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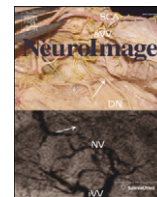
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The cortical representation of simple mathematical expressions

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ABSTRACT

Written mathematical notation conveys, in a compact visual form, the nested functional relations among abstract concepts such as operators, numbers or sets. Is the comprehension of mathematical expressions derived from the human capacity for processing the recursive structure of language? Or does algebraic processing rely only on a language-independent network, jointly involving the visual system for parsing the string of mathematical symbols and the intraparietal system for representing numbers and operators? We tested these competing hypotheses by scanning mathematically trained adults while they viewed simple strings ranging from randomly arranged characters to mathematical expressions with up to three levels of nested parentheses. Syntactic effects were observed in behavior and in brain activation measured with functional magnetic resonance imaging (fMRI) and magneto-encephalography (MEG). Bilateral occipito-temporal cortices and right parietal and precentral cortices appeared as the primary nodes for mathematical syntax. MEG estimated that a mathematical expression could be parsed by posterior visual regions in less than 180 ms. Nevertheless, a small increase in activation with increasing expression complexity was observed in linguistic regions of interest, including the left inferior frontal gyrus and the posterior superior temporal sulcus. We suggest that mathematical syntax, although arising historically from language competence, becomes “compiled” into visuo-spatial areas in well-trained mathematics students.

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“Words and language, whether written or spoken, do not seem to play any part in my thought processes. The psychological entities that serve as building blocks for my thought are certain signs or images, more or less clear, that I can reproduce and recombine at will.”

Albert Einstein

Introduction

The origin of the uniquely human ability for mathematics is a classical philosophical debate which, in recent years, has progressively been turned into an experimental question in cognitive neuroscience (Carey, 1998; Changeux and Connes, 1995; Dehaene, 1997). There is a growing consensus that the most basic of human intuitions, in domains such as number, space and time originate from brain mechanisms inherited from our evolution and present in uneducated humans as well as many

other animal species (Carey, 2009; Dehaene and Brannon, 2011; Gilmore et al., 2007; Halberda et al., 2008; Izard et al., 2011; Nieder and Dehaene, 2009). However, only humans, with education, seem to turn these primitive approximate concepts into a formal mathematical system. The role of language in this cultural construction of mathematics remains heavily debated. On the one hand, the invention of verbal counting and the creation of written and spoken number words and expressions are thought to have played a prominent role in the near-simultaneous emergence of writing and mathematics in ancient Sumer and Greece (Kline, 1972). Many mathematical expressions, such as $a^2 + b^2 = c^2$, have a nested hierarchical structure reminiscent of the constituent structure of language (Ernest, 1987). Indeed, the expression $a^2 + b^2 = c^2$ can be drawn using a linguistic tree where, for instance, a^2 or $a^2 + b^2$ are valid sub-constituents, while $b^2 = c^2$ is not—just like “the car is red” is not a valid sub-constituent of the sentence “the truck that passes the car is red”. The developmental psychologist Elizabeth Spelke hypothesizes that language provides an essential mental “glue” that enables the human mind to assemble new complex concepts from simple primitives (Condry and Spelke, 2008; Spelke, 2003). The general hypothesis has been proposed that the human species would be endowed with a single ability to recursively “merge” any two mental objects to form a third one, a competence that would underlie all uniquely human abilities

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for recursion in language, mathematics and other domains such as music, spatial navigation or social relations (Fadiga et al., 2009; Hauser et al., 2002; Tettamanti and Weniger, 2006).

On the other hand, starting around the 15th century, as arithmetic expressions became increasingly complex, the history of mathematics indicates a systematic decrease in the use of language and words, and the emergence of many compact visuo-spatial mathematical notation devices (Cajori, 1928). Mathematicians realized that spatial configurations of symbols could be used to capture nested structures. Examples include separating the numerator and denominator of fractions by a horizontal line, or using opening and closing parentheses as devices delineating the constituents of a nested algebraic structure. Furthermore, as exemplified by the opening quote by Albert Einstein, many practicing mathematicians and physicists professed the strong intuition that mathematics is primarily visuo-spatial rather than linguistic in nature. Indeed, some neuropsychological experimental data point to a dissociation of arithmetical and algebraic abilities from the language faculty. For instance, patients with severe global aphasia or semantic dementia may remain able to perform nested arithmetic computations (Cappelletti et al., 2001; Delazer et al., 1999; Rossor et al., 1995; Varley et al., 2005; Zamarian et al., 2006) and even simplify or transform algebraic problems like $2a + 5a + 11 + 3 = ?$ (Klessinger et al., 2007). Although rote knowledge of arithmetic tables may depend upon verbal memory, the conceptual understanding of the link between Arabic numerals and the corresponding quantities, as well as the ability to combine these quantities into simple operations, can be selectively impaired by left parietal lesions outside of classical language areas (Lemer et al., 2003).

Behavioral, neuropsychological and brain imaging data further suggest that some numerical operations, such as approximation, only require a mapping from visual representations of the digits in symbols in the bilateral occipito-temporal cortex to quantity representations in the bilateral intraparietal sulci, without linguistic mediation (Cohen and Dehaene, 1996, 2000; Dehaene and Cohen, 1995; Dehaene et al., 1999; Gazzaniga and Smylie, 1984; Ischebeck et al., 2006). This relative independence of some mathematical concepts from language is confirmed by psychological studies of remote Amazonian and Aboriginal populations with a reduced language for number (e.g. “one, two, many”), which indicate an impressive mastery of complex numerical and geometrical concepts without language—yet the data also reveal significant conceptual change with education to counting and to number words, including the emergence of a precise, linear concept of number (Butterworth et al., 2008; Dehaene et al., 2008; Gordon, 2004; Pica et al., 2004).

The confusion may arise, at least in part, from a failure to distinguish the many levels of representation that are available, both within language (from phonology to morphology, lexicon, recursive syntax, conceptual structure...) and within mathematics (from approximate quantity concepts to exact numbers, operations, syntactically organized expressions...). In the present study, we specifically investigated the representation of elementary algebraic expressions such as “ $1 + (4 - (2 + 3))$ ”, with the goal to determine if the cerebral structures that are responsible for parsing such nested structures are shared with those that compute the syntax of linguistic expressions. We capitalized on our previous neuroimaging study of the constituent structure of sentences (Pallier et al., 2011). In this study, subjects were scanned with functional magnetic resonance imaging (fMRI) while they viewed a series of 12 words, which parametrically varied from a random word list to syntactically correct word pairs, triplets, etc.... all the way to a full 12-word sentence. This parametric variation of syntactic constituents, either with semantically meaningful materials or with “jabberwocky” sentences in which the content words had been replaced by pseudo-words, identified a set of left-hemispheric brain regions, along the left superior temporal sulcus as well as in the left inferior frontal cortex and putamen, whose activation increased monotonically with the number of nested constituents, suggesting a central contribution of these regions to the representation of nested linguistic constituents.

Here, by analogy with this prior linguistic experiment, we always presented strings of 11 identical symbols, but variously arranged from random noise, e.g. “ $4 - +) 3) (+ 2 (1$ ” to well-structures, e.g. “ $((3 - 2) + 4) + 1$ ”, thus defining 4 levels of increasing complexity and embedding (see Fig. 1). Note that in the number domain, any syntactically well-formed expression is also semantically meaningful. Thus, syntax and semantics could not be separated in our design, which was solely concerned with how the brain represents elementary mathematical expressions with nested embeddings. Nevertheless, we reasoned that, if the syntactic structures of language are required for such mathematical expressions, then we should replicate, with these algebraic stimuli, a monotonic increase in activation with expression complexity in some or all of the previously observed language areas. If, on the other hand, the processing of simple numerical expressions requires solely a mapping from visual regions to the intraparietal quantity system, then our contrast for the constituent size of mathematics might only reveal these regions, which lie entirely outside of the language system (Pallier et al., 2011).

Our strategy is predicated upon the hypothesis that human subjects readily parse mathematical expressions into their constituent structure, which is supported by behavioral studies (Jansen et al., 2003, 2007; Ranney, 1987). For instance, well-formed strings such as “ $7 - x$ ” are better remembered than ill-formed ones such as “ $7(x)$ ”, and genuine constituents of mathematical expressions (e.g. “ $4 - x^2$ ” in “ $(4 - x^2)y - 7$ ”) are better remembered than similar non-constituent substrings (e.g. “ $4 - x^2$ ” in “ $4 - x^2(y - 7)$ ”) (Jansen et al., 2003, 2007). Recently, we measured eye movement trajectories while mathematically trained subjects computed nested arithmetic operations such as $4 + (3 - (2 + 1))$. As early as the second eye fixation, the eye moved to the deepest nested level of parentheses (here $2 + 1$), then progressively traced its way up the syntactic tree (Schneider et al., submitted for publication). Such data suggest that mathematical expressions can be quickly parsed. In the present work, we will provide much stronger behavioral and brain imaging evidence for this statement.

There has been comparatively little work on the brain mechanisms underlying mathematical parsing. A few neuroimaging studies examined algebraic transformations (Danker and Anderson, 2007; Qin et al., 2003; Sohn et al., 2004) and concluded to a specific role of bilateral posterior parietal cortex, rather than perisylvian language areas, in the mental displacement of the constituents needed to resolve equations such as $19 - 7x = 5$ (e.g. bring $7x$ to the right side, etc.). This conclusion fits with behavioral studies which indicate that, during equation solving the physical form of mathematical expressions is manipulated mentally in a visual rather than a verbal form (Landy and Goldstone, 2007a; Landy and Goldstone, 2007b, 2010). Yet only a single study to date specifically probed the cerebral bases of the syntax of logical formulae (Friedrich and Friederici, 2009). By contrasting hierarchical expressions versus lists of similar symbols, this study found only a minor involvement of Broca's area, and a major role for the parietal cortex. Our design aimed to significantly extend this logic by (1) using a parametric design where the complexity of mathematical expressions was varied monotonically in four successive levels; (2) providing behavioral evidence for the nested representation of elementary mathematical expressions, even in a same-different task that did not require explicit parsing; (3) providing both fMRI and magneto-encephalography (MEG) evidence on the cerebral localization and speed with which these expressions are parsed; and (4) exploring the influence of the spatial layout of the mathematical expression on brain activity.

In exploring these questions, we capitalized on the complementarity of fMRI and MEG. fMRI provided a spatially accurate but temporally integrated overview of how brain activity varies with the complexity of mathematical expressions. Conversely MEG allowed us to ask at what time this complexity first affects brain activity, and what form and coarse cortical localization this early syntactic effect exhibits.

