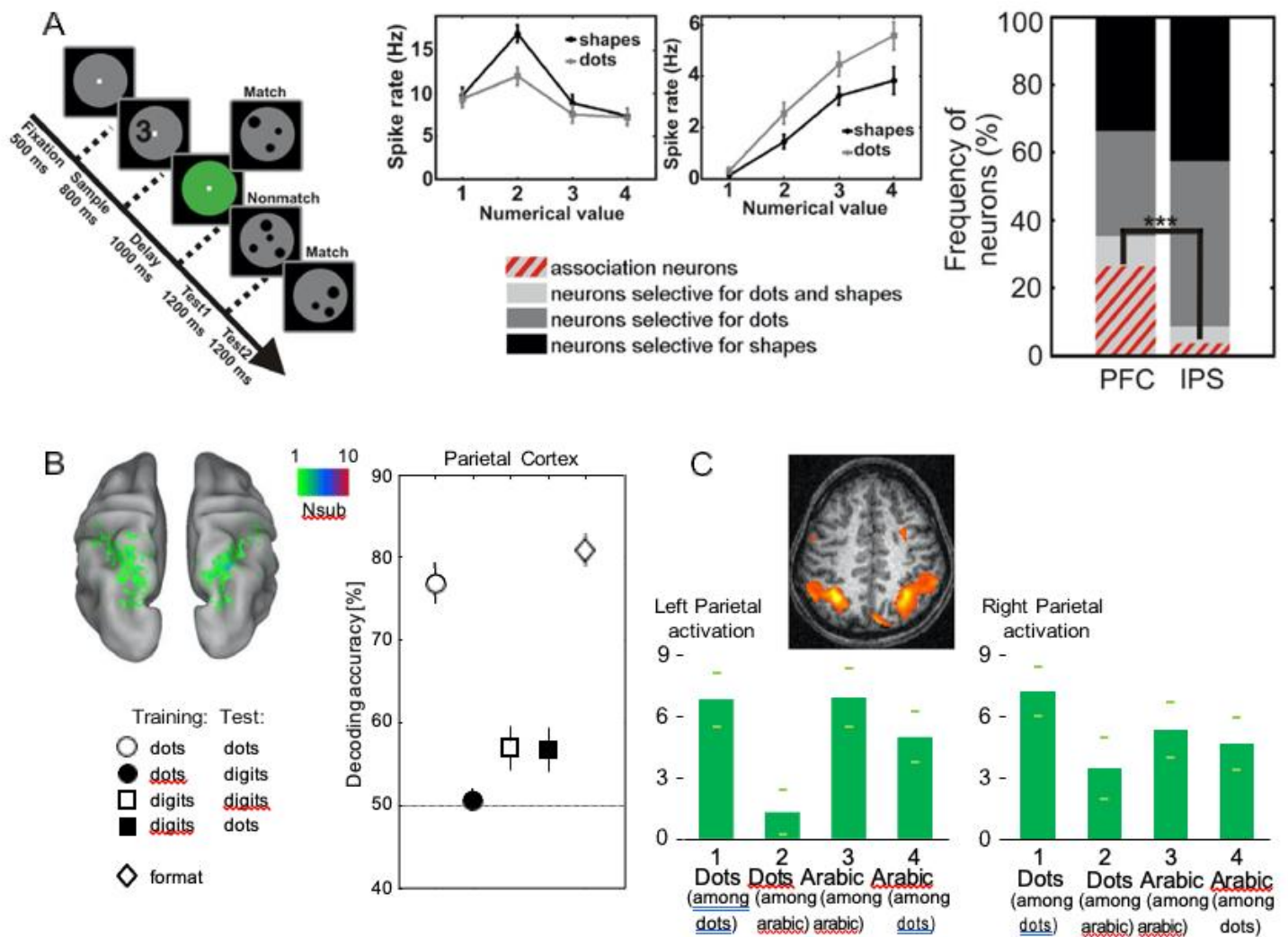


Fig. 5. Neuroscientific evidence regarding the semantic representation of magnitude from symbols: A) In macaque monkeys trained to perform a delayed match-to-sample task (left panel) with small numbers of dots and the corresponding Arabic number symbols, many neurons in posterior parietal and prefrontal cortex were selective for number in one or the other format

(right panel). “Association neurons” with similar numerical preference and tuning profile (of which two examples are shown in the middle panel) were also observed, but were much more prevalent in prefrontal than posterior parietal cortex (Diester and Nieder, 2007). Figure reproduced from the original paper. B) Using a similar (delayed number discrimination) task in a group of human subjects, high-resolution fMRI activity patterns evoked by different sample numbers in intraparietal cortex could be discriminated by multivariate decoding. While a classifier trained on activity from numbers of dots was at chance for discrimination of digit-related activity, a classifier trained on digit-evoked activity did generalise its performance to activity evoked by dots, suggesting that a component of the pattern is invariant to format, but probably intermixed with format-specific representations of non-symbolic number within the same global region in a way that the methods did not allow to distinguish (Eger et al., 2009). Reproduced from the original paper. C) Using fMRI adaptation to number within and across symbolic and non-symbolic formats, release from adaptation occurred in human intraparietal cortex as a function of the ratio between deviant and habituation number, irrespective of format (Piazza et al., 2007). Adapted from the original paper.

