

Research Report

Attentional shifts induced by uninformative number symbols modulate neural activity in human occipital cortex

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ABSTRACT

Number processing interacts with space encoding in a wide variety of experimental paradigms. Most intriguingly, the passive viewing of uninformative number symbols can shift visuo-spatial attention to different target locations according to the number magnitude, i.e., small/large numbers facilitate processing of left/right targets, respectively. The brain architecture dedicated to these attention shifts associated with numbers remains unknown. Evoked potential recordings indicate that both early and late stages are involved in this spatio-numerical interaction, but the neuro-functional anatomy needs to be specified. Here we use, for the first time, functional magnetic resonance imaging (fMRI) to investigate attentional orienting following uninformative Arabic digits. We show that BOLD response in occipital visual regions is modulated by the congruency between digit magnitude (small/large) and target side (left/right). Additionally, we report higher BOLD responses following large (8, 9) compared to small (1, 2) digits in two bilateral parietal regions, yielding a significant effect of digit magnitude. We propose and discuss the view that encoding of semantic representations related to number symbols in parietal cortex leads to shifts in visuo-spatial attention and enhances visual processing in the occipital cortex according to number-space congruency rules.

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1. Introduction

An ever-growing amount of behavioral studies indicates that numerical representations and visuo-spatial processes are tightly linked (for reviews see Walsh, 2003; Fias & Fischer, 2005; Hubbard, Piazza, Pinel & Dehaene, 2005; de Hevia, Vallar & Girelli, 2008). The most classical demonstration of this connection between numbers and space is the Spatial Numerical Association of Response Codes (SNARC) effect first described by Dehaene, Bossini, and Giraux (1993) who observed that participants respond faster with their left hand to small numbers and with their right hand to large numbers. According to the mental number line view (Dehaene, 1997), this behavioral pattern indicates that (in western cultures) numerical values of increasing magnitudes are mentally organized as a continuum oriented from left to right (Hubbard et al., 2005, 2009; Hubbard, Piazza, Pinel, & Dehaene, 2009).

Another striking demonstration of the link between numerical and spatial domains was provided by Fischer, Castel, Dodd and Pratt (2003), who reported that participants detect a target more rapidly in the left hemifield, if it is preceded by a small number (e.g., 1 or 2) and more rapidly in the right hemifield if preceded by a large number (e.g., 8 or 9). This is evidence that centrally presented uninformative digits shift visuo-spatial attention to different hemifields (i.e., left and right hemifield) according to their magnitude (i.e., small and large; see also Galfano, Rusconi, & Umiltà, 2006; Ristic, Wright, & Kingstone, 2006). Related research using a temporal onset judgement paradigm (Casarotti, Michielin, Zorzi, & Umiltà, 2007) demonstrated that these attentional effects are specifically linked to numerical information rather than ordinal stimuli in general, as no attentional allocation was found when letters instead of numbers were used as cues (see also Dodd, Van der Stigchel, Adil Leghari, Fung, & Kingstone, 2008).

Next to these two seminal approaches an impressive amount of studies support the link between numbers and space in healthy subjects using other paradigms such as number line bisection (Fischer, 2001; Calabria & Rossetti, 2005; de Hevia, Girelli, & Vallar, 2005; Longo & Lourenco, 2007; Loetscher, Bockisch & Brugger, 2008; Ashkenazi & Henik, 2010), reproduction of interval length (de Hevia, Girelli, Bricolo, & Vallar, 2008),

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random number generation (Loetscher, Bockisch, Nicholls, & Brugger, 2010), luminosity discrimination (Nicholls, Loftus, & Gevers, 2008), manual grasping (Andres, Seron, & Olivier, 2005; Lindemann, Abolafia, Girardi & Bekkering, 2007) and priming (backward priming: Stoianov, Kramer, Umiltà, & Zorzi, 2008; forward priming: Herrera & Macizo, 2011).