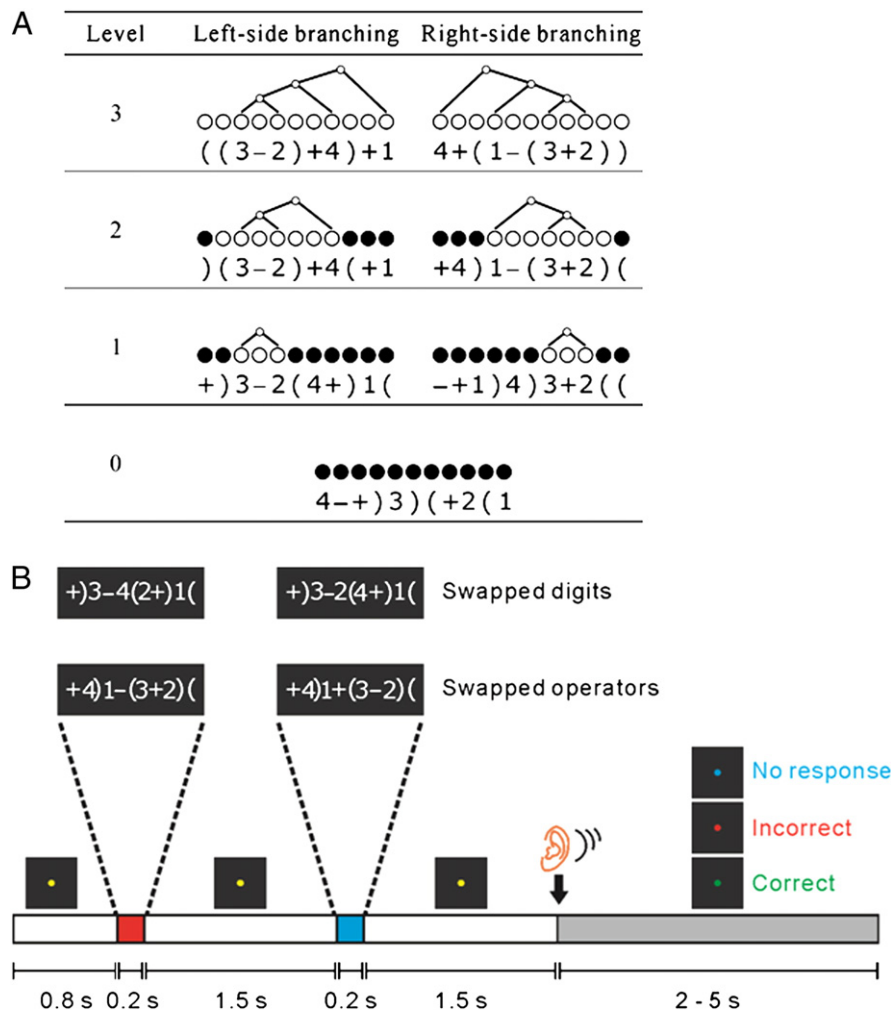


Fig. 1. Experimental stimuli permitting a parametric manipulation of the complexity of mathematical expressions. (A) Stimulus design. The stimuli consisted of strings of 11 mathematical symbols, identical in all conditions, but whose arrangements varied from completely random (level 0) to increasingly nested levels of parenthesizing (levels 1, 2, 3). The deepest level of parentheses could appear either to the left or to the right of fixation (left- vs right-branching), thus creating a total of seven experimental conditions. (B) Time course of a trial. Two successive strings from the same experimental condition were presented sequentially at a 1.7 s interval (red and blue bars). In half the trials, the two strings were the same. In the other half, the second string was generated by swapping the positions of two digits or two operation signs (+ and −). Subjects judged whether the two strings were the same or different. Note that this task does not require explicit syntactic parsing or mathematical calculation. The subjects received visual and auditory feedback, with a change of fixation color from yellow to green for correct button press, red for incorrect button press, and blue when no response was made within 1.7 s from the onset of the second string. The red and blue horizontal bars denote the presentation periods of two strings.

Methods

Subjects

24 native French speakers took part in both MEG and fMRI experiments (5 females; age range 19–27 years, mean 21.6, SD 2.2) after giving written informed consent. 22 subjects were right-handed with a laterality quotient (LQ) of at least 69, and the other two were mixed (LQ = 20 and 40), as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects received general mathematical education in French universities. The experiment was part of a general research program on functional neuroimaging of the human brain sponsored by the Atomic Energy Commission (Denis Le Bihan) and approved by the regional ethical committee (Comité de Protection des Personnes, hôpital de Bicêtre).

Stimuli and task

Stimuli were strings of eleven symbols, always comprising the four digits 1 to 4, two “+” and one “−” sign, and two pairs of round parentheses. The ordering of these symbols defined four levels of

expression complexity (see Fig. 1 for examples). Well-formed expressions (level 3) comprised three nested levels of calculations, either organized from left to right (left-branching) or from right to left (right-branching) (center embedding was not used). Note that, although this 3-level nested tree structure corresponded to a defined calculation, the task given to the subjects did not require any calculation. Lower levels of complexity (levels 2, 1, and 0) were generated by breaking this tree organization, node after node. Level-2 stimuli were created by swapping the outer opening and closing parentheses and shuffling the symbols outside them. This resulted in a partial formula with two levels of nesting, surrounded by mathematical non-sense. Similarly, level-1 stimuli were generated by swapping the inner parentheses and shuffling all the symbols outside them—resulting in a small island of preserved arithmetic (e.g. $3+4$) within otherwise non-sensical materials. Finally, level-0 stimuli were generated by shuffling the locations of all symbols.

Shuffling was constrained to guarantee that the resulting order was syntactically incorrect. To this end, the shuffled parts never contained sequences NON, (N) or (ON), where N is a digit and O is an operation symbol, nor consecutive digits such as “12” which could be perceived as 2-digit numbers.

Every trial started with a yellow fixation dot on the center of screen. After 800 ms, two white strings were sequentially presented for 200 ms each, separated by a 1500 ms inter-stimulus interval (Fig. 1). The two strings were identical to each other in 50% trials (same or “no-swapping” trials). In the remaining trials, the second string differed from the first one in the locations either of two digits (25%) or of two “+” and “−” operation signs (25%). Note that the syntactic structure was not affected by the swapping. Subjects decided whether the second string was identical to the first one, by pressing either right or left thumb buttons (randomized across subjects). This memory task does not require explicit syntactical parsing or mathematical calculation. We therefore could probe the automatic or implicit processing of algebraic structure. The subjects were encouraged to memorize the entire string. To maintain motivation, visual and auditory feedback was provided on every trial, 1500 ms after the offset of the second string. The visual feedback was given by the color of the fixation point: green for correct responses, red for incorrect responses, and blue when no response was recorded within 1500 ms. The auditory feedback consisted in three different sounds. After an intertrial period of 3000 ms in MEG and ranging from 2000 to 5000 ms in fMRI, the fixation point went back to yellow, indicating the start of the next trial.

The symbols were equally spaced using a fixed-point Lucida Console font. Strings subtended 4° of horizontal and 0.6° of vertical visual angle. The experiment was controlled with E-Prime 1.2 software (Psychological Software Tools, Inc., Pittsburgh, PA) and projected on a translucent screen with a digital-light-processing projector (PT-D7700E, Panasonic; frame rate: 60 Hz). Viewing distance was 100 cm in fMRI and 82 cm in MEG.

The experiment consisted of eight runs of MEG recording and seven or eight runs of fMRI recording, in this order in half of the subjects and in the reverse order in the others. Each run consisted of 16 level-0 trials and 8 trials at each of the other levels and branching conditions (1–3, left or right branching). The ratio of no-swapping, digit-swapping and operator-swapping trials was identical across all conditions and runs.

Behavioral data analyses

Responses before the onset of feedback stimuli (i.e., <1700 ms from the onset of second string) were used for analyses of error rates and response times. Behavioral responses in MEG and fMRI recordings did not differ significantly and were merged. The influence of experimental conditions was examined with analysis of variances (ANOVAs) using SPSS software (SPSS, Inc., Chicago), with subjects treated as a random factor. In post hoc multiple comparisons, corrected p -values (p_c) was obtained using Scheffé's procedure, as well as uncorrected p -values (p_{uc}) using t -tests.

To probe the effect of position and other variables on performance, we measured the error rate and response time as a function of the 11 positions inside the strings where two digits or two operators could be swapped. To estimate these values, we averaged across all trials in which a given position had been swapped, regardless of where the other swapped symbol was. As a consequence, each trial was counted twice (once for each of the two swapped locations). We then regressed these data with a linear model defined as:

$$EF(x, DS, L, LS, BS) = EF_{GA} + a \times x + b \times DS + c \times L + d \times LS + e \times BS + error,$$

where x is a location of one of the swapped symbols ($x = -5, -4, \dots, +5$). DS is the nature of swapped symbols (operator: -1 ; digit: $+1$); L is the syntactic level (0 to 3); LS notes a local syntactic effect, defined as -1 when the symbol was located outside of a well-formed expression, and $+1$ when it was inside; BS is the branching side of the entire expression (left: -1 ; right: $+1$; 0 for level 0). The regression intercept

EF_{GA} (= grand average in the level 0) and the regression coefficients of each variable were obtained by minimizing mean square of error over all subjects and string conditions, using a method of least-square-with-known-covariance as implemented in Matlab software (Mathworks, Inc.). Because error rate in each conditions and subject was estimated from different numbers of trials (1–25 trials), we weighted the square of the error by the number of trials. The significance of the coefficients was tested with a permutation method. A similar linear regression analysis was also carried out for RT . The error rates and RT s (in ms) were ultimately regressed as:

$$ER = 0.331 + 0.017 \times x - 0.095 \times DS - 0.034 \times L - 0.001 \times LS + 0.010 \times BS,$$

$$RT = 829.5 + 2.7 \times x - 28.3 \times DS - 10.9 \times L + 6.0 \times LS + 7.4 \times BS.$$

fMRI acquisition and analyses

fMRI data were acquired on a 3 Tesla MR system (Siemens Trio-Tim Syngo) as T2*-weighted echo-planar image (EPI) volumes. Thirty transverse slices covering the whole brain were obtained with a TR of 1.6 s and a voxel size of $4 \times 4 \times 4$ mm ($TE = 30$ ms, flip angle = 72° , no gap). Accurate timing of the stimuli relative to fMRI acquisition was achieved with an electronic trigger at the beginning of each run. For each participant, anatomical images were obtained using a sequence of magnetization prepared rapid gradient echo (MPRAGE) with 160 slices with a voxel size of $1 \times 1 \times 1.1$ mm, covering the entire brain ($TR = 2.3$ s, $TE = 3$ ms, flip angle = 9° , no gap).

The data were processed with SPM5 (Wellcome Department of Cognitive Neurology, software available at <http://www.fil.ion.ucl.ac.uk/spm/>). Anatomical images were normalized to the standard brain template defined by the Montreal Neurological 152-brains average. Functional images were corrected for slice-timing differences and realigned to the first image to correct for head movements. The functional images were spatially normalized using the parameters obtained in the normalization of the anatomical images, resampled with a voxel size of $3 \times 3 \times 3$ mm, and smoothed with a 5 mm Gaussian kernel. Experimental effects at each voxel were estimated using a multi-session design matrix. A general linear model was created, which included 21 trial types (seven tree structures and three swapping types), each modeled by the canonical hemodynamic response function and its first-order time derivative, and 6 individual motion parameters to capture remaining signal variations due to head movements. The first and second strings were approximated as a single stimulus. The stimulus duration was modeled as 1.9 s, which was the period from the onset of the first string to the offset of the second. The model also included high-pass filtering above 1/128 Hz. Individually-estimated BOLD responses, smoothed with an 8 mm Gaussian kernel, were then entered into a random-effect group analysis. An analysis of variance model (ANOVA) was designed with one regressor per condition and per participant to remove a main effect of subjects. To search for effects of complexity, we used a positive and negative linear contrast over levels 0 to 3 ($-3 - 1 \ 1 \ 3$), with weights spread over subconditions. (The contrasts used are detailed in Table S1.) Maps were thresholded at voxel-wise $p < .001$ and we report the qFDR p -values computed by SPM8 (Chumbley and Friston, 2009).