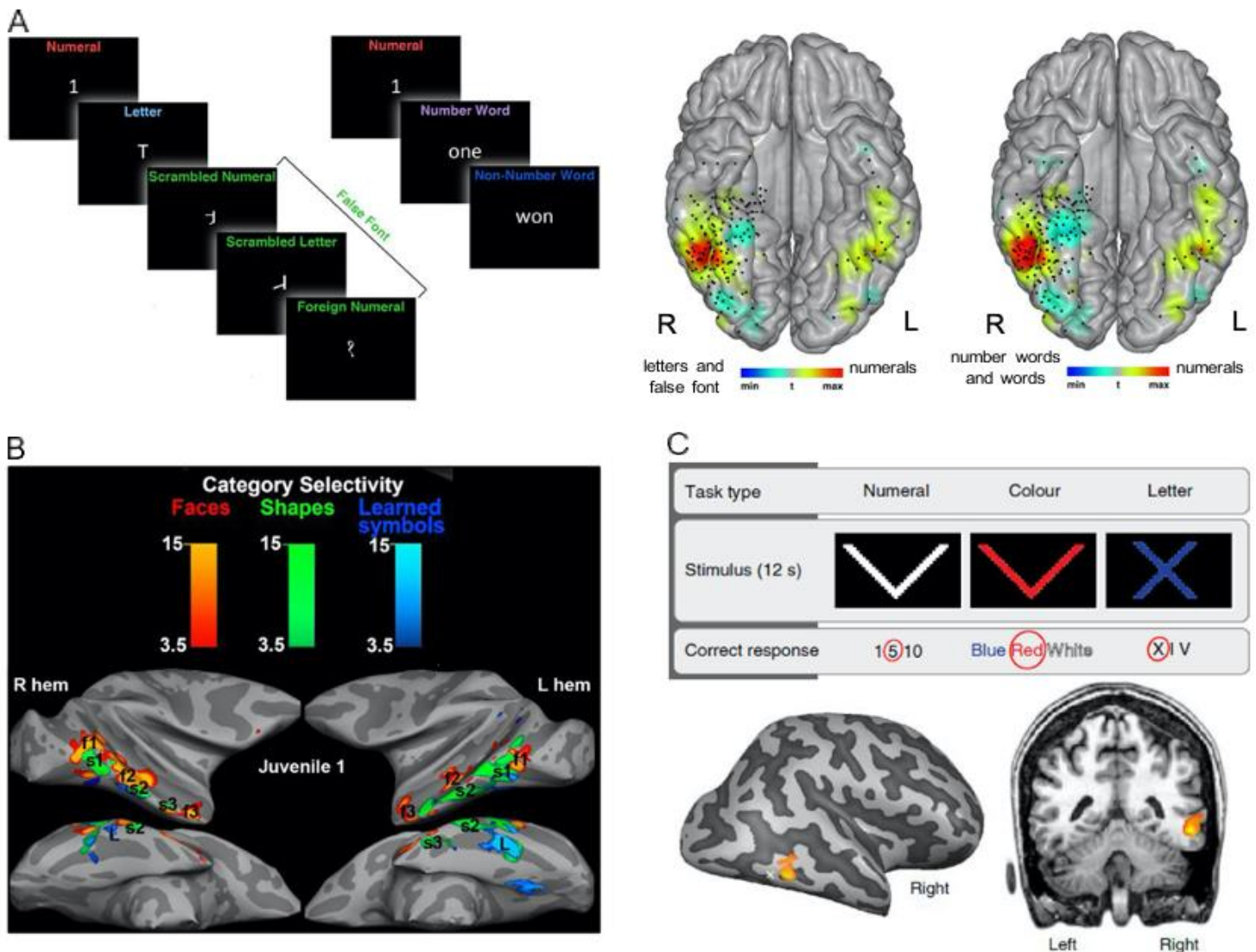


Fig. 6. Neuroscientific evidence supporting some degree of regional specificity for the processing of visual number symbols in

the ventral stream: A) Stimuli used in a recent intracranial recording study (Shum et al., 2013) investigating the ventral stream response selectivity for numerical symbols' shapes, contrasting different visual stimuli: Experiment 1 (left) controlled for morphological similarity across stimuli and used single numerals, single letters, scrambled numerals, scrambled letters, and foreign numerals. Experiment 2 (middle) controlled for phonological similarity and used numerals, number words, and non-number words. Results (right) showed that responses to Arabic digits when compared to semantically or phonologically similar (number words and phonologically similar non-number words) as well visually similar stimuli (letters, foreign numbers and false font – data not shown) were centred in a right infero-temporal region, termed the “visual numeral area” by these authors. Reproduced from Shum et al., 2013. B) Using fMRI in macaque monkeys who had learned magnitude associations for a certain number of symbols, activations for learned symbols (as opposed to other shapes or faces) were observed in ventral visual cortex regions of the younger monkeys (who achieved higher proficiency with the symbols than older monkeys) (Srihasam et al., 2012). Reproduced from the original paper. C) A region close to the one described by Shum et al. was activated in blind subjects processing visual input via an auditory substitution device, when they made numerical as opposed to non-numerical judgements on Roman numerals (Abboud et al., 2015). Reproduced from the original paper.

more surface appearance of numerical symbols: one is auditory/ linguistic, and encodes number words, and the other is visual and encodes the visual shape of Arabic digits. This last node thus re- presents the processing stage where numerical symbols are re- cognised, but not yet associated to their meaning.

The ventral stream of primate visual cortex plays a central role in object recognition. FMRI has revealed sub-regions in the ventral pathway which respond selectively to certain object categories (natural categories such as faces and bodies, but also symbolic categories that do not have a long evolutionary history, such as written words; see e.g., Op de Beeck et al. (2008), for a review). What determines for which visual categories neuronal re- presentation can give rise to such macroscopic areas that appear entirely specific, is not entirely understood. One possibility is that category-selective areas develop for highly relevant categories where highly similar exemplars need to be finely discriminated. It has been suggested, in fact, that the clustering of neurons with similar response properties not only reduces neural transmission costs but also critically enhances the capacity of fine discrimina- tions between exemplars by favouring comparative interactions and inhibition (Tsao and Livingstone, 2008). On the other hand, differential connections with upstream areas involved in semantic or other kinds of further processing for one category but not an- other (e.g., intraparietal cortex for Arabic digits but not for non number-related shapes/symbols) could be responsible for func- tional segregation at the level of ventral visual cortex.

The combination of these accounts might predict that regions specialized for the visual processing of (symbolic) number form could also exist, at least in subjects with high numeracy skills. Neuropsychological investigations have provided to date only partial support to this prediction, as there is evidence in favour of single but not double dissociations between the ability to re- cognise Arabic digits vs. other symbols: several patients with pure alexia, with lesions in the fusiform gyrus, unable to identify letters and/or words, show intact or relatively spared identification of Arabic digits, (e.g., Cohen and Dehaene, 1995; Starrfelt and Behr- mann, 2011, for a review). The

opposite case (impaired digit identification in the context of spared letter string recognition), has been sometimes reported, but only in patients with lesions in temporal-parietal regions, and of which deficits were related to the semantic and phonological processing of digits and not to their pure visual recognition (e.g., Marangolo et al., 2004), see Piras and Marangolo (2009) for an overview. This could be related to the fact that digits are less numerous than letters and thus more easily visually identifiable (as also suggested by chronometric studies in non-brain lesioned subjects). An alternative (or concurrent) possibility is that, contrary to words, digits might be bilaterally represented in the ventral stream. A bilateral system for recognising digits would be more resilient to ischaemic lesions, thus explaining why a selective visual impairment would be less easily found for the recognition of digits than words. That the visual form of digits might be bilaterally represented is also suggested by reports of split-brain patients, with callosal lesions that prevents cortical cross-hemispheric transfer, who can correctly identify digits and number words with both their left and their right hemisphere (Seymour et al., 1994). Because of this evidence, a bilateral representation of the visual form of numbers is also assumed by the aforementioned triple-code model (Dehaene and Cohen, 1995).

1.3.2. Neurophysiology and imaging

Evidence from neurophysiological and functional imaging methods for a specific system for recognising the identity of Arabic symbols as opposed to other categories of objects in the ventral stream were rather sparse and unconvincing until recently. Initial evidence came from a study using intracranial electrophysiological recordings in epilepsy patients, which reported some recording sites with preferential responses to Arabic digits over a few other object categories such as faces, words, and false fonts (Allison et al., 1994). However, the recording sites were highly variable in their location, and the control conditions did not closely match Arabic digits in morphology, phonology and meaning. Subsequent fMRI studies comparing ventral stream activation for Arabic digits to well-matched controls (digits vs. letters or letter strings) in some cases found no difference (Eger et al., 2003), or found regions more active for letter strings compared to digits but not the reverse (Polk et al., 2002). One study, however, described a weak preferential activation for digits over number words in a right fusiform region, but no effect in the reverse direction, during a comparison task (Pinel et al., 1999). Even though a meta-analysis of imaging studies related to numerical processing yielded several foci in fusiform and occipital regions (Arsalidou and Taylor, 2011), this can hardly count as evidence for visual selectivity for number form, since the studies in the database were very heterogeneous and included comparisons versus passive fixation or other baseline conditions insufficiently matched for visual input characteristics, attention and other factors. A more recent fMRI study reported the finding that during a matching task, Arabic digits elicited stronger activations in the right lateral occipital cortex compared to alphabetical stimuli (Park et al., 2012). However, the visual region in question appears surprisingly posterior, and thus early in the visual processing hierarchy (likely overlapping with the posterior part of the lateral occipital complex) compared with other category-selective ventral stream regions. Furthermore, this region activated even stronger for false fonts than Arabic digits, and its activation profile across conditions mirrored reaction times in the matching

task, suggesting that the degree of activation could at least partially reflect task-related effort.