The functional significance of the mental number line concept is supported by studies on patients suffering from spatial neglect. These patients not only misplaced the midpoint of physical lines when required to bisect them, but also made similar misplacement errors when requested to bisect numerical intervals (Zorzi, Priftis, & Umiltà, 2002; Zorzi, Priftis, Meneghello, Marenzi, & Umiltà, 2006; Priftis, Zorzi, Meneghello, Marenzi, & Umiltà, 2006; Umiltà, Priftis, & Zorzi, 2009; but see also Doricchi, Guariglia, Gasparini, & Tomaiuolo, 2005). When asked what number is halfway between 1 and 9, left neglect patients consistently reported a number larger than the expected response, such as 7, shifting the response towards the right end of the mental number line.

Furthermore, TMS studies using SNARC (Rusconi, Turatto, & Umiltà, 2007; Rusconi, Buetti, Walsh, & Butterworth, 2011) and bisection paradigms (Göbel, Calabria, Farnè, & Rossetti, 2006; Cattaneo, Silvanto, Pascual-Leone, & Battelli, 2009) demonstrated that parietal and frontal regions play a critical role in number-space associations. ERP studies also showed that the visual system might play a significant role in number-space interactions. Two independent studies using the target detection task, initially developed by Fischer et al. (2003) indicated that passively viewing uninformative digits before performing lateral target detections induced both early and late modulations of event-related potentials located at anterior and central electrode sites (Saliillas, El Yagoubi, & Semenza, 2008; Ranzini, Dehaene, Piazza, & Hubbard, 2009; see also Schuller, Hoffmann, & Schiltz, 2011). Recently it has also been reported that cortical excitability in early visual cortex is modulated by number magnitude such that small/large magnitudes (associated with the left/right visual space) facilitated the perception of phosphenes after TMS was applied on the right/left visual cortex (Cattaneo, Silvanto, Battelli, & Pascual-Leone, 2009).

There are also a few fMRI experiments that investigated the interaction between visuo-spatial and arithmetic processing (Zago & Tzourio-Mazoyer, 2002; Zago et al., 2008; Knops, Thirion, Hubbard, Michel, & Dehaene, 2009; Rotzer et al., 2009). Using an ingenious multivariate classifier approach, Knops et al. (2009) showed that BOLD signal in parietal regions controlling visuo-spatial orienting also play an important role in mental arithmetic. Moreover, Kötter, Lonnemann, Willmes, and Knops, (2011) used multivariate pattern analysis to explore the neuronal correlates of a landmark task on numerical and physical intervals. They showed that congruent and incongruent number-space interactions produce distinguishable patterns of voxel activation in the intraparietal sulcus, more precisely in intraparietal regions involved in arithmetics. Since both space and numbers are thought to be represented in this region, Kötter et al., 2011 took this finding to suggest an early integration of number and space. In addition number-space interactions were also observed in regions involved in motor response selection/preparation and consequently Kötter argued that number and space interact both at early and late processing stages. Nonetheless, whether parietal regions also contribute to visuo-spatial attention shifts induced by the passive viewing of single digits remains an open question. To the best of our knowledge, there are currently no fMRI studies investigating attentional orienting following numerical symbols, without arithmetical and/or working memory requirements.

On a more general level, the neuronal correlates of visuo-spatial attention have successfully been highlighted by intense fMRI work. It is now well-established that early visual BOLD

response to peripheral stimuli is enhanced when visuo-spatial attention is oriented towards their location (for reviews see Kanwisher & Wojciulik, 2000; Corbetta & Shulman, 2002). Moreover, it has very recently been shown that activity in visual areas is not only modulated when the attentional shifts concern external perceptual stimulations, but also when they refer to internal memory representations (Munneke, Belopolsky, & Theeuwes, 2012). Indeed, BOLD signal in early visual regions was altered by words cueing different object positions in working memory (for similar behavioral evidence see Salverda & Altmann, 2011). The attentional cues that have been investigated range from central predictive (e.g., Huddleston & DeYoe, 2008) to peripheral non-predictive (e.g., Müller & Kleinschmidt, 2007), with a few studies also using central non-predictive cues such as eye gaze or arrows (Hietanen, Leppanen, Nummenmaa, & Astikainen, 2008; Engell, Nummenmaa, Oosterhof, Henson, Haxby, & Calder, 2010). However, as mentioned above, no fMRI study on visuo-spatial orienting used Arabic digits as non-predictive central cues yet.