Functional localizer for linguistic and calculation regions

Regions showing an effect of expression complexity were compared with those involved in language and calculation, as localized by a brief event-related functional localizer described in detail elsewhere (Pinel et al., 2007). Briefly, this short fMRI scan was primarily designed to isolate, in a reliable and individual manner, the brain correlates of early vision, left- and right-hand motor commands, sentence

reading, speech listening and mental calculation. Ten different types of stimuli were presented in random order, at a rhythm of approximately one every 4.8 s. Twenty flashing checkerboard sectors were displayed to identify retinotopic areas. Twenty rest periods (black screen) served as null events for better hemodynamic deconvolution. The rest of the stimuli comprised 20 short meaningful sentences (e.g. “One can easily find a taxi in Paris”), 20 verbal commands to click the right or the left button, and twenty simple one-digit subtraction problems (a task selected to ensure a strong activation of the various components of the number processing system). In each of these categories, 10 stimuli were presented auditorily, as spoken sentences (1.2–1.7 s long), while 10 were presented visually through rapid serial visual presentation (four successive screens of 1–3 words and 250 ms duration, separated by 100 ms intervals). In total 100 trials were recorded for a duration of 5 min. Functional images for the localization were acquired in 17 of the 24 subjects with a TR of 2.4 s with a voxel size of $3 \times 3 \times 3$ mm. In the other 7 subjects, the functional localizer could not be run due to the limited duration of the fMRI experiment. The experimental protocol was organized as a fast event-related paradigm. The 100 trials were presented in a fixed sequence with a stochastic SOA (4200 ms, 4500 ms, 4800 ms, 5100 ms or 5400 ms; mean SOA = 4.8 s) for better deconvolution of the hemodynamic signal. The entire sequence took approximately 5 min. The functional images were treated with SPM as described earlier. The effects of stimuli and tasks at each voxel were estimated in each subject using a multi-session design matrix, and the individually-estimated BOLD responses were subsequently entered into a random effect group analysis to examine contrasts of interest. The present study used two contrasts: visual calculation vs. checkerboards, which functionally isolated an area in the posterior part of the left inferior temporal cortex; and visual and auditory calculation tasks relative visual and auditory non-numerical sentences, in order to localize regions involved in calculation.

MEG data acquisition and preprocessing

Each subject was comfortably seated inside a magnetically shielded room (single-layer with active compensation; Electa, Helsinki, Finland). Magnetic field responses were measured with a 306-channel Neuromag Vectorview system (Elekta), containing a magnetometer and two orthogonal planar gradiometers located at each of 102 positions on the inner, lower surface of the helmet-shaped dewar. The subjects were encouraged not to blink from the start of a trial until the sound feedback. Blinks, eye movements and heart beats were simultaneously measured with a horizontal electrooculogram (EOG; lateral to the left and right outer canthus of the eyes), a vertical EOG (above and below the left eye) and an electrocardiogram (ECG) for off-line noise reduction. The head position relative to the sensor array was monitored continuously during the recording by feeding sinusoidal currents (293–321 Hz) to four Head-Position-Indicator (HPI) coils attached to the scalp. Positions of three anatomical fiducials (nasion and left and right pre-auricular points) relative to the HPI coils were measured with a 3D digitizer (Fastrak, Polhemus, VT) before MEG recording. All signals were band-pass filtered below 330 Hz and above 0.03 Hz, and sampled at 1 kHz.

In preprocessing for noise reduction, we first removed sensors that were noisy during whole recording. Next, environmental field noise was filtered out by applying the Signal Space Separation (SSS) method (Taulu et al., 2005), as implemented with the Maxfilter software (Elekta). Then, MEG signals at the removed sensors were interpolated with the SSS method. MEG signals acquired from different head positions were converted to those estimated for a reference head position chosen close to the mean over the whole recording.

The Matlab-based Fieldtrip toolbox, developed at the Donders Institute (<http://www.ru.nl/neuroimaging/fieldtrip/>), was used for further analyses of the MEG data. The MEG signals were low-pass filtered below 80 Hz and notch-filtered to eliminate power line noise at 50 Hz. We extracted epochs between 800 ms before the onset of the first string and 1500 ms after the offset of the second string. Trials contaminated by

muscle, saccadic and sensor-jump noises were discarded. Independent Component Analysis (ICA) was used to remove blink artifacts. We first down-sampled the MEG data to 200 Hz in order to carry out ICA together across all runs and conditions. Next, MEG data were decomposed into 102 time-independent components, and components temporally correlated with the vertical EOG signal in eye blinks were discarded. We also excluded other artifacts such as heart beat and sensor noises, based on their temporal patterns. Finally we recombined the remaining components to obtain cleaned-up MEG signals (see Supplementary Figs. S3 and S4 for illustrations of the method).

The MEG signals were averaged with respect to the onset of the first string (defined as 0 ms). The number of trials could vary across conditions, which, with residual noise, can create artifactual differences in the estimates of the power of event-related averages. We avoided any influence of the number of trials on the estimation of power by first dividing the trials of level 0 in two sets (thus equalizing the number of trials with the other levels), and similarly dividing the no-swapping trials into two sets, computing power, and then averaging the resulting signals in each set.

MEG sensor-level analyses using cluster statistic

Signals from the planar gradiometers were used to identify the latencies with which the structure of mathematical expressions was extracted. The effect of expression complexity was statistically tested with a dependent-sample regression using the same contrast vector as in fMRI analyses. In a topographic analysis, the significant differences between conditions were determined across subjects using a nonparametric randomization method, available within FieldTrip toolbox, that identifies significant clusters of sensors (Maris et al., 2007). The method corrects for multiple comparisons over sensor locations and latencies, taking advantage of the fact that a difference in neural activation is usually detectable by a group of neighboring sensors. However, in our MEG system, differently oriented gradiometers at neighboring sensor locations can have quite different sensitivities to a neural current depending on its flowing orientation. To obtain a signal indicator that is sensitive to all orientations of current flow, the variances of the two orthogonal gradiometers at a given location were summed, and the combined signal was submitted to nonparametric randomization analysis. Each condition was normalized by dividing by the mean over all conditions at the latency of -300 ms.

Cluster analysis consisted in three steps. First, the effect of expression complexity was statistically tested, separately at each location and latency, using a dependent-sample regression, with a threshold of $p < 0.05$. We quantified the effect with the same contrast vector as in fMRI analyses (Table S1, “overall syntactic level effect”). Second, neighboring locations, defined as sensors distant by less than 4.5 cm, were clustered at each latency (spatial clusters consisting of fewer than two locations were discarded), and the spatial clusters that were adjacent in time were combined into a single spatio-temporal cluster. Third, cluster size was measured by summing the t -values across sensors and latencies within each cluster (t_{sum}). Note that the resulting measure could be positive or negative, thus allowing us to identify brain activations that increased or decreased with syntactic complexity in a single step. The significance of t_{sum} was assessed using a nonparametric Monte-Carlo method, where we repeatedly shuffled the power measures across conditions, extracted clusters as previously, and compiled the distribution of the largest and smallest t_{sum} values. The randomization was repeated 1000 times, thus providing an estimate of the distribution of these min and max values. Clusters of original data were deemed significant when their t_{sum} values were above 97.5% or below 2.5% of the Monte-Carlo distribution (two tailed test, corrected $p < 0.05$).

MEG source analyses

Using the averaged MEG signals, we estimated the neural electrical activities at each cortical peak where a significant effect of expression

complexity was obtained in the whole-brain fMRI analysis. The use of peaks defined from another data set circumvents the problems of statistical circularity. The positions defined in fMRI group analyses (MNI coordinates) as showing the largest effect were transformed into an individual MRI coordinate by an inverse normalization method, as implemented in SPM5. The sensor positions on the MEG coordinate system were also transformed into the individual MRI coordinate by fitting the fiducial positions relative to the HPI coils to those extracted on the anatomical images. The lead fields of the sensors for each peak position were calculated using an anatomically realistic forward head model (Nolte, 2003). We then applied the linearly constrained minimum variance (LCMV) beamforming to the averaged evoked fields (van Veen et al., 1997). Event-related changes in temporal variance were computed by sliding a time window, allowing for a calculation of the covariance matrix of all gradiometer combinations and for the ensuing adaptation of spatial filtering in steps of 20 ms. The half size of the beamformer window was set to 100 ms. The spatial filter was common to all experimental conditions. A regularization parameter, set to 10% of the mean diagonal of the matrix, was incorporated to stabilize the matrix inversion required in the methods. To test for a syntactic effect, the normalized power at each peak was submitted to the same dependent-sample regression analysis as above, with the threshold set to $p < 0.05$. Clustering of significant t values was carried out only in the time domain, and the significance of t_{sum} values was tested at the corrected-level by using the above nonparametric Monte-Carlo method, pulling the randomized distribution together across all tested peaks.

Results

Behavioral evidence for syntactic parsing of algebraic expressions

Behavioral responses in MEG and fMRI recordings did not differ significantly and were merged. Subjects experienced little difficulty in performing the requested same-different task with two successive strings of arithmetic symbols (~15% errors). The only condition with a large number of misses was when the second string was generated by swapping two operation signs (operator-swapping; ~40% errors) (Fig. 2). Importantly, subjects were increasingly more likely to detect whether or not a string was changed as the string was increasingly syntactically organized, indicating that structure of the expression was implicitly processed. An ANOVA on error rates with trial type (digit-swapping, operator-swapping, or no-swapping) and expression complexity, performed separately in left-branching and right-branching trials, revealed a main effect of syntactic structure (left branching: $F_{3,69} = 18.3$, $p < 10^{-8}$; right branching: $F_{3,69} = 18.1$, $p < 10^{-8}$). Furthermore, we found a significant interaction between these two factors (left branch: $F_{6,138} = 3.7$, $p < 10^{-2}$; right branch: $F_{6,138} = 12.0$, $p < 10^{-6}$). This was due to the fact that the complexity effect was much larger when two operators were swapped than when two digits were swapped, suggesting that the memory encoding of operation signs strongly depends on the encoding of the overall syntactic structure, while digits tend to act more as free-floating semantic elements that are easily remembered regardless of the syntactic frame. Indeed, a highly significant monotonic effect of expression complexity was found within the operator-swapping condition (left branch: $F_{3,69} = 8.8$, $p < 10^{-4}$; right branch: $F_{3,69} = 19.0$, $p < 10^{-6}$). By contrast, in the digit-swapping condition, a main effect of complexity was significant only for right branching expressions (left branch: $F_{3,69} = 1.9$, $p > 0.1$; right branch: $F_{3,69} = 12.3$, $p < 10^{-5}$), and this effect was not monotonic, but reflected a higher error rate at level 1. Finally, within the no-swapping condition (same expression presented twice), a monotonic effect of expression complexity was significant for left branching expressions ($F_{3,69} = 10.6$, $p < 10^{-5}$) and marginal for right branching expressions ($F_{3,69} = 2.3$, $p < 0.1$) (Fig. 2, top).

Response times confirmed that syntax had a dominant effect (Fig. 2, bottom). ANOVAs revealed significant main effects of swapping type (left branch: $F_{2,46} = 11.4$, $p < 10^{-4}$; right branch: $F_{2,46} = 14.4$, $p < 10^{-4}$)

and a significant main effect of expression complexity, indicating that same-different judgments were increasingly faster as the strings showed a greater amount of syntactic structure ($F_{3,69} = 7.3$, $p < 10^{-3}$; $F_{2,46} = 6.2$, $p < 10^{-3}$). There was no significant interaction ($F_{6,138} = 2.1$, $p > 0.05$; $F_{6,138} = 0.8$, $p > 0.1$).

We also analyzed performance on “different” trials as a function of the location of the swapped digits and operators (regression analysis, see Methods and Supplementary Fig. 1). Higher error rates and longer RT were observed as the position of the swapped symbols moved from left to right (errors: $p < 0.01$; RTs: $p < 10^{-3}$), an effect which could reflect the direction of reading. RTs were also faster for left-branching than for right-branching expressions ($p < 0.01$), suggesting faster processing when syntactic structure was congruent with reading direction. This effect was marginal for errors ($p < 0.1$).