A small subset of studies, however, some of which more recent, report more convincing findings: first, cortical stimulation of some small regions of infero-temporal cortex selectively interferes with the reading of Arabic digits compared to words (Roux et al., 2008). Second, a region in the infero-temporal gyrus, investigated using intracranial recordings, responds more strongly to Arabic digits than control conditions which are well-matched in terms of visual (letters, false fonts), semantic (number words) or phonological (phonologically similar non-number words) similarity (Shum et al., 2013). These authors have argued that for this region (referred to as “visual numeral area”) responses to number could have been usually missed by fMRI studies since they fall into areas affected by signal loss due to susceptibility artifacts in temporal areas around the ear channels. Interestingly, a functional imaging study in macaque monkeys which had been trained first to choose the larger of two non-symbolic numerosities, and later to perform the same task on symbols (thus indirectly associating symbols with quantitative meaning) observed regions selective for trained symbols (as opposed to untrained shapes and faces) in ventral temporal cortex (Srihasam et al., 2012). Possibly such activations can be detected in monkeys because less signal drop-out occurs (due to a lesser development of air-filled cranial structures). On the other hand, these results could suggest that such regions only develop when a high level of visual proficiency with number symbols is reached (as was the case for the younger monkeys in that study).

Very recently, activation of a region close to the one described by Shum et al. (2013) was even found in a human fMRI study in blind subjects who were processing symbolic numbers via an auditory substitution device (Abboud et al., 2015). Subjects were presented in that study with Roman numerals which, depending on the condition, they processed either as numbers or letters. The “visual numeral area” was thus activated when the same given set of symbols was explicitly processed as numbers, suggesting that this region may not be purely dedicated to the perceptual processing of visually presented Arabic digits, but rather to forms that are differentiated from other ones because of their link to their common numerical content, and that irrespective of the input modality. This finding also suggests that signal drop-out does not systematically prevent preferential activations for numbers in this part of the brain from being found, and that instead the task carried out on the stimuli could play an important role.

In sum, it seems that the ventral visual stream can develop some degree of specificity for processing the surface forms (being it visually or auditorily apprehended) of numbers (vs. other categories of objects) in certain subregions of the infero-temporal cortex. However, a lot remains to be understood. First, no study has to date tackled the question of the representational geometry of responses to individual digits in this putative inferotemporal cortical number patch, thus characterizing the precise kind of number-related information that is encoded in that part of the brain. In agreement with the triple code model we would expect a non-semantic, shape-dependent code, which would contrast with the quantity-based representation of the intra-parietal number responsive regions. Second, we miss a systematic study that relates the specific location of this ventral visual number region to the

other category-specific patches dedicated to other object categories in the ventral stream. Finally, we still have no idea to what extent the activation of this region is reproducible across subjects and tasks.

2. Discussion

In this article, we have reviewed evidence from different behavioural and neuroscientific methods regarding the underpinnings of numerical representations in the human (and to some extent macaque) brain. So far, this evidence rather convincingly supports a critical role of both parietal cortex and occipito-temporal cortex in supporting number representations, with each region supporting different aspects of numbers: the ventral stream/ infero-temporal cortex appears involved in processing the shape of numerical symbols, and is thus important in number recognition and reading. The dorsal visual stream/intra-parietal cortex, on the contrary, appears to encode both the meaning of numerical symbols (i.e., quantities) and the cardinality of concrete sets, thus supporting any numerical task requiring semantic processing of numbers and/or numerosity. Beyond this clear broad picture, several more subtle issues are still open and some are the subject of current investigations. In what follows we are going to address them.

2.1. Is there an input format (symbolic vs. non-symbolic) invariant representation of numerical quantity in intraparietal cortex?

While a critical role for intra-parietal cortex in abstract format invariant representation of numerical quantity had been proposed early on the basis of neuropsychological and pioneering imaging findings (Dehaene and Cohen, 1995; Dehaene et al., 2003), the degree of format invariance of numerical representations in this region has remained an issue of some controversies with the introduction of new imaging techniques. The results of both fMRI adaptation and decoding methods have given rise to different interpretations in this respect, as both methods find that intraparietal cortex is sensitive to both number and input format (symbolic vs. non-symbolic). Moreover, as reviewed earlier, recent decoding studies have even in some cases failed to find generalisation of numerical information across formats (symbolic and versus non-symbolic). Considering that potential format-invariant neuronal populations, which in any case could only arise as a result of associative learning at the endpoint of two separate processing pathways (one for symbolic and the other for non-symbolic number), might be sparse, thus not occupy much cortex and need not necessarily be sampled in a way to be easily detectable by fMRI pattern recognition, we think that positive results for generalisation across format should be considered as more important than negative ones. Also, computational models have proposed two sequential stages of the extraction of numerosity (summation and place coding), and suggested that combined selectivity to symbolic and non-symbolic formats would arise at the latter place coding stage only (Verguts and Fias, 2004). Since neurophysiological data suggest that the summation process plausibly occurs in certain sub-regions of intraparietal cortex (Roitman et al., 2007), such a model

predicts that a mixture of neuronal representations will be likely picked up by analysis methods lacking spatial resolution, for example through focussing on rather large regions of interest or intraparietal cortex as a whole, or also as a result of smoothing and/or inter-subject averaging. Thus, while a view that wants to equate parietal cortex with a single (format invariant) representation is likely too simplistic, in our opinion the present human imaging data are compatible with a hierarchical model where, for each format, the processing of number, which is initially format-specific, culminates in some neuronal populations with combined selectivity for symbolic and non-symbolic formats within parts of that cortex.

2.2. Is there functional specificity for number representations?

Influenced by cognitive scientists who have proposed a modular organisation of the mind, neuroscientists have among other things attempted to determine whether a modular account might also be applicable at the level of functional brain organisation (e.g. Kanwisher, 2010, for a review). In this context, it has been proposed to make a distinction between regional specificity and functional specificity. While regional specificity is taken to indicate that a given processing is carried out by one brain region as opposed to another, for a given brain region to qualify as being functionally specific (and a potential correlate of a “module”), it has been required to respond strongly to one function or one category, but not, or at least much less, to a large number of other categories or functions tested. To date a few regions within the ventral object processing pathway do correspond to these criteria of functional specificity, since they respond much more strongly to one category (e.g., faces, places, or bodies) than many other kinds of objects.

2.2.1. A) For symbolic number in the ventral stream

For what concerns symbolic numbers, and their representation in the ventral stream, if we apply the same criteria used to consider activation foci for other categories in this part of the brain as functionally specific (macroscopic regions in individual subjects activated strongly for their preferred category and much less for many other categories tested), the case of number appears to be so far a less strong one. The few studies finding positive results for preferential responses to numbers as opposed to well-matched control categories did not all agree in the precise location, the degree of preferences for numbers over other conditions appears more subtle, and to our knowledge such differences have not yet been observed during simple low-level perceptual tasks (for example passive viewing) as it is the case for the other category-selective infero-temporal regions. However, in addition to the technical factors already suggested to potentially contribute to making number-related activation foci hard to detect with fMRI (signal drop-out), for a completely culturally determined object category as the one of numerical symbols, it might appear to some extent unreasonable to expect an equally strong or macroscopically extensive preferential activation as for the natural categories mentioned (faces, places, bodies). Thus, given that we are more frequently engaged in reading written words than with reading Arabic digits, functional specialisation for Arabic digits could

be even more subtle than the one for words (which is itself more subtle than the one for faces, for example), providing a further reason for why it could go undetected in many cases in individual subjects with the current imaging methods.