In the present fMRI study, we addressed whether number-related attentional shifts would be reflected by an amplified visual response to right and left visual field stimulation depending on the digit magnitude being presented at the centre of the screen. Participants were scanned while performing a lateral color discrimination task that was preceded by a brief, uninformative and centrally presented digit (i.e., 1, 2, 8 and 9). Our study addressed two main questions.

First, based on previous evidence that attention amplifies the neural responses of the visual neuronal populations selectively coding the attended location, we expected that occipital regions representing left and right targets would have their responses to the target selectively amplified when preceded by small and large digits, respectively. To reveal such attentional modulations, the occipital regions responding to the lateral portions of the visual field containing the target were localized in each participant individually using subject-level visual localizer. In line with the initial behavioural observations by Fischer et al. (2003) and the neuro-imaging data on visuo-spatial attention (e.g., Huddleston and DeYoe, 2008; Somers, Dale, Seiffert, & Tootell, 1999), we hypothesized that the attentional shifts induced by the centrally presented numbers should lead to an amplification of the BOLD response in visual areas, when left/right targets are preceded by small/large digits, respectively. Especially the observation that semantic cues with spatial meaning can bias early visual activity (Munneke et al., 2012, see also Soto, Rotshtein, Hodsoll, Mevorach, & Humphreys, 2012) suggests that Arabic digit cues could induce semantic processing and spatio-numerical interactions at central semantic stages, which in turn modulate the visual response to lateral targets. The subject-level visual localizer was specifically designed to optimally capture these attentional effects associated with early number-space interactions.

Our second question pertained to the functional role of parietal and frontal regions in the attentional shifts driven by numbers. Based on a group-level task localizer, we highlighted the parietal cortex and the other regions that were involved in the sensori-motor aspects of the lateral target discrimination task. The effects of number-space interactions as well as digit magnitude were then investigated in these regions. Because parieto-frontal regions play a critical role both in numerical processing (for reviews see Cohen Kadosh, Lammertyn, & Izard, 2008; Ansari, 2008; Nieder & Dehaene, 2009) and spatial attention orienting (for reviews see Kastner & Pinsk, 2004; Corbetta, Patel, & Shulman, 2008), we expected that visuo-spatial orienting associated with numerical stimuli might affect activity in regions of this sensori-motor network. Besides early representational associations in parietal and occipital cortex, particularly the late number-space interactions occurring at response-related stages

should become visible with this second approach (Salillas et al., 2008; Ranzini et al., 2009; see also Koten et al., 2011).

2. Materials and methods

2.1. Subjects

Twenty-one right-handed adults (13 males mean age 23 ± 3) with normal or corrected-to-normal vision and no history of neurological disease participated in our experimental project in exchange of course credits.

2.2. Procedure

Subjects performed three experiments during one fMRI scanning session. The data of one subject had to be discarded due to excessive head motion during scanning.

Imaging was performed using a 3T head scanner at the University of Maastricht (Allegra, Siemens Medical Systems, Erlangen, Germany) provided with standard head coil. T2*-weighted echo-planar imaging (EPI) used BOLD contrast as an indirect marker of local neuronal activity (Ogawa, Lee, Kay, & Tank, 1990). Twenty-five 5 mm oblique transverse slices were acquired (no gap, TR=1500 milliseconds, TE=28 milliseconds, flip angle=67 degrees, matrix size=64 × 64, FOV=224 mm, in-plane resolution 3.5 × 3.5 mm). Each subject performed one block localizer run (subject-level visual localizer) of 432 TRs (approximately 648 s), two slow event-related (SER) localizer runs (group-level task localizer) of 315 TRs each (approximately 472.5 s), and two SER runs of the main experiment of 640 TRs each (approximately, 960 s).