We also probed the data for a semantic effect of the type of operation (+ or −). Because addition is commutative while subtraction is not, we reasoned that subjects may have more difficulty detecting swapped digits around a plus sign (where there was no semantic difference from the first string to the second) than around a minus sign (where the semantics of the two strings differed). We submitted the behavioral data from trials in which digits were swapped around an operation sign (e.g. first expression = “ $(3 - 2) + 4(1 +$ ”, second expression = “ $(2 - 3) + 4(1 +$ ”), to an ANOVA with factors of operation sign, expression complexity and branch side. Indeed there was a significant main effect of operation sign for error rates ($F_{1,24} = 5.1$, $p < 0.05$), and a marginal trend for RTs ($F_{1,25} = 3.3$, $p < 0.1$), with higher error rates and longer RTs around an addition than around a subtraction. The result revealed a sensitivity of the task performance to the semantic of mathematical strings.

In summary, the behavioral results indicate that performance was sensitive to the structural complexity and left-to-right organization of mathematical expressions, as well as to semantic factors (the commutativity of addition and non-commutativity of subtraction), although none of these factors were directly relevant to the memory task. We then turned to the brain correlates of the syntax effect.

Brain effects of mathematical syntax

Fig. 3 illustrates the brain regions where an effect of expression complexity was significant in the whole brain analysis (see also Table 1). The effect took the form of an elevated activation for unstructured stimuli, which decreased as the amount of syntactic structure increased. Decreases in activation as a function of expression complexity were obtained in bilateral lateral occipital and posterior fusiform regions. These effects were larger in the right hemisphere than the left (see t -values and cluster sizes in Table 1). In the right hemisphere, a decrease in activation with expression complexity was also found in superior occipital, inferior parietal and precentral regions. The effect did not differ significantly on trials with swapped digits, swapped operators, or no swapping (no significant voxels, even when lowering the thresholds to uncorrected $p < 0.001$ and cluster size > 5 voxels). This observation is important because it did not exclude an existence of a genuine effect of expression complexity in common over all swapping conditions. We did not obtain significant fMRI results that were fully explained with an effect of task difficulty (which was much higher on swapped operator trials). In the converse direction, no positive effect of expression complexity reached significance in the whole brain analysis ($p_{\text{FDR}} > 0.05$).

We examined the localization of these syntactic effects (i.e. decreases of activation as a function of expression complexity) relative to areas involved in arithmetic calculation and reading. Our published functional localizer (Pinel et al., 2007) involves hearing or reading a subtraction problem (e.g. “please compute $11 - 3$ ”) and mentally computing the result. These activations are compared to hearing or reading standard sentences matched in length. Localizer data were available in 17 of the 24 subjects. As previously described (Pinel et al., 2007), calculation activated

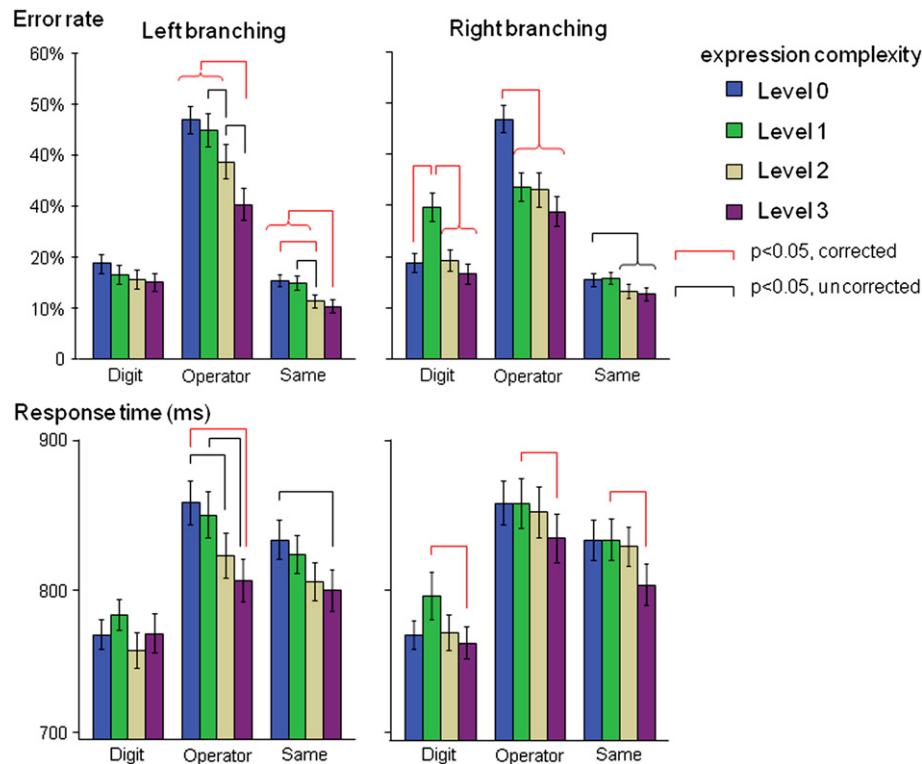


Fig. 2. Behavioral performance recorded during the fMRI and MEG sessions, indicating an implicit effect of the structure of mathematical expression on same–different judgments. Error rates (top) and response times relative to the onset of the second string (bottom) are presented as a function of expression complexity (four colors). We separated the trials as a function of whether the two strings were the same, or whether two digits or two operators were swapped (“digit” and “operator”). Red lines note a pair of conditions showing significantly different means with a corrected p -value of less than 0.05 (Scheffé’s procedure), black lines indicated an uncorrected p -value of less than 0.05 (paired t -test). Error bars represent ± 1 SE.

the right intraparietal region (Fig. 4A, top-left panel, blue cluster), and the medial part of the region overlapped with the region showing an expression complexity effect (red). The contrast also isolated an area in the right precentral region, which again overlapped almost entirely with the expression complexity effect (Fig. 4A, middle-left panel). We also compared the location of syntactic effects in the fusiform gyrus with the “visual word form area” (VWFA) activation evoked by reading the calculation problems relative to viewing checkerboards. The latter contrast evoked activity in the left infero-temporal cortex (Fig. 4A, bottom-left panel), peaking at classical VWFA coordinates ($[-48, -54, -12]$ in the Montreal Neurological Institute, MNI, coordinates). The fusiform region showing an effect of mathematical syntax was just posterior and medial to this cluster, and they did not overlap.

We also searched for regions involved in detecting changes in digits or operators in mathematical expressions. To this aim, we contrasted trials where the digits were swapped from the first to the second expression, or where the operators were swapped, to trials in which the mathematical expression remained the same, where we expected a lower level of activity (repetition suppression). A broad set of regions, covering the bilateral inferior parietal, lateral temporal, inferior frontal and precentral cortices as well as basal ganglia, was observed primarily when digits were swapped (Fig. 4B; see Table 2). Among these, a right inferior parietal region showed a higher activation both for swapped digits and for swapped operators (yellow area) compared to repeated expressions. Interestingly, the medial part of this region, coinciding with the intraparietal sulcus, overlapped with the region showing an expression complexity effect (red area). In contrast, although a right precentral region also showed a high activation for the swapped digits and operators relative to the same string (middle left panel, noted by open arrow), it did not include the precentral region with a syntax effect. Bilateral inferior temporal regions also showed a higher activation for swapped digits and swapped operators, just

anterior to the region with an expression complexity effect (Fig. 4B, bottom right).

Search for positive effects of mathematical syntax

Given the surprising absence of syntax effects in language-relevant areas, and in fact of any positive effect of syntax (i.e. regions showing an increasing activation with the expression complexity of mathematical expressions), we implemented a 3-step search, specifically focusing on language areas previously shown to exhibit a significantly positive effect of constituent size in written sentences (Pallier et al., 2011).

First, we searched for areas showing a positive linear effect of syntactic complexity in mathematical expressions over the 24 subjects, using the small-volume correction of SPM to restrict the search to a mask consisting of just the voxels with a significant positive effect of constituent size in Pallier et al. (2011), as well as the symmetrical right-hemispheric regions. No significant positive effect of the expression complexity of mathematical expressions was observed, either at voxel-based threshold $p < 0.001$, or at a lower threshold $p < 0.01$ ($p_{FDR} > 0.05$ in both cases).

As a second step, we analyzed the mean BOLD signal over the 24 subjects within the 7 left-hemispheric regions of interest (ROIs) reported in Table S5 of Pallier et al. (2011) as showing a positive effect of constituent size in sentences (inferior gyrus pars orbitalis: IFGorb; inferior gyrus pars triangularis: IFGtri; putamen; temporal pole: TP; temporo-parietal junction: TPJ; anterior superior temporal sulcus: aSTS; posterior STS: pSTS). We added an eighth region, the left-hemispheric Brodmann’s area 44, defined as a 10-mm diameter sphere centered at $[-42, 10, 22]$ on the MNI coordinates in Amunts et al. (2004) and intersected with the subject’s gray matter voxels. The MarsBar package was used to extract the mean fMRI signal within each ROI, condition, and subject. Such a ROI analysis may achieve

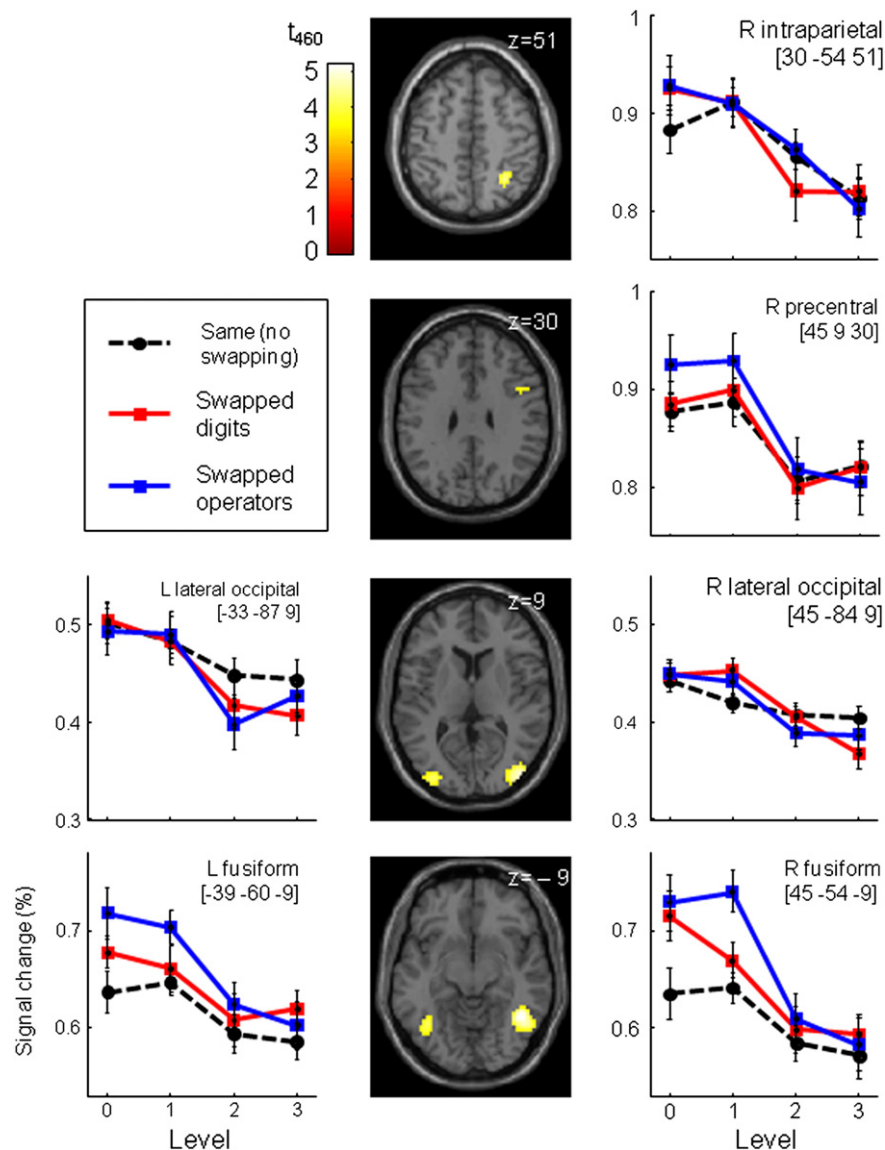


Fig. 3. Effects of mathematical expression complexity identified with fMRI. For illustration, images are thresholded at $p < 0.001$ voxel-wise and cluster size > 15 voxels. SPM analysis only revealed regions of decreasing activation with increasing expression complexity in seven brain regions.

greater sensitivity than voxel-level SPM-type analyses, both because we are averaging over an entire region, and because we are applying a Bonferroni correction only for the small number of regions tested (8 regions). However, this analysis only identified a small monotonic increase in fMRI activation with the expression complexity of

mathematical expressions in the left putamen ($t_{23} = 4.15$, uncorrected $p < 0.0005$, Bonferroni corrected $p < 0.005$; see Supplementary Fig. S2).