2.2.2. B) For symbolic and non-symbolic number in the dorsal stream

While the ventral visual pathway has a relatively circumscribed and well understood functional role in object recognition, the function of intra-parietal cortex as part of higher-order association cortex is a much more broad and complex one. It involves, for example, spatial and action-related aspects of perception, including transformation of reference frames for multi-sensory and sensory motor integration (see, e.g., Cohen and Andersen, 2002; Culham and Valyear, 2006), as well as cognitive functions such as attention, working memory, episodic memory retrieval and mental imagery which are traditionally conceived of and studied as separate entities, but can also be conceptualised in terms of top-down modulation of externally (or internally) evoked representations as a common substrate (see, e.g., Lueckmann et al., 2014, for a review). This extent of uncertainty about how to define the most parsimonious set of basic “functions” of intraparietal cortex makes the question of functional specificity for numerical quantity a highly complicated one to address.

The particular regions (LIP/VIP) located along the intraparietal sulcus of the macaque monkey mentioned earlier to house neurons responsive or selective to different types of numerosity information are part of a series of sub-regions which play a role in sensory-motor integration and code for space in different reference frames (with respect to the eye in posterior LIP, the head in VIP, and the hand in the even more anterior AIP), also see (Hubbard et al., 2005, for a review). While we have reviewed evidence from both macaque neurophysiology and human fMRI regarding the parietal representation of number, the question of whether the IPS has undergone during evolution some changes in topographic organisation, and potentially also function, is worth considering. Human fMRI studies have proposed some candidate homologues of macaque areas LIP, VIP, and AIP (see e.g., Sereno and Huang, 2014, for a review), and a series of visual field maps has been found lining the IPS in both humans and macaque monkeys (Arcaro et al., 2011; Silver and Kastner, 2009). Nevertheless, there seems to be no one-to-one correspondence between field maps across species, and some areas located on the lateral wall of the IPS in macaques (LIP) appear have moved over to the medial wall in humans (Grefkes and Fink, 2005; Sereno and Huang, 2014), as the results of a differential expansion of the inferior parietal lobe in humans which could be related to symbolic/language-related processing. The extent to which these evolutionary changes may not only have displaced but also changed some characteristics of numerical representations during evolution currently remains an open question.

Human neuroimaging studies point to some degree of location specificity of numerical processing with respect to a few other landmark functions along the IPS: mental arithmetic activates regions between and partially overlapping with regions implicated in spatial attention and eye movement posteriorly, and other regions involved in pointing or grasping more anteriorly (Simon et al., 2002). Another study has found the activations for calculation to partly overlap with the human functional equivalent of LIP but to a lesser degree VIP, and to further extend into more

lateral parts of the IPS (Hubbard et al., 2008). These and other comparisons with the more general literature suggest that at a coarse scale, calculation-related activations overlap on the one hand with parietal parts of the dorsal attention network (see, e.g., Lueckmann et al., 2014) and on the other hand with the slightly more lateral so-called multiple-demand system (Duncan, 2010) which has been hypothesised to be important for controlling subtask assembly in complex goal-directed behaviour, and been shown to be modulated by task difficulty across a variety of number and non-number related tasks (Fedorenko et al., 2013). This overlap may not come as a big surprise given that a complex task such as calculation requires both attending to internal representations as well as manipulating these in an orderly fashion. Preferential activations for calculation as opposed to, for example, reading or more basic sensory-motor integration can therefore hardly count as evidence for domain specificity for number per se. Still, in addition to the issue of precisely matching task components to isolate a representation of number, one might wonder about the general usefulness of the mentioned strong definition of functional specificity which is implying the assumption of a one-to-one correspondence between a cognitive function/representation and a given macroscopic brain area. Functional specificity needs to also be considered at different spatial scales than the one of a macroscopic brain region. A given neural network could be concerned with a single function, nevertheless the neurons in question might be laid out in the brain in a way which is inter-mixed with (but nevertheless separated from) different networks concerned with other functions. Conventional functional neuroimaging studies, especially when employing normalisation, smoothing/ROI average signals, and inter-subject averaging, are insufficient to provide evidence in favour of or against functional specialisation at this level.

It also remains important to consider that long before functional imaging studies had seen the light of day, neuropsychology had already demonstrated that a marked and specific inability to understand numbers and mentally manipulate them can arise after brain lesions to parietal cortex (Cipolotti et al., 1991). While parietal lesions can also induce impairments in sensory motor skills such as eye-movements, visuo-spatial attention, grasping and motor planning, these impairments do not need to occur in association with acalculia. Importantly, even for the case of higher-level functions, which are often impaired together with calculation skills (as in the famous Gerstmann's Syndrome: writing, left-right orientation, and finger gnosis), calculation impairments can doubly dissociate from each of them (see Rusconi et al., 2010, for a review). These data need to be taken into account and integrated with neurophysiology and neuroimaging, as they do suggest some degree of separation of number processing from other high-level parietal cortex functions.

In addition, some recent data from electrophysiological recordings in epileptic patients (Dastjerdi et al., 2013), providing better spatial resolution as compared to conventional functional imaging, have demonstrated that a few recording sites in intra-parietal cortex which showed stronger activity during calculation than non-numerical episodic memory retrieval, also were preferentially activated under natural conditions during everyday activity when the patients referred to numerical concepts (as opposed to periods involving for example speaking, attending, moving eyes or hands). These initial results are promising since such recordings under real life conditions provide a means to screen for numerical responses compared to a large number of other activities, but may also in

the future be complemented with some more controlled experiments targeting the more precise representational characteristics of these responses.

For what concerns the finest available spatial scale of single cell neurophysiological recordings, while several studies now have replicated the results that there are neurons in intra-parietal cortex which are selective for a given individual numerosity, it is worth noting that those very same neurons also respond to other features in addition to number (e.g., the direction of visual motion, the location of tactile stimulation, the size of visual objects (Nieder et al., 2006)). This suggests that if a very strict definition of functional specificity is applied (absent or much smaller response to categories or stimulus features other than number), this may not necessarily apply to number representation at this finest scale either. It is important to bear in mind that these neurophysiological studies were not designed to test the question of modularity per se, responses to number were thus not compared to many other categories, and for the other responses reported we do not know their strength compared to the responses for number. Therefore, it is still not entirely clear in how far these neurons should be primarily considered “number” specific neurons, or in how far their combined response properties could be indicative of a more general function for which to date we haven't yet found the appropriate conceptualisation.

2.3. A code for generalised quantity or ordinality in parietal cortex?

What, if any, could be the more general function carried out by intra-parietal neuronal populations which also appear to be re-presenting numerical quantity? It has been previously argued that due to their macroscopic implication in sensory-motor transformations relevant for action, parietal regions may be well-suited for the processing of quantitative information in general (Buetti and Walsh, 2009). Indeed, activations are observed in partially overlapping sub-regions of parietal cortex during various quantitative comparison tasks, not only on number but also size, luminance, length, or duration (e.g., Cantlon et al., 2009; Dormal et al., 2012; Dormal and Pesenti, 2009; Fias et al., 2003; Pinel et al., 2004). Such common activations, however, could mainly reflect the processes of comparison (which need not necessarily occur within the same regions as those that extract and represent quantity within each dimension). Neuropsychological data, however, are currently more conclusive than brain imaging in this sense, and provide evidence that the processing of different types of quantities can be selectively dissociated from numerical skills; for example, in dyscalculia, characterized by an impaired processing of number, the processing of time and line length can be preserved (Cappelletti et al., 2014), whereas number processing skills can be preserved in patients suffering from impairments in time processing (Cappelletti et al., 2011). Also, TMS of left parietal sites impairs numerical but not temporal duration judgements (Dormal et al., 2008). Neurophysiology has further shown that the representation of numerosity and other quantitative parameters, such as line length, for example, is carried out by partly non-overlapping neuronal populations (different neurons do respond to number or length, or to both parameters although mostly not with preference for the same relative magnitudes) even though within the same brain area (Tudusciuc and Nieder, 2007). These findings speak against a

completely general magnitude code at the level of single neurons, but potentially for a population code which, through partly orthogonal contributions of the same neurons to different quantitative dimensions, can represent several quantitative dimensions. In humans, more studies using the within-category discrimination approaches, suited to more finely characterize the representational space for different quantities in parietal cortex would be desirable, thus going beyond mere large-scale activation overlap to determine which quantitative dimensions are coded in parietal cortex, and whether or not they are encoded in specific sub-regions.