Finally, we performed an analysis of individual ROIs using the subject-specific analysis toolbox available in SPM software (SPM_SS) (Fedorenko et al., 2010) for the 17 subjects in whom we had time to run an additional functional language localizer (Pinel et al., 2007). For each subject, within each of the eight group ROIs reported by Pallier et al. (2011), we first used our functional localizer to identify voxels activated by spoken or written sentences relative to rest (voxel $p < 0.001$, uncorrected). The SPM_SS automatically identified these voxels and then extracted, within each ROI, the subject-specific contrast value for a positive linear effect of expression complexity. As argued by Fedorenko et al. (2010), this single-subject approach may be more sensitive than group analyses, because it focuses on individually defined functional regions which need not be consistently localized across subjects. At $p_{FDR} < 0.05$, this analysis determined that 3 out of the 8 regions contained a significant positive effect: IFGorb (mean coordinates across subjects = $[-45, 33, -7]$, $t = 2.30$, d.f. = 10.4, uncorrected $p < 0.05$), IFGtri ($[-51, 20, 17]$, $t = 3.79$, d.f. = 4.91, uncorrected $p < 0.01$) and pSTS ($[-50, -41, 3]$, $t = 2.21$, d.f. = 14.4, uncorrected $p < 0.05$). Plots of activation (Fig. 5)

Table 1

Location and size of significant effects of mathematical expression complexity in fMRI. Note these effects indicated a decreasing activation with increasing constituent structure.

Region	Left hemisphere					Right hemisphere				
	t	Size	X	Y	Z	t	Size	X	Y	Z
Lateral occipital	4.1	114	-33	-87	9	4.8*	287 ^a	45	-84	9
Posterior parietal						4.1	27	-69	42	
Intraparietal sulcus						4.4	30	-54	51	
Fusiform	4.0	67	-39	-60	-9	5.2*	202	45	-54	-9
Precentral						3.6	21	45	9	30

* Peak-level $p_{FDR} < 0.05$ (voxel $p < 0.001$); others, uncorrected $p < 0.001$ (cluster size > 15 voxels).

^a Cluster includes lateral occipital, posterior parietal and intraparietal regions in the right hemisphere.

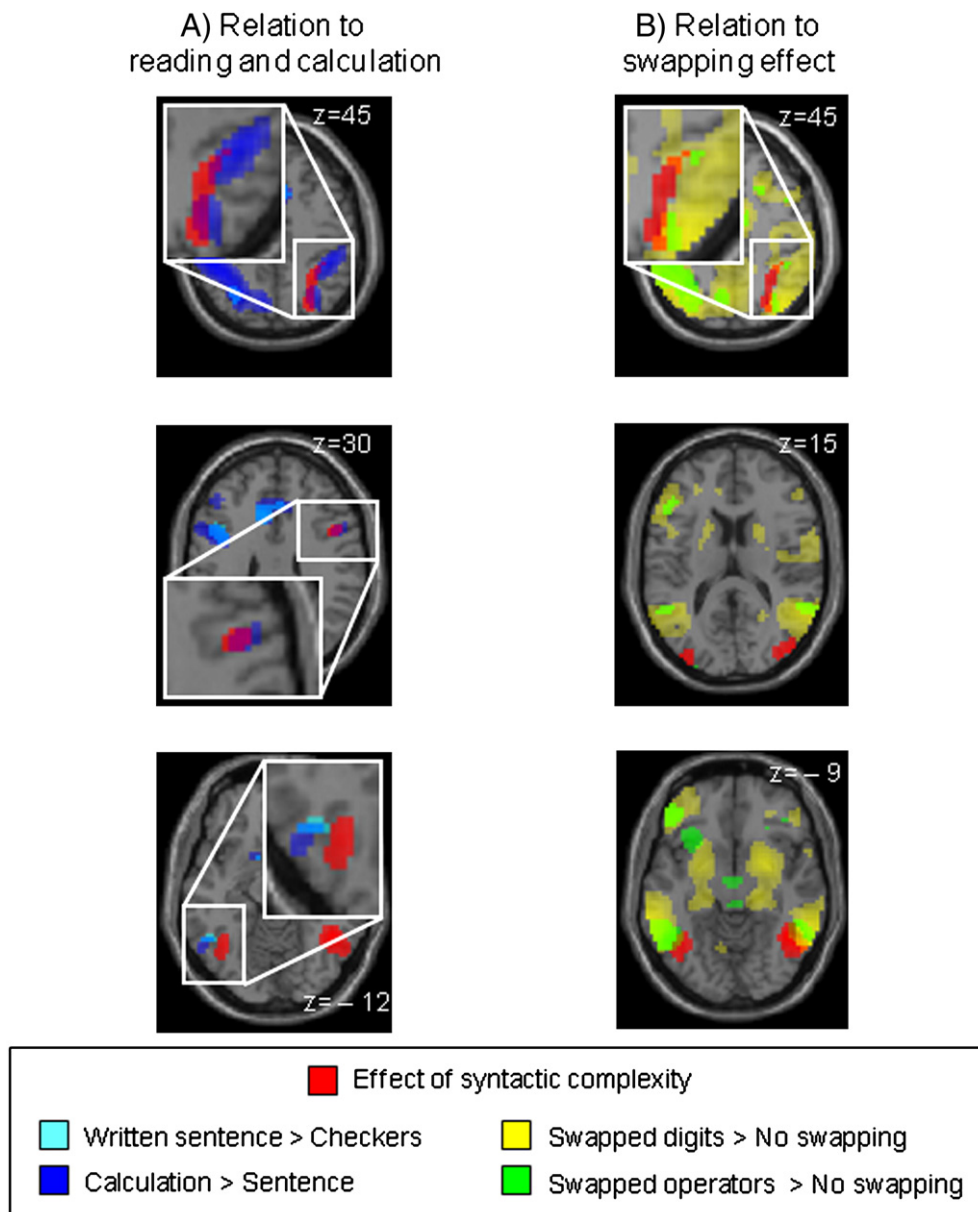


Fig. 4. Spatial relation of the observed effects of mathematical expression complexity (in red) to other fMRI activations. (A) Relation to fMRI effects observed during reading and calculation localizers. The right parietal and right precentral effects of expression complexity overlapped largely with the activations observed during mental calculation (blue), although these were bilateral. In the fusiform gyrus, the complexity effect fell just medial to the location of the visual word form area in the left hemisphere), and a strong activation was also seen in the right symmetrical fusiform location. (B) Relation to the fMRI effect of swapping two symbols (different > same trials). Most noteworthy, the occipital and fusiform effects of syntax fell just posterior to bilateral activations evoked by swapping operators or swapping digits. For illustration, images are thresholded at voxel $p < 0.001$.

showed that these increases, although significant, were weak and non monotonic. Indeed, there was a decrease in the swapping conditions from the level 0 to 1. They occurred in the context of a clear activation relative to rest in IFGtri, a near-zero activation for pSTS, and an overall deactivation pattern in IFGorb. Note that the left putamen could not be analyzed because there were not enough subjects with significant voxels at $p < 0.001$ in this ROI. When the localizer threshold was lowered to $p < 0.05$, a small but significant effect was also seen in the putamen ($t = 2.17$, d.f. = 7.7, uncorrected $p < 0.05$).

A similar search for decreasing activation as a function of complexity, using the same 3-step approach and focusing on the six main regions showing a decreasing activation with constituent size in Pallier et al.'s (2011) sentence study, did not reveal any significant effects.

In summary, there was little overlap between the regions showing an effect of mathematical expression complexity and those previously

identified as showing a syntactic complexity effect in the language domain (Pallier et al., 2011). Although weak positive effects of math complexity were observed in focused linguistic ROIs, our main finding was a decreasing activation with increasing levels of expression complexity in posterior occipital and fusiform regions, the right intraparietal and the right precentral cortex.

Occipital activation depending on the location of parentheses

Further evidence for a role of early visual cortices in the processing of math expressions came from the observation of an effect of the spatial side on which parentheses appeared. Within level-3 expressions, contrasting expressions with a left-sided versus a right-sided deeper level of nested parentheses revealed a systematically greater activation in the occipital pole contralateral to the parenthesized

Table 2

Locations of peak effects of swapping symbols (different strings> same strings) in fMRI (voxel $p < 0.001$, cluster size > 5 voxels).

Region	Digit swapping > no swapping								Operator swapping > no swapping							
	Left hemisphere				Right hemisphere				Left hemisphere				Right hemisphere			
	t	X	Y	Z	t	X	Y	Z	t	X	Y	Z	t	X	Y	Z
Angular and inferior parietal	9.9*	-33	-66	42	8.4*	39	-72	39	6.5*	-33	-63	42	4.3*	42	-78	27
Supramarginal	9.3*	-57	-51	33					6.4	-60	-51	33				
Middle and inferior temporal	7.3	-63	-42	-9	7.2	66	-51	-6	5.7*	-51	-54	-6	5.0*	54	-51	-9
Hippocampus	4.2	-21	-24	-9	5.5	21	-21	-12								
Amygdala	5.7	-18	0	-15	6.9	24	3	-12								
Putamen	4.8	-24	6	3	4.9	30	-6	3								
Rolandic operculum					4.1	63	9	3								
Precentral					4.1	66	3	15					5.0*	33	-18	54
Middle frontal gyrus	6.8	-33	9	57	4.3	42	12	48								
Superior frontal	5.8	-18	15	63	5.8	21	21	48								
Inferior frontal	5.6	-45	39	-15	4.2	51	39	-15					4.7*	-48	39	-12
Middle frontal					4.0	36	42	-15								
Cerebellum	3.7	15	-84	-30	4.8	27	-69	-30								

Bold peaks indicate regions also passing an additional test for digit swapping > operator swapping (peak-level $p_{FDR} < 0.05$).

* Peak-level $p_{FDR} < 0.05$; others, uncorrected $p < 0.001$.

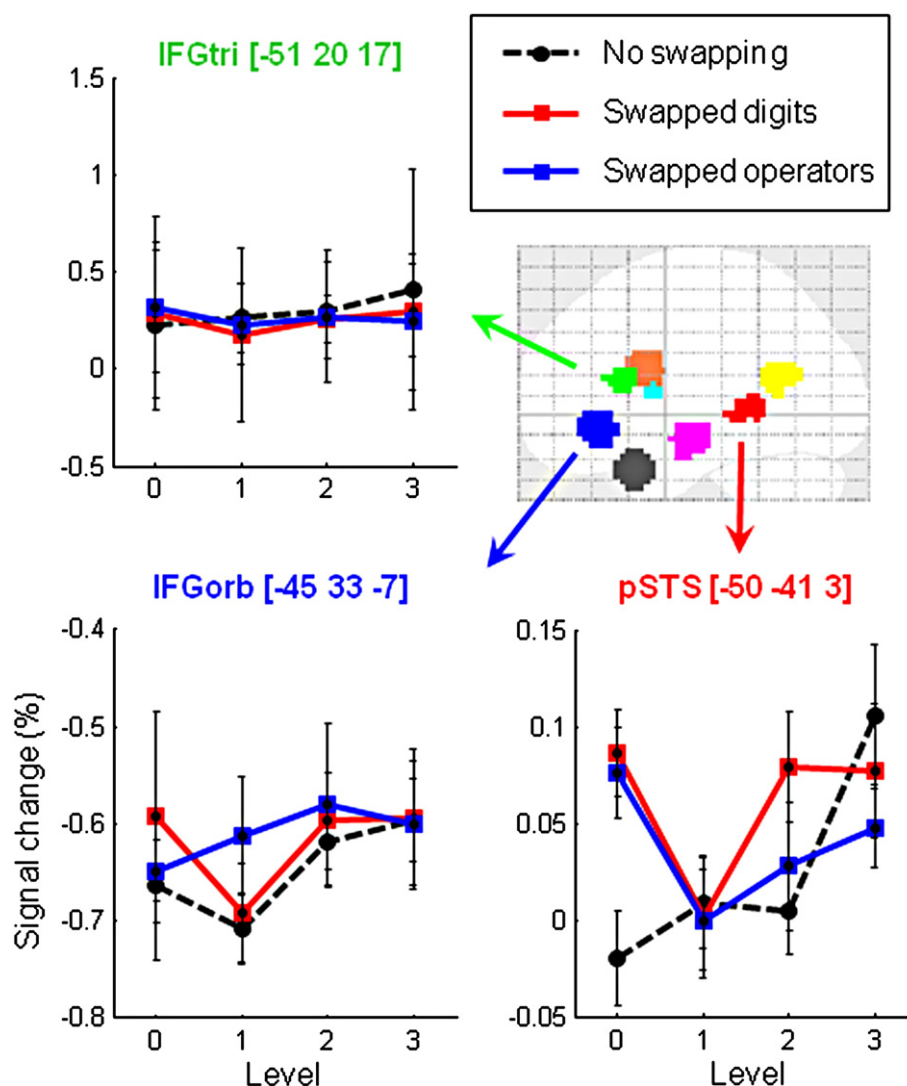


Fig. 5. Very small positive effects of mathematical syntax were identified by searching individually defined language-related regions-of-interest (ROIs). Within each of 8 group-defined regions (top right), we first located, within each participant, the voxels responsive to spoken and written sentences ($p < 0.001$). The average fMRI signals within these voxels were then submitted to a t -test for an effect of mathematical expression complexity. Three regions showed a modestly significant effect ($p < 0.05$, corrected for 8 ROIs), whose response profile was however neither monotonous nor very stable across conditions.

region (Fig. 6). The effect was replicated at level-2, again. Activation was amplified contralateral to the side where the parenthesized calculation appeared (e.g. $(2+3)-1$). However, for level 1 stimuli, the effect seemingly reversed and now occurred in regions ipsilateral to the well-formed part of the expression (though now at a lower statistical threshold, $p_{UC} < 0.001$, cluster size > 10 voxels).

Further analyses showed that this apparent ipsilateral response to syntactic structure was, in fact, a contralateral response to parentheses. By design, level-1 expressions were the only ones in which the well-formed mathematical expression was systematically not parenthesized. In fact, correctly ordered opening and closing parentheses were occasionally presented, but always outside the well-formed region, e.g., $+(2+)-1(2+)+4$. It therefore seemed possible that the occipital regions did not respond to the side of the well-formed arithmetic expression, e.g. $3-1$ in the above example, but to the presence of parentheses enclosing any symbols in the contralateral visual field, e.g. $(2+)$ in the above example. To examine this possibility, we classified level-1 stimuli into those with or without correctly ordered parentheses, e.g., $+(2+)-1(2+)+4$ versus $+)3-1(2+(4)$. In the lateral occipital cortex where the original ipsilateral effect had been found, whenever correct parentheses were present, we indeed observed a contralateral amplification of visual activation (striped bars at the bottom of Fig. 6; $p < 0.05$, two-tailed paired t -test). When correct parentheses were absent, the spatial side where the well-formed part of the formula appeared did not have any effect (filled bars; $p > 0.05$). In brief, the side of amplified activation of the occipital cortex depended on the presence of contralateral parentheses, not syntax. Still, an effect of syntax branching side was identified in left and right occipital regions originally identified as sensitive to branching side in the well-formed level-3 formulas ($p < 0.05$) (Fig. 6, top row). The results thus suggest that the effects of

branching and of parentheses localize to slightly different occipital regions of the contralateral hemisphere.

We also examined the influence of parentheses within the random strings (level 0). The small set of trials in which a pair of normal parentheses was presented on either left or right side were contrasted. No systematic contralateral effect was observed.

Latencies with which mathematical expressions are parsed

The occipital and fusiform effects observed in fMRI suggest that mathematical expressions can be quickly parsed at an early visual level. To probe the latency with which math syntax impacts on brain activation, we replicated our entire paradigm with magneto-encephalography (MEG) in the same subjects. We focused on signals recorded from planar gradiometers, which show peak responses at sensors located above neural currents, and computed the temporal variance of averaged signals within a time window of 200 ms, summed over the two orthogonal gradiometers at each location, thus yielding an estimate of the power of the local gradient. The change in signal power was evaluated by sliding the window from -300 to 3000 ms, and identifying the significant spatio-temporal clusters of sensors ($p < 0.05$, corrected for multiple comparisons across time and space; see Methods). Three clusters showing a significant effect of expression complexity were identified (Fig. 7). It is noteworthy that all clusters showed *increasing* activation with increasing expression complexity in the MEG responses, whereas the converse was true in the fMRI. The first cluster unfolded from 40 ms to 260 ms after the onset of the first string. Taking into account the half window size of 100 ms, the result indicated that the effect arose around 140 ms at the latest. Its topography began over the

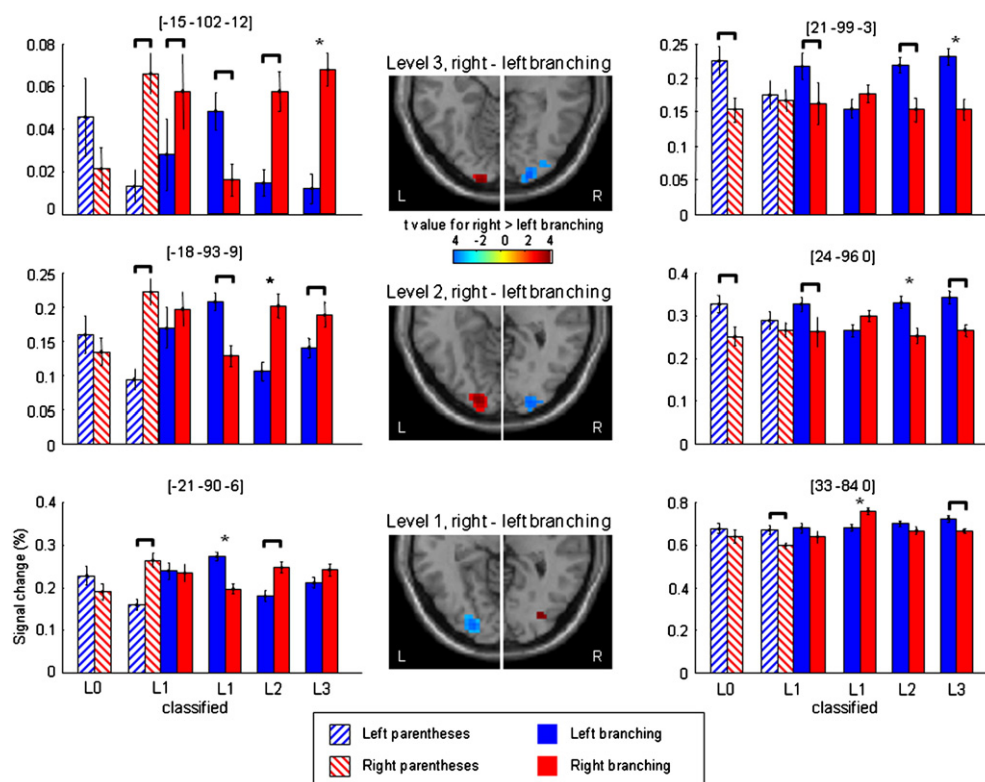


Fig. 6. Retinotopic influences of left- and right-branching mathematical expressions. In each row of graphs, we first used SPM to identify voxels whose activation differed for left versus right branching expressions (voxel $p < 0.001$, cluster size > 10), separately for levels 3 (top), 2 (middle), and 1 (bottom). We then plotted the activation in each level (L0–L3). Asterisks denote data from pairs of conditions originally used to determine the ROI, and which might therefore be overestimated due to “double-dipping”. Activations are generally stronger contralateral to the deeper level of parentheses (level 3, top; level 2, middle). The paradoxical ipsilateral effects seen at level 1 (bottom) dissolve once the level-1 and level-0 strings are sorted as a function of where pairs of correctly-ordered opening and closing parentheses were present (labeled as “L1 classified”). Even if they enclosed a syntactically ill-formed string, parentheses almost systematically generated an increased contralateral activation (see text for details).

right parieto-temporal region, then unfolded over bilateral occipital and temporal regions. The second cluster occurred from 225 to 510 ms over the left parietal, temporal and frontal regions. The last one was between 1735 and 2730 ms (i.e., 35–1030 ms after the onset of second string), distributing over the whole right hemisphere and the central region.

The latency with which mathematical expressions were parsed was also estimated by reconstructing the activation of the seven cortical peaks showing a mathematical complexity effect in the fMRI data (Table 1), using linearly constrained minimum variance (LCMV) beamforming (see Methods). This method selectively enhances the evoked signals generated at a specific brain location while attenuating those originating from other locations. In the right hemisphere, the inferior temporal cortex was the first region that showed a significantly increased activation as a function of expression complexity for the presentation of the first string, as indicated in Fig. 6 ($p < 0.05$ at cluster level). It started at 80 ms and continued until 320 ms. Considering the half window size of 100 ms, the result indicated that the syntactic effect arose before 180 ms. Subsequently an expression complexity effect reached significance in the right posterior parietal region (560–820 ms and 1420–1700 ms) and the lateral occipital region (720–1120 ms). Around the time of presentation of the second string, we again observed a significant effect of expression complexity in the right inferior temporal (1660–1940 ms), right lateral occipital (1780–2020 ms) and right precentral cortex (2540–2760 ms) regions. Again, all three regions exhibited a positive effect of complexity: unlike the fMRI responses, no negative effect was found in the MEG responses. In the left hemisphere, we did not obtain any significant effects. We also searched for lateralized MEG responses to left and right branching formulas, but without identifying any significant responses.