On the other hand, number symbols have quantitative as well as order-related meaning, and it has been suggested that some, in particular anterior parts of human intraparietal cortex, are involved in the processing of the latter and not the former, since they were activated to the same degree during decisions as to which symbolic number was larger or which letter came earlier in the alphabet, as opposed to a dimming detection task on the same stimuli (Fias et al., 2007). Also, the IPS was found to be activated equivalently during production of words referring to numbers or months, but less so for production of animal names (Ischebeck et al., 2008). However, a reanalysis of the data of Fias et al. (2007) using multivariate decoding revealed that although the region's overall activation level was equivalent, the detailed pattern within the region allowed to distinguish between the number and letter conditions (Zorzi et al., 2011), suggesting that at a finer scale, these regions do either encode ordinal information separately for different categories, or do encode cardinal in addition to ordinal information.

To conclude, without even considering higher-level arithmetic or mathematical skills, the mere representation of number in humans is a complex and multifaceted entity. Neuroscientific findings indicate that areas important for the representation of approximate numerosity are reproducibly localised in intraparietal cortex. As for number in the mathematical sense, in its symbolic forms, while sub-regions of ventral visual cortex show some specialisation for the pre-semantic recognition of their surface form, neuronal association with a pre-existing representation of non-symbolic number in parietal cortex provides a plausible mechanism by which number symbols acquire their meaning during learning and are processed semantically.

Can these regions be considered as functionally specific for number? The intraparietal cortex in particular which is involved in a wide range of other cognitive and sensory-motor functions, does hardly correspond to the notion of a "number module", especially at a macroscopic scale. Nevertheless, some results from methods sensitive to finer scales so far suggest that (at least some aspects of) the representation of number are not entirely overlapping with the one of other magnitudes, nor simply reflecting a general representation of ordinality.

Some important questions remain. First, while intra-parietal areas constitute an important node for the representation of approximate number, the precise implementation of the initial extraction of numerosity information in the different modality-specific sensory cortices, and how this information can be brought into a common format to enable automatic comprehension of numerosity across sensory modalities, still needs to be understood.

Second, although symbols appear to be grounded through associating their shape with the pre-existing non-symbolic magnitude code, the representation of large multi-digit numbers as precise entities as accessed via symbols

may rely on additional complex combinations of knowledge and rule-based processing, the neuroscientific correlates of which remain rather elusive and were not in the focus of this review. Finally, most current work has investigated stimulus-evoked numerical representations. Understanding in how far some of the same representations are employed when internally generating numerical concepts (e.g., during imagery or mental calculations) and how these representations are combined or transformed during numerical operations, will be an important challenge for cognitive neuroscientists in the future.

References

- Abboud, S., Maidenbaum, S., Dehaene, S., Amedi, A., 2015. A number-form area in the blind. *Nat. Commun.* 6, 6026.
- Allison, T., McCarthy, G., Nobre, A., Puce, A., Belger, A., 1994. Human extrastriate visual cortex and the perception of faces, words, numbers, and colors. *Cerebr. Cortex* 4, 544–554.
- Anobile, G., Cicchini, G.M., Burr, D.C., 2014. Separate mechanisms for perception of numerosity and density. *Psychol. Sci.* 25, 265–270.
- Anobile, G., Turi, M., Cicchini, G.M., Burr, D.C., 2012. The effects of cross-sensory attentional demand on subitizing and on mapping number onto space. *Vis. Res.* 74, 102–109.
- Ansari, D., 2008. Effects of development and enculturation on number representation in the human brain. *Nat. Rev. Neurosci.* 9, 278–291.
- Ansari, D., Dhital, B., 2006. Age-related changes in the activation of the intraparietal sulcus during nonsymbolic magnitude processing: an event-related functional magnetic resonance imaging study. *J. Cogn. Neurosci.* 18, 1820–1828.
- Arcaro, M.J., Pinsk, M.A., Li, X., Kastner, S., 2011. Visuotopic organization of macaque posterior parietal cortex: a functional magnetic resonance imaging study. *J. Neurosci.* 31, 2064–2078.
- Ariely, D., 2001. Seeing sets: representation by statistical properties. *Psychol. Sci.* 12, 157–162.
- Arrighi, R., Togoli, I., Burr, D.C., 2014. A generalized sense of number. *Proc. Biol. Sci. /R. Soc.*, 281.
- Arsalidou, M., Taylor, M.J., 2011. Is 2 + 2 = 4? Meta-analyses of brain areas needed for numbers and calculations. *NeuroImage* 54, 2382–2393.
- Barnea-Goraly, N., Eliez, S., Menon, V., Bammer, R., Reiss, A.L., 2005. Arithmetic ability and parietal alterations: a diffusion tensor imaging study in velocardiofacial syndrome. *Brain Res. Cogn. Brain Res* 25, 735–740.
- Barth, H., La Mont, K., Lipton, J., Spelke, E.S., 2005. Abstract number and arithmetic in preschool children. *Proc. Natl. Acad. Sci. USA* 102, 14116–14121.
- Buckley, P.B., Gillman, C.B., 1974. Comparisons of digits and dot patterns. *J. Exp. Psychol.* 103, 1131–1136.

- Buetti, D., Walsh, V., 2009. The parietal cortex and the representation of time, space, number and other magnitudes. *Philos. Trans. R. Soc. Lond. Ser. B, Biol. Sci.* 364, 1831–1840.
- Bulthé, J., De Smedt, B., Op de Beeck, H., 2014. Format-dependent representations of symbolic and non-symbolic numbers in the human cortex as revealed by multi-voxel pattern analyses. *NeuroImage* 87, 311–322.
- Bulthé, J., De Smedt, B., Op de Beeck, H.P., 2015. Visual number beats abstract numerical magnitude: format-dependent representation of arabic digits and dot patterns in the human parietal cortex. *J. Cogn. Neurosci.*, 1–12.
- Burr, D., Ross, J., 2008. A visual sense of number. *Curr. Biol.* 18, 425–428.
- Burr, D., Turi, M., Anobile, G., 2010. Subitizing but not estimation of numerosity requires attentional resources. *J. Vis.* 10, 20.
- Butterworth, B., Cappelletti, M., Kopelman, M., 2001. Category specificity in reading and writing: the case of number words. *Nat Neurosci.* 4 (8), 784–786.
- Cantlon, J.F., Brannon, E.M., Carter, E.J., Pelphrey, K.A., 2006. Functional imaging of numerical processing in adults and 4-y-old children. *PLoS Biol.* 4, e125.
- Cantlon, J.F., Platt, M.L., Brannon, E.M., 2009. Beyond the number domain. *Trends Cogn. Sci.* 13, 83–91.
- Cappelletti, M., Barth, H., Fregni, F., Spelke, E.S., Pascual-Leone, A., 2007. rTMS over the intraparietal sulcus disrupts numerosity processing. *Exp. Brain Res.* 179, 631–642.
- Cappelletti, M., Butterworth, B., Kopelman, M., 2001. Spared numerical abilities in a case of semantic dementia. *Neuropsychologia* 39, 1224–1239.
- Cappelletti, M., Chamberlain, R., Freeman, E.D., Kanai, R., Butterworth, B., Price, C.J., Rees, G., 2014. Commonalities for numerical and continuous quantity skills at temporo-parietal junction. *J. Cogn. Neurosci.* 26, 986–999.
- Cappelletti, M., Didino, D., Stoianov, I., Zorzi, M., 2014. Number skills are maintained in healthy ageing. *Cogn. Psychol.* 69, 25–45.
- Cappelletti, M., Freeman, E.D., Cipolotti, L., 2011. Numbers and time doubly dissociate. *Neuropsychologia* 49, 3078–3092.
- Castelli, F., Glaser, D.E., Butterworth, B., 2006. Discrete and analogue quantity processing in the parietal lobe: a functional MRI study. *Proc. Natl. Acad. Sci. USA* 103, 4693–4698.
- Cavdaroglu, S., Katz, C., Knops, A., 2015. Dissociating estimation from comparison and response eliminates parietal involvement in sequential numerosity perception. *NeuroImage* 116, 135–148.
- Cipolotti, L., Butterworth, B., Denes, G., 1991. A specific deficit for numbers in a case of dense acalculia. *Brain* 114, 2619–2637.
- Cohen Kadosh, R., Bahrami, B., Walsh, V., Butterworth, B., Popescu, T., Price, C.J., 2011. Specialization in the human brain: the case of numbers. *Front. Hum. Neurosci.* 5, 62.
- Cohen Kadosh, R., Cohen Kadosh, K., Kaas, A., Henik, A., Goebel, R., 2007. Notation-dependent and -independent representations of numbers in the parietal lobes. *Neuron* 53, 307–314.
- Cohen, L., Dehaene, S., 1995. [Reading numbers in pure alexia: effects of the task and hemispheric specialization].

Revue Neurol. 151, 480–485.

Cohen, Y.E., Andersen, R.A., 2002. A common reference frame for movement plans in the posterior parietal cortex. *Nat. Rev. Neurosci.* 3, 553–562.

Cordes, S., Brannon, E.M., 2008. The difficulties of representing continuous extent in infancy: using number is just easier. *Child Dev.* 79, 476–489.

Cordes, S., Brannon, E.M., 2011. Attending to one of many: when infants are surprisingly poor at discriminating an item's size. *Front. Psychol.* 2, 65.

Coubart, A., Izard, V., Spelke, E.S., Marie, J., Streri, A., 2014. Dissociation between small and large numerosities in newborn infants. *Dev. Sci.* 17, 11–22.

Culham, J.C., Valyear, K.F., 2006. Human parietal cortex in action. *Curr. Opin. Neurobiol.* 16, 205–212.

Dakin, S.C., Tibber, M.S., Greenwood, J.A., Kingdom, F.A.A., Morgan, M.J., 2011. A common visual metric for approximate number and density. *Proc. Natl. Acad. Sci. USA* 108, 19552–19557.

Damarla, S.R., Just, M.A., 2015. Decoding the representation of numerical values from brain activation patterns. *Hum. Brain Mapp.*

Dastjerdi, M., Ozker, M., Foster, B.L., Rangarajan, V., Parvizi, J., 2013. Numerical processing in the human parietal cortex during experimental and natural conditions. *Nat. Commun.* 4, 2528.

Dehaene, S., 1992. Varieties of numerical abilities. *Cognition* 44, 1–42.

Dehaene, S., Changeux, J.P., 1993. Development of elementary numerical abilities: a neuronal model. *J. Cogn. Neurosci.* 5, 390–407.

Dehaene, S., Cohen, L., 1995. Towards an anatomical and functional model of number processing. *Math. Cogn.* 1, 83–120.

Dehaene, S., Dupoux, E., Mehler, J., 1990. Is numerical comparison digital? Analogical and symbolic effects in two-digit number comparison. *J. Exp. Psychol. Hum. Percept. Perform.* 16, 626–641.

Dehaene, S., Piazza, M., Pinel, P., Cohen, L., 2003. Three parietal circuits for number processing. *Cogn. Neuropsychol.* 20, 487–506.

Diester, I., Nieder, A., 2007. Semantic associations between signs and numerical categories in the prefrontal cortex. *PLOS Biol.* 5, 2684–2695.

Dormal, V., Andres, M., Dormal, G., Pesenti, M., 2010. Mode-dependent and mode-independent representations of numerosity in the right intraparietal sulcus. *NeuroImage* 52, 1677–1686.

Dormal, V., Andres, M., Pesenti, M., 2008. Dissociation of numerosity and duration processing in the left intraparietal sulcus: a transcranial magnetic stimulation study. *Cortex* 44, 462–469.

Dormal, V., Dormal, G., Joassin, F., Pesenti, M., 2012. A common right fronto-parietal network for numerosity and duration processing: an fMRI study. *Hum. Brain Mapp.* 33, 1490–1501.

Dormal, V., Pesenti, M., 2009. Common and specific contributions of the intraparietal sulci to numerosity and length processing. *Hum. Brain Mapp.* 30, 2466–2476.

- Dormal, V., Seron, X., Pesenti, M., 2006. Numerosity-duration interference: a Stroop experiment. *Acta Psychol.* 121, 109–124.
- Droit-Volet, S., Clément, A., Fayol, M., 2003. Time and number discrimination in a bisection task with a sequence of stimuli: a developmental approach. *J. Exp. Child Psychol.* 84, 63–76.
- Drucker, D.M., Aguirre, G.K., 2009. Different spatial scales of shape similarity re- presentation in lateral and ventral LOC. *Cerebr. Cortex* 19, 2269–2280.
- Duncan, J., 2010. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn. Sci.* 14, 172–179.
- Durgin, F.H., 2008. Texture density adaptation and visual number revisited. *Current Biol.* 18, R855–R856, author reply R857–R858.
- Eger, E., Michel, V., Thirion, B., Amadon, A., Dehaene, S., Kleinschmidt, A., 2009. Deciphering cortical number coding from human brain activity patterns. *Curr. Biol.* 19, 1608–1615.
- Eger, E., Pinel, P., Dehaene, S., Kleinschmidt, A., 2015. Spatially invariant coding of numerical information in functionally defined subregions of human parietal cortex. *Cerebr. Cortex.* 25 (5), 1319–1329, Epub 2013 Nov 28.
- Eger, E., Sterzer, P., Russ, M.C., Giraud, A.-L., Kleinschmidt, A., 2003. A supramodal number representation in human intraparietal cortex. *Neuron* 37, 719–725.
- Eliez, S., Blasey, C.M., Menon, V., White, C.D., Schmitt, J.E., Reiss, A.L., 2001. Functional brain imaging study of mathematical reasoning abilities in velocardio- facial syndrome (del22q11.2). *Genet. Med.: Off. J. Am. Coll. Med. Genet.* 3, 49–55.
- Fedorenko, E., Duncan, J., Kanwisher, N., 2013. Broad domain generality in focal regions of frontal and parietal cortex. *Proc Natl Acad Sci U S A* 110, 16616–16621, Epub 2013 Sep 23.
- 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, 8952–8956.
- Fias, W., Lammertyn, J., Reynvoet, B., Dupont, P., Orban, G.A., 2003. Parietal re- presentation of symbolic and nonsymbolic magnitude. *J. Cogn. Neurosci.* 15, 47–56.
- Gebuis, T., Reynvoet, B., 2012. The interplay between nonsymbolic number and its continuous visual properties. *J. Exp. Psychol. Gen.* 141, 642–648.
- Gilmore, C., Attridge, N., Clayton, S., Cragg, L., Johnson, S., Marlow, N., Simms, V., Inglis, M., 2013. Individual differences in inhibitory control, not non-verbal number acuity, correlate with mathematics achievement. *PloS One* 8, e67374.
- Gilmore, C.K., McCarthy, S.E., Spelke, E.S., 2007. Symbolic arithmetic knowledge without instruction. *Nature* 447, 589–591.
- Gordon, P., 2004. Numerical cognition without words: evidence from Amazonia. *Science* 306, 496–499.
- Grefkes, C., Fink, G.R., 2005. The functional organization of the intraparietal sulcus in humans and monkeys. *J.*