Discussion

We begin by summarizing the results. When mathematically trained adults judged whether two successive strings of mathematical symbols were the same or different, performance improved monotonically with the amount of mathematical structure in the stimulus, from a random list to a well-structured expression. Thus, subjects were sensitive to the complexity of mathematical expressions. fMRI localized this complexity effect to a set of cortical regions in bilateral fusiform and lateral occipital cortex, with a right-hemispheric lateralization, as well as right inferior parietal and right precentral regions. MEG revealed that the first effect of mathematical expression complexity occurred ~140 ms after the first string, and arose primarily from the right occipito-temporal area, with a subsequent activation of right posterior parietal, occipital and right precentral areas. All of these regions were located outside of classical language areas. When searching specifically within left perisylvian language areas localized in a previous linguistic study (Pallier et al., 2011), however, a weak positive effect of expression complexity was observed in left IFG (pars triangularis and orbitalis), posterior STS and putamen.

Parsing of mathematical expressions in ventral visual cortex

Our results suggest that the parsing of mathematical expressions starts early on during visual processing and relies importantly on the fusiform cortex. Thus, the brain mechanisms underlying the visual identification of well-formed mathematical strings bear partial similarity with those of visual word recognition. Indeed, the site showing a decreasing activation with mathematical expression complexity in the left fusiform gyrus was localized at $[-39, -60, -9]$ (MNI coordinates),

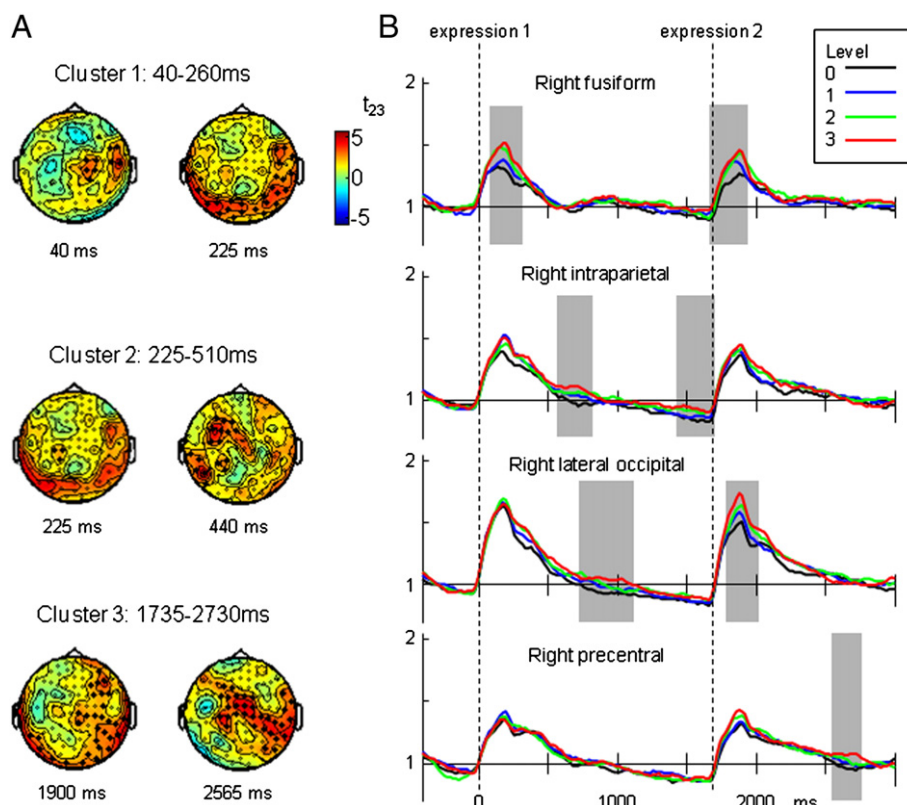


Fig. 7. Identification of the time course of mathematical expression complexity effects using MEG. (A) Topographical plots showing the three clusters of MEG gradiometers (marked by thick black dots) showing a significant regression of MEG power with expression complexity. (B) Reconstructed signal power at cortical peaks showing a complexity effect in fMRI. Four of these ROIs showed significant MEG effects, arranged here in sequential order from top to bottom. Note that both analyses reveal significant and monotonically increasing effects of complexity within 200 ms in the right ventral temporal region.

very close to the classical coordinates of the visual word form area (VWFA) (e.g. $[-42, -57, -15]$; Cohen et al., 2002). A localizer for sentence reading, run in a subset of the subjects, suggests that mathematical expressions actually activate a fusiform region slightly mesial and posterior to the VWFA (Fig. 4A). Most importantly, the parsing of mathematical expressions relates even more strongly to the right fusiform gyrus, at coordinates (MNI = $[45, -54, -9]$) very close to the fusiform face area (FFA) ($[40, -56, -15]$; Kanwisher et al., 1997).

Both the VWFA and the FFA are part of the ventral visual pathway which is thought to encode the spatial configuration of visual parts, such as the relative locations of letters in a word (Dehaene et al., 2004, 2005; Grainger et al., 2006; Vinckier et al., 2007), or of the eyes and mouth in a face, to yield a unique neural code for the overall shape (Barton et al., 2002; Brincat and Connor, 2004; Dehaene et al., 2005; Freiwald et al., 2009; Liu et al., 2010). This sensitivity to spatial configuration, particularly in the right fusiform gyrus, may contribute to the recognition of the structure of mathematical expressions. Behaviorally, the processing of equations shows a sharp sensitivity to symbol configurations (Kirshner, 1989; Landy and Goldstone, 2007a; Landy and Goldstone, 2007b). For instance, inappropriate spacing (e.g. $2 + 3 \times 4$) leads to frequent errors in operation order: in spite of the subjects' efforts to maintain the normal precedence of operations, they seem to reflexively evaluate the spatial configuration of symbols and link it to a syntactic structure (Landy and Goldstone, 2007b). Our results suggest that shape analysis in the ventral occipito-temporal cortex may be a key operation underlying the fast computation of the structure of mathematical expression. This implies that, when a well-trained subject views a mathematical expression, the earliest processing stages may be more akin to orthographic word processing (e.g. identifying the parts of the expression, whether they are legal or not, etc.) than to genuinely syntactic parsing.

During reading, the VWFA is thought to play a key role in processing all of a word's letters in a parallel rather than serial fashion (Dehaene et al., 2005; Forget et al., 2009). Expert readers show essentially constant naming times, regardless of the number of letters in a word, at least below ~8 letters (Cohen et al., 2008; Lavidor and Ellis, 2002). The VWFA plays a particular role in this parallel process, since patients in whom it is impaired no longer read words in a rapid parallel fashion, but using letter-by-letter reading (Cohen et al., 2003; Warrington and Shallice, 1980). The fusiform gyrus may play a similar role for mathematical expressions in mathematically trained subjects. Indeed, our MEG results revealed a significant and monotonically increasing influence of math syntax in the right occipito-temporal region as early as ~140–180 ms following the onset of the expression, which implies that the entire expression was processed in parallel at an early visual stage. Behaviorally, we did observe a small left-to-right gradient on trials with two different strings: response times increased slightly as the two swapped symbols were located further to the right of the expression. However, the slope of that effect was only ~3 ms per symbol (Fig. S4), for an overall effect of ~30 ms over the entire string. This value is much smaller than the slope of ~50–500 ms per letter typically seen during serial letter-by-letter reading in children, alexic patients, or normal adults reading under degraded conditions (Cohen et al., 2008). It may simply indicate an attentional left-to-right reading bias during the comparison process of the same-different task, as also suggested by the fact that eye movements are slightly faster towards the left than towards the right-hand part of a mathematical expression (Schneider et al., submitted for publication). In brief, a parallel encoding of symbols is clearly needed to explain the speed with which effects of mathematical syntax can be observed in MEG recordings (present research) and in eye movements (Schneider et al., submitted for publication).

It is interesting to compare the speed of parsing mathematical expressions with the speed of processing linguistic sentences. Event related potential studies on linguistic syntax have often observed an

early left anterior negativity (ELAN) as a component of the neural response to syntactic violations (Friederici and Kotz, 2003). The ELAN can be observed between 150 and 250 ms from the onset of a word that violates the syntax constructed from the preceding words, and syntactic violation effects have been reported as early as 120 ms for the visual modality (Dikker et al., 2009) and 40–80 ms for auditory modality (Herrmann et al., 2009). In our visual study, the latency of the first syntactic effect for mathematical expressions (140–180 ms) was comparable with these estimates. However, an important difference is that the detection of syntactic violations in sentences typically requires only the processing of a *single* word in relation to a syntactic context that was computed much earlier, based on the preceding words. By contrast, in the present work, the entire syntactic structure of mathematical expressions was constructed from eleven simultaneously present symbols.

Our results leave open the possibility that the early parsing stage we observe is only a first pass during which only a coarse syntactic frame is formed, perhaps based primarily on the location of the parentheses and operators. A subsequent serial process may be needed to fill this frame with the specific numbers involved and obtain a complete representation of the algebraic string (Cohen and Dehaene, 1991). Eye movements support this possibility: when subjects are asked to perform nested calculations, e.g. $4 + (3 - (2 + 1))$, their eye movements betray a two-stage process (Schneider et al., submitted for publication). First, their eyes move quickly to the deepest level (here $2 + 1$), which implies that they quickly parsed the initial string for syntax. This fast syntactic parsing obviously relies on both parentheses and operators, as the eye also goes quickly to the deepest tree location in expressions like $1 - (2 + 3 \times 4)$ where operator precedence is the only cue. In a second stage, subjects serially move their eyes to the successive levels of the syntactic hierarchy and, at each step, recover the digit identities needed for calculation (Schneider et al., submitted for publication).

Additional support for distinct syntactic and semantic stages of formula processing arises from the present behavioral results. In our same-different task, the detection of the swapping of two operators varied considerably with syntax: it was much easier to detect that a plus and a minus sign had been swapped within a correct expression than within a random sequence of symbols (Fig. 2). Strikingly the influence of syntax was much smaller, or inexistent when subjects detect whether two digits had been swapped (Fig. 2). This finding fits with the hypothesis that operators are integrated faster than digits into the syntactic frame. A similar dissociation between syntactic and numerical information was previously reported during the naming of multi-digit numbers (Cohen and Dehaene, 1991): digits 0 and 1, which play a syntactic role in numbers like 2016 (specifying respectively the absence of hundreds and the need to transform the final 6 in a “-teen” word), can be selectively preserved in patients with number naming deficits.

In the future research, MEG could be used to track this putative two-stage process (fast bottom-up syntactic parsing, followed by semantic filling-up). Our present results merely indicate that syntactic parsing of mathematical expressions starts early in occipito-temporal cortices, and only later (>500 ms) reaches significance in the right intraparietal and precentral areas. This aspect of our findings fits with prior fMRI findings of a strong contribution of these regions to algebraic problem solving (Danker and Anderson, 2007; Qin et al., 2003; Sohn et al., 2004). MEG suggests that they actually come into play at a late stage in the processing of math syntax. These regions are frequently involved in working memory and could have been used to hold the first expression in mind while waiting for the second one to appear, as required by our same-different task. They are also frequently co-activated during number processing and mental calculation (Dehaene et al., 2003; Ischebeck et al., 2006; Zago et al., 2008), and our study revealed a significant overlap of calculation and syntax effects (Fig. 4A). Both working memory and number representation

may therefore have contributed to their activation in the present study.

In all of these regions, the direction of the fMRI syntactic effect was a progressive decrease in fMRI signal as the algebraic structure of the stimulus increased. In MEG, however, power increased with syntax. A very similar dissociation of MEG and fMRI effects has been previously reported by others when comparing words with a hierarchy of increasingly unstructured strings in the fusiform gyrus (Vartiainen et al., 2011). It may be understood as a trade-off between a positive effect of stimulus structure on initial feed-forward processing, versus a negative effect on later sustained activity. Indeed, our MEG results show that, in the initial feedforward processing stage, more structured mathematical expressions induce a stronger active representation in the ventral visual cortex, similar to the increase in left fusiform activation when flashing letter strings forming increasingly closer approximations of real words (Pammer et al., 2004; Vartiainen et al., 2011). This positive effect of stimulus structure is also seen in some fMRI studies of reading, provided that an implicit reading task is used to maximizing feedforward processing, for instance by flashing stimuli at a fast rate under passive or minimal instructions (Ben-Shachar et al., 2007; Turkeltaub et al., 2003; Vinckier et al., 2007). However, in tasks requiring one-back memorization (such as the present same-different task) or stimulus naming, fMRI effects typically reverse, with more activation now being evoked by non-sense strings than by words (Bruno et al., 2008; Kronbichler et al., 2004; Schurz et al., 2009; Vartiainen et al., 2011). This is presumably because the less structured items are now processed more slowly and with greater difficulty, resulting in an extended period of late neural amplification and causing greater fMRI activation after temporal integration of brain activity by the slow hemodynamic response function (Dehaene and Cohen, 2011). A similar explanation is likely to hold here, as we have direct behavioral evidence that syntactically structured expressions were easier to memorize than unstructured ones, and fMRI signals followed the same direction (more activation for less structured stimuli). MEG signals, however, gave direct evidence that the activation of the ventral occipito-temporal pathway initially increased with the amount of structure in mathematical expressions, exactly as with alphabetic stimuli (Vartiainen et al., 2011).

A minor role for language areas in mathematical syntax?

A major goal of our study was to investigate the role of classical perisylvian language areas in mathematical syntax. The present design paralleled our earlier research on the constituent structure of language, where we used a hierarchy of increasingly complex linguistic stimuli to demonstrate that moving from a random word list to a full sentence led to monotonic increases in brain activation in several classical language areas along the left superior temporal sulcus and inferior frontal cortex (Pallier et al., 2011; see also Humphries et al., 2006; Mazoyer et al., 1993; Vandenberghe et al., 2002). Remarkably, these linguistic regions showed only small or absent effects of mathematical syntax. No positive effect was identified by whole-brain search. Only when searching within a small number of individually defined regions of interest, based on a distinct sentence-processing language localizer, was a small positive effect of increasing mathematical constituent structure observed in four left-hemispheric regions: IFGtri, IFGorb, posterior STS and putamen (with higher significance for the IFGtri and putamen regions).

The results are therefore ambiguous. On the one hand, they replicate an earlier study of logical mathematical formulae (Friedrich and Friederici, 2009), which identified only a small overlap of mathematical and language syntax effects in the left IFGtri, in the context of a much larger and unique contribution of the parietal cortex to mathematics. Part of the IFGtri is involved in the learning of new grammatical rules, both inside and outside the language domain (Bahlmann et al., 2008; Friederici et al., 2006; Musso et al., 2003; Opitz and Friederici, 2007),

and even when hierarchical structure is conveyed by visual symbols (Bahlmann et al., 2009; Hoen et al., 2006). Our ROI-based individual analyses confirm that these regions make a small contribution to mathematical syntax. It is noteworthy that the few language areas that we observed as showing a small positive effect of mathematical syntax are precisely those that, in our previous study (Pallier et al., 2011), were jointly sensitive to sentence syntax with both real words and with meaningless “jabberwocky” stimuli. Thus, this set of regions, and particularly the IFG, may form a network for learning arbitrary syntactic structures, regardless of whether they are meaningful or meaningless, provided that they conform to well-defined principles of recursive embedding. In other words, these regions are a good candidate for a universal recursive system common to several domains of human activity (Fadiga et al., 2009; Hauser et al., 2002; Tettamanti and Weniger, 2006), including language (Musso et al., 2003; Pallier et al., 2011), mathematics (present work, and Friedrich and Friederici, 2009), music (Koelsch, 2005; Maess et al., 2001; Patel, 2003; Sammler et al., 2009) and visuo-spatial domains (Bahlmann et al., 2009).

On the other hand, however, it is striking that this contribution of language areas to mathematical syntax was so small as to be barely detectable, both in the present research and in previous work (Friedrich and Friederici, 2009). Our results indicate that, although IFG may contribute to encoding the syntax of mathematical expressions, it does not appear to play a dominant role, which instead is taken up by fusiform, parietal and precentral cortices. It even seems possible that the small effect we observed in language areas could arise from artifactual factors, such as a tendency to name mathematical expressions on a small percentage of trials. This would have resulted in an additional activation proportional to the amount of nested constituent structure, but epiphenomenal and unnecessary to the encoding of mathematical expressions. Indeed, by directly contrasting algebraic and syntactic transformations, but using as input sentences of equivalent complexity, a recent study found no overlap at all between the two domains in the left inferior frontal cortex (Monti et al., in press). Most importantly, strong neuropsychological evidence indicates that the comprehension and manipulation of complex arithmetic and algebraic expressions can remain intact in severely agrammatic aphasic patients (Cappelletti et al., 2001; Delazer et al., 1999; Klessinger et al., 2007; Rossor et al., 1995; Varley et al., 2005; Zamarian et al., 2006).

A possible reconciliation of these observations may arise after considering that, so far, the populations studied here and in previous studies comprised relatively expert adults, well trained in mathematics, and in whom simple algebra may therefore be routinized. As a result, the processing of simple mathematical expressions may have become “compiled” into early the occipito-temporal visual cortex, together with parieto-precentral systems for algebraic manipulation, and may no longer put strong demands on language areas—a situation perhaps similar to second-language acquisition, where higher proficiency in past-tense formation leads to a decrease in IFG activation (Tatsuno and Sakai, 2005). However, the syntax of language may still provide an essential contribution to the understanding of nested mathematical structures during their acquisition in childhood. Indeed, adults acquire novel grammatical rules, including those of artificial sequential or visuo-spatial languages, using neural mechanisms involving the left inferior frontal gyrus and overlapping with classical Broca's area (Hoen et al., 2006; Musso et al., 2003; Tettamanti et al., 2002, 2009). To evaluate the hypothesis that a similar language-based mechanism is at work in the acquisition of mathematical rules, the present experimental design would benefit from being replicated in a developmental study.

Early retinotopic cortex and the processing of parentheses

A final unexpected observation was that the presence of parentheses in a mathematical expression modulates fMRI activity at an early

visual level in the occipital pole. Activation was clearly retinotopic since it was strictly contralateral to the side of the screen where an opening and a closing parentheses were presented in the correct order (even if their content was not syntactically correct). This finding confirms that algebraic processing, in expert participant, recruits early visual processing. It is consistent with two non-exclusive interpretations. First, attention could be automatically attracted to the location of parentheses, because mathematical training has tagged such regions as relevant units. This interpretation is consistent with eye movement data showing that the eyes rapidly move to the deepest level of parenthesizing during an algebraic calculation task (Schneider et al., submitted for publication). However, it leaves open the mechanisms by which the parenthesized region is identified in the first place. It also predicts the existence of contralateral activations in the posterior parietal cortex, the standard source of visual attentional effects, although no such activity could be detected.

An alternative possibility is a bottom-up grouping mechanism, whereby left and right parentheses would be automatically paired at an early visual level, creating a visual region of enhanced neuronal firing. Gestalt psychologists already noted how parentheses and brackets are preferentially grouped according to closure rather than proximity (e.g. () () [] []). The unification of opening and closing parentheses may be analogous to the integration of visual contours, a classical low-level visual process which allows multiple disconnected line segments or Gabor patches to be integrated into a single curve, provided that partial colinearity cues are present (Hess et al., 2003; Kovacs, 2000). As a result of contour integration, the line segments themselves, but also the region they enclose, are enhanced psychophysically (Kovacs and Julesz, 1994; Marcus and Van Essen, 2002). Furthermore, in tight analogy to the present findings, brain activity coding for the enclosed retinotopic region is amplified in striate and extrastriate visual cortices (Kourtzi and Huberle, 2005; Li et al., 2006; Stettler et al., 2002). Contour integration is a late developing process (Kovacs et al., 1999) which is sensitive to learning and education: with training, the visual system learns to tolerate greater amounts of spacing and angular separation between consecutive line segments (Li and Gilbert, 2002; Li et al., 2008), and learning to read specifically enhances contour integration (Szwed, 2012). We therefore speculate that mathematical training may similarly enhance this automatic grouping process and extend it to matching parentheses, thus explaining the enhanced occipital activation that we observed with fMRI.

Historically, surrounding a paragraph with a line is an ancient method for drawing attention to a section of text, already used in ancient Egyptian writing for the cartouches containing king names. The cultural invention of parentheses may be seen as a trimmed-down version of this surrounding method, now achieved with just two movable elements, the opening and closing parentheses. While more appropriate for the printing press, our fMRI results suggest that these small movable elements () are still capable, with minimal training, of evoking automatic visual grouping and enhanced processing. Under this interpretation, algebraic notation, with its systematic nesting of parentheses, would provide yet another example of “neuronal recycling” (Dehaene, 2009; Dehaene and Cohen, 2007)—the reuse, for a cultural purpose, of evolutionary ancient cortical mechanisms.

Conclusions, limitations and future directions

The present results lead us to conclude that, in mathematically trained adults, mathematical expressions are quickly parsed at an early visual level in bilateral ventral occipito-temporal cortices. However, in closing, a few additional words of caution are in order. Our explorations of mathematical formulae are clearly at their inception, and the present study suffers from a number of limitations that should be overcome in future research.

First, our results are limited to elementary arithmetic expressions that are so simple as to be accessible to any person who completed compulsory school-based education. It is possible that a stronger reliance on language areas would be observed if we extended our study to more complex algebraic expressions such as integrals, sums, square roots, etc.

Second, the task performed during neuro-imaging may play an important role in the results we observed. We opted for a same-different judgment task because it could be performed with all stimuli irrespective of their syntactic organization, and therefore made the complexity manipulation incidental. However, as noted earlier, the task could have had the undesirable effect of increasing late brain activations for the more deconstructed stimuli, for which the behavioral decision was more difficult, thus possibly masking areas where neuronal activity actually transiently increases with syntactic complexity (as seen in MEG). In the future, it will therefore be important to probe the replicability of the present fMRI study with other tasks.

Third, although we endeavored to selectively manipulate the complexity of mathematical expressions while keeping exactly the same elementary symbols and total amount of visual stimulation, we cannot exclude the presence of more sophisticated confounds. For instance, obviously our mathematical expressions contained a greater number of correctly ordered parentheses as the complexity level increased. It remains possible that the parentheses alone, rather than the digits, operators, or even nested syntax, were a major factor in our results.

Finally, because we focused on numerical expressions rather than algebraic expressions with Roman or Greek symbols, syntax and semantics could not be distinguished in our stimuli: any well-formed expression was also semantically meaningful. In particular, mental calculation was possible only starting at level 1 and was increasingly afforded by the more complex stimuli. If the subjects attempted to perform the implied calculation, such a strategy might have differentially affected the activations observed at different complexity levels. In the future, this feature of our design could be corrected by introducing novel meaningless algebraic symbols, similar to “Jabberwocky” in the language domain.

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Appendix A. Supplementary data

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