Anat. 207, 3–17.

Halberda, J., Mazocco, M.M.M., Feigenson, L., 2008. Individual differences in non-verbal number acuity correlate with maths achievement. *Nature* 455, 665–668.

Harvey, B.M., Klein, B.P., Petridou, N., Dumoulin, S.O., 2013. Topographic representation of numerosity in the human parietal cortex. *Science* 341, 1123–1126.

Holloway, I.D., Battista, C., Vogel, S.E., Ansari, D., 2012. Semantic and perceptual processing of number symbols: evidence from a cross-linguistic fMRI adaptation study. *J. Cogn. Neurosci.* 25, 388–400.

Hubbard, E.M., Diester, I., Cantlon, J.F., Ansari, D., Opstal, F. v., Troiani, V., 2008. The evolution of numerical cognition: from number neurons to linguistic quantifiers. *J. Neurosci.* 28, 11819–11824.

Hubbard, E.M., Piazza, M., Pinel, P., Dehaene, S., 2005. Interactions between number and space in parietal cortex. *Nat. Rev. Neurosci.* 6, 435–448.

Hyde, D.C., Boas, D.A., Blair, C., Carey, S., 2010. Near-infrared spectroscopy shows right parietal specialization for number in pre-verbal infants. *NeuroImage* 53, 647–652.

Isaacs, E.B., Edmonds, C.J., Lucas, A., Gadian, D.G., 2001. Calculation difficulties in children of very low birthweight: a neural correlate. *Brain: J. Neurol.* 124, 1701–1707.

Ischebeck, A., Heim, S., Siedentopf, C., Zamarian, L., Schocke, M., Kremser, C., Egger, K., Strenge, H., Scheperjans, F., Delazer, M., 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, 894–909.

Itti, L., Koch, C., 2001. Computational modelling of visual attention. *Nat. Rev. Neurosci.* 2, 194–203.

Izard, V., Dehaene-Lambertz, G., Dehaene, S., 2008. Distinct cerebral pathways for object identity and number in human infants. *PLOS Biol.* 6, e11.

Izard, V., Sann, C., Spelke, E.S., Streri, A., 2009. Newborn infants perceive abstract numbers. *Proc. Natl. Acad. Sci. USA* 106, 10382–10385.

Kanwisher, N., 2010. Functional specificity in the human brain: a window into the functional architecture of the mind. *Proc. Natl. Acad. Sci. USA* 107, 11163–11170.

Knops, A., Piazza, M., Sengupta, R., Eger, E., Melcher, D., 2014. A shared, flexible neural map architecture reflects capacity limits in both visual short-term memory and enumeration. *J. Neurosci.* 34, 9857–9866.

Koch, C., Ullman, S., 1985. Shifts in selective visual attention: towards the underlying neural circuitry. *Hum. Neurobiol.* 4, 219–227.

Koechlin, E., Naccache, N., Block, E., Dehaene, S., 1999. Primed numbers: exploring the modularity of numerical representations with masked and unmasked priming. *J. Exp. Psychol.: Hum. Percept. Perform.* 25, 1882–1905.

Kucian, K., Loenneker, T., Dietrich, T., Dosch, M., Martin, E., von Aster, M., 2006.

Impaired neural networks for approximate calculation in dyscalculic children: a functional MRI study. *Behav. Brain Funct.: BBF* 2, 31.

Lemer, C., Dehaene, S., Spelke, E., Cohen, L., 2003. Approximate quantities and exact number words: dissociable

systems. *Neuropsychologia* 41, 1942–1958.

Livingstone, M.S., Srihasam, K., Morocz, I.A., 2010. The benefit of symbols: monkeys show linear, human-like, accuracy when using symbols to represent scalar value. *Anim. Cogn.* 13, 711–719.

Lueckmann, H.C., Jacobs, H.I.L., Sack, A.T., 2014. The cross-functional role of frontoparietal regions in cognition: internal attention as the overarching mechanism. *Prog. Neurobiol.* 116, 66–86.

Marangolo, P., Nasti, M., Zorzi, M., 2004. Selective impairment for reading numbers and number words: a single case study. *Neuropsychologia* 42, 997–1006.

Matsuzawa, T., 2009. Symbolic representation of number in chimpanzees. *Curr. Opin. Neurobiol.* 19, 92–98.

Mazzocco, M.M.M., Feigenson, L., Halberda, J., 2011. Impaired acuity of the approximate number system underlies mathematical learning disability (dyscalculia). *Child Dev.* 82, 1224–1237.

McCrink, K., Wynn, K., 2004. Large-number addition and subtraction by 9-month-old infants. *Psychol. Sci.* 15, 776–781.

Molko, N., Cachia, A., Rivière, D., Mangin, J.F., Bruandet, M., Le Bihan, D., Cohen, L., Dehaene, S., 2003. Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. *Neuron* 40, 847–858.

Morgan, M.J., Raphael, S., Tibber, M.S., Dakin, S.C., 2014. A texture-processing model of the ‘‘visual sense of number’’. *Proc. Biol. Sci./R. Soc.* 281, 20141137.

Mussolin, C., De Volder, A., Grandin, C., Schlaegel, X., Nassogne, M.-C., Noel, M.-P., 2010. Neural correlates of symbolic number comparison in developmental dyscalculia. *J. Cogn. Neurosci.* 22, 860–874.

Naccache, L., Dehaene, S., 2001. The priming method: imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. *Cerebr. Cortex* 11, 966–974.

Nieder, A., 2005. Counting on neurons: the neurobiology of numerical competence. *Nat. Rev. Neurosci.* 6, 177–190.

Nieder, A., 2012. Supramodal numerosity selectivity of neurons in primate prefrontal and posterior parietal cortices. *Proc. Natl. Acad. Sci. USA* 109, 11860–11865.

Nieder, A., Diester, I., Tudusciuc, O., 2006. Temporal and spatial enumeration processes in the primate parietal cortex. *Science* 313, 1431–1435.

Nieder, A., Merten, K., 2007. A labeled-line code for small and large numerosities in the monkey prefrontal cortex. *J. Neurosci.* 22, 5986–5993.

Nieder, A., Miller, E.K., 2004. A parieto-frontal network for visual numerical information in the monkey. *Proc. Natl. Acad. Sci. USA* 101, 7457–7462.

Notebaert, K., Nelis, S., Reynvoet, B., 2010a. The magnitude representation of small and large symbolic numbers in the left and right hemisphere: an event-related fMRI study. *J. Cogn. Neurosci.* 23, 622–630.

Notebaert, K., Pesenti, M., Reynvoet, B., 2010b. The neural origin of the priming distance effect: distance-dependent recovery of parietal activation using symbolic magnitudes. *Hum. Brain Mapp.* 31, 669–677.

- Nys, J., Content, A., 2012. Judgement of discrete and continuous quantity in adults: number counts!. *Q. J. Exp. Psychol.* 65, 675–690.
- Op de Beeck, H.P., Haushofer, J., Kanwisher, N.G., 2008. Interpreting fMRI data: maps, modules and dimensions. *Nat. Rev. Neurosci.* 9, 123–135.
- Park, J., Brannon, E.M., 2013. Training the approximate number system improves math proficiency. *Psychol. Sci.* 24, 2013–2019.
- Park, J., Brannon, E.M., 2014. Improving arithmetic performance with number sense training: an investigation of underlying mechanism. *Cognition* 133, 188–200.
- Park, J., DeWind, N.K., Woldorff, M.G., Brannon, E.M., 2015. Rapid and direct encoding of numerosity in the visual stream. *Cerebr. Cortex.*
- 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, 39–50.
- Piazza, M., 2010. Neurocognitive start-up tools for symbolic number representations. *Trends Cogn. Sci.* 14, 542–551.
- Piazza, M., Facoetti, A., Trussardi, A.N., Berteletti, I., Conte, S., Lucangeli, D., Dehaene, S., Zorzi, M., 2010. Developmental trajectory of number acuity reveals a severe impairment in developmental dyscalculia. *Cognition* 116, 33–41.
- Piazza, M., Fumarola, A., Chinello, A., Melcher, D., 2011. Subitizing reflects visuo-spatial object individuation capacity. *Cognition* 121, 147–153.
- Piazza, M., Izard, V., Pinel, P., Le Bihan, D., Dehaene, S., 2004. Tuning curves for approximate numerosity in the human intraparietal sulcus. *Neuron* 44, 547–555.
- Piazza, M., Mechelli, A., Price, C., Butterworth, B., 2006. Exact and approximate judgements of visual and auditory numerosity: an fMRI study. *Brain Res.* 1106, 177–188.
- Piazza, M., Pica, P., Izard, V., Spelke, E.S., Dehaene, S., 2013. Education enhances the acuity of the nonverbal approximate number system. *Psychol. Sci.* 24, 1037–1043.
- Piazza, M., Pinel, P., Le Bihan, D., Dehaene, S., 2007. A magnitude code common to numerosities and number symbols in human intraparietal cortex. *Neuron* 53, 293–305.
- Pica, P., Lemer, C., Izard, V., Dehaene, S., 2004. Exact and approximate arithmetic in an Amazonian indigene group. *Science* 306, 499–503.
- 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, 1473–1479.
- 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, 983–993.
- Piras, F., Marangolo, P., 2009. Word and number reading in the brain: evidence from a voxel-based lesion-symptom Mapping study. *Neuropsychologia* 47, 1944–1953.
- Polk, T.A., Stallcup, 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, 145–159.

Pylyshyn, Z.W., 2001. Visual indexes, preconceptual objects, and situated vision. *Cognition* 80, 127–158.

Roggeman, C., Fias, W., Verguts, T., 2010. Saliency maps in parietal cortex: imaging and computational modeling. *NeuroImage* 52, 1005–1014.

Roitman, J.D., Brannon, E.M., Platt, M.L., 2007. Monotonic coding of numerosity in macaque lateral intraparietal area. *PLOS Biol.* 5, 1672–1682.

Rousselle, L., Noel, M.-P., 2008. The development of automatic numerosity processing in preschoolers: evidence for numerosity-perceptual interference. *Dev. Psychol.* 44, 544–560.

Roux, F.E., Lubrano, V., Lauwers-Cances, V., Giussani, C., Démonet, J.F., 2008. Cortical areas involved in Arabic number reading. *Neurology* 70, 210–217.

Rusconi, E., Pinel, P., Dehaene, S., Kleinschmidt, A., 2010. The enigma of Gerstmann's syndrome revisited: a telling tale of the vicissitudes of neuropsychology. *Brain* 133, 320–332.

Santens, S., Roggeman, C., Fias, W., Verguts, T., 2010. Number processing pathways in human parietal cortex. *Cerebral Cortex* 20, 77–88.

Sawamura, H., Shima, K., Tanji, J., 2002. Numerical representation for action in the parietal cortex of the monkey. *Nature* 415, 918–922.

Sereno, M.I., Huang, R.-S., 2014. Multisensory maps in parietal cortex. *Curr. Opin. Neurobiol.* 24, 39–46.

Seymour, S.E., Reuter-Lorenz, P.A., Gazzaniga, M.S., 1994. The disconnection syndrome. Basic findings reaffirmed. *Brain: J. Neurol.* 117, 105–115.

Shum, J., Hermes, D., Foster, B.L., Dastjerdi, M., Rangarajan, V., Winawer, J., Miller, K. J., Parvizi, J., 2013. A brain area for visual numerals. *J. Neurosci.* 33, 6709–6715.

Silver, M.A., Kastner, S., 2009. Topographic maps in human frontal and parietal cortex. *Trends Cogn. Sci.* 13, 488–495.

Simon, O., Mangin, J.F., Cohen, L., Le Bihan, D., Dehaene, S., 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron* 33, 475–487.

Srihasam, K., Mandeville, J.B., Morocz, I.A., Sullivan, K.J., Livingstone, M.S., 2012. Behavioral and anatomical consequences of early versus late symbol training in Macaques. *Neuron* 73, 608–619.

Starrfelt, R., Behrmann, M., 2011. Number reading in pure alexia – a review. *Neuropsychologia* 49, 2283–2298.

Thioux, M., Pillon, A., Samson, D., De Partz, M.P., Noël, M.P., Seron, X., 1998. The isolation of numerals at the semantic level. *NeuroCase* 4, 371–389.

Thompson, R.F., Mayers, K.S., Robertson, R.T., Patterson, C.J., 1970. Number coding in association cortex of the cat. *Science* 168, 271–273.

Tsao, D.Y., Livingstone, M.S., 2008. Mechanisms of face perception. *Annu. Rev.*

Neurosci. 31, 411–437.

Tudusciuc, O., Nieder, A., 2007. Neuronal population coding of continuous and discrete quantity in the primate posterior parietal cortex. *Proc. Natl. Acad. Sci. USA* 104, 14513–14518.

Verguts, T., Fias, W., 2004. Representation of number in animals and humans: a neural model. *J. Cogn. Neurosci.* 16, 1493–1504.

Viswanathan, P., Nieder, A., 2013. Neuronal correlates of a visual "sense of number" in primate parietal and prefrontal cortices. *Proc Natl Acad Sci U S A* 110, 11187–11192, Epub 2013 Jun 17.

Vogel, S.E., Goffin, C., Ansari, D., 2014. Developmental specialization of the left parietal cortex for the semantic representation of Arabic numerals: an fMR- adaptation study. *Dev. Cogn. Neurosci.* 12C, 61–73.

Wynn, K., 1992. Addition and subtraction by human infants. *Nature* 358, 749–750. Zorzi, M., Di Bono, M.G., Fias, W., 2011. Distinct representations of numerical and non-numerical order in the human intraparietal sulcus revealed by multivariate pattern recognition. *NeuroImage* 56, 674–680.