A high-resolution T1-weighted anatomical data set encompassing the whole head was acquired in each session by means of ADNI sequence (TR=2250 ms, TE=26 ms, flip angle=9 degrees, matrix size=256 × 256, FOV=256 mm², 192 slices, slice thickness=1 mm, no gap, total run time=8 min 26 s).

2.3. Stimuli and experimental paradigm

Visual stimuli were presented using Eprime 1.1 against a uniformly gray background (see Fig. 1). They were projected onto a translucent screen at the head of the scanner bore by means of a LCD projector and viewed by the subjects through a mirror placed within the RF coil at a viewing distance of 57 cm. Behavioural responses were collected via a button box. In all 3 experiments subjects were asked to fixate the central fixation cross all along the run (plus sign, Arial, bold, 28 pt). The central cross subtended a visual angle of 1.3×1.3 degrees. All other centrally presented stimuli (digits in the main

experiment runs and brackets in the group-level task localizer runs) had the same font characteristics as the central cross. The cross was flanked by 2 lateral rectangles presented at an eccentricity of 5 degrees. The rectangles were defined by a 2-pixel black border on the grey background and their size was 74 by 56 pixels. At a screen resolution of 640×480 pixels, one lateral rectangle subtended a visual angle of 4.4×3.5 degrees. The two lateral rectangles delimited the regions of the visual field where the target could appear (Fig. 1).

The main experiment was a within-subject factorial design consisting of the factors (a) numerical magnitude (small/large) and (b) target side (left/right). Each trial started by a light grey central cross flanked by lateral rectangles (1000 ms), which acted as a warning cue, then a digit appeared for 600 ms, which was replaced by a black cross of variable duration (7900–11,400 ms). 400 ms after digit onset the lateral rectangles were filled with white noise (arrays of 16×12 squares of 4.5×4.5 average size in pixel; luminance: 0.52 and contrast: 0.1) until target offset (variable noise duration: 600/850/1100 ms). White noise was used to invoke a response in occipital visual regions coding for the lateral rectangles. Targets (asterisks in Arial font, bold, 20 pt) appeared for 100 ms centrally in one of the lateral rectangles filled with white noise. There were twelve trials with a 900 ms digit-target SOA in each target side condition because number-space interactions were observed with SOAs of this range in previous studies (Fischer et al., 2003; Galfano et al., 2006). Rare longer digit-target SOA (1150 and 1400 ms) trials (4 per target side condition) were included to introduce some temporal variation in the stimulus presentation and attenuate subjects' expectations. They were discarded from subsequent analyses. After target offset, the black fixation cross and empty lateral rectangles stayed on the screen for a variable interval (7500, 9000, 10,500 ms). Subjects responded with the right index and middle fingers whether target color was green or red. We explicitly told the subjects that the digits were task-irrelevant. Participant's responses were not speeded and the main experiment was specifically designed to optimize BOLD response to the lateral target regions.

Targets subtended a visual angle of 0.7×0.7 degrees. Target side (left, right), target color (red, green) and digit value (1, 2, 8 and 9) varied randomly within a run. On average, digits subtended 1.8×1.05 degrees of visual angle. In order to prevent the Simon effect (related to the spatial compatibility between the side of the target and the side of the key to press) from contaminating the results, response keys were counterbalanced across runs. Each run consisted of 12 trials per experimental condition yielding a total of 24 trials per experimental condition for each participant. In addition, each run comprised 16 catch trials (in which no lateral target appeared) as well as 20 long-SOA trials.

The group-level task localizer was identical to the main experiment, except that central digits were replaced by neutral bracket symbols, which were chosen because their visual angle (2.2×1.2 degrees) approximately matched the average visual angle of the digits presented in the digit runs. Technical issues prevented the first three subjects to perform the group-level task localizer experiment. Response keys were also counterbalanced across the two runs of the group-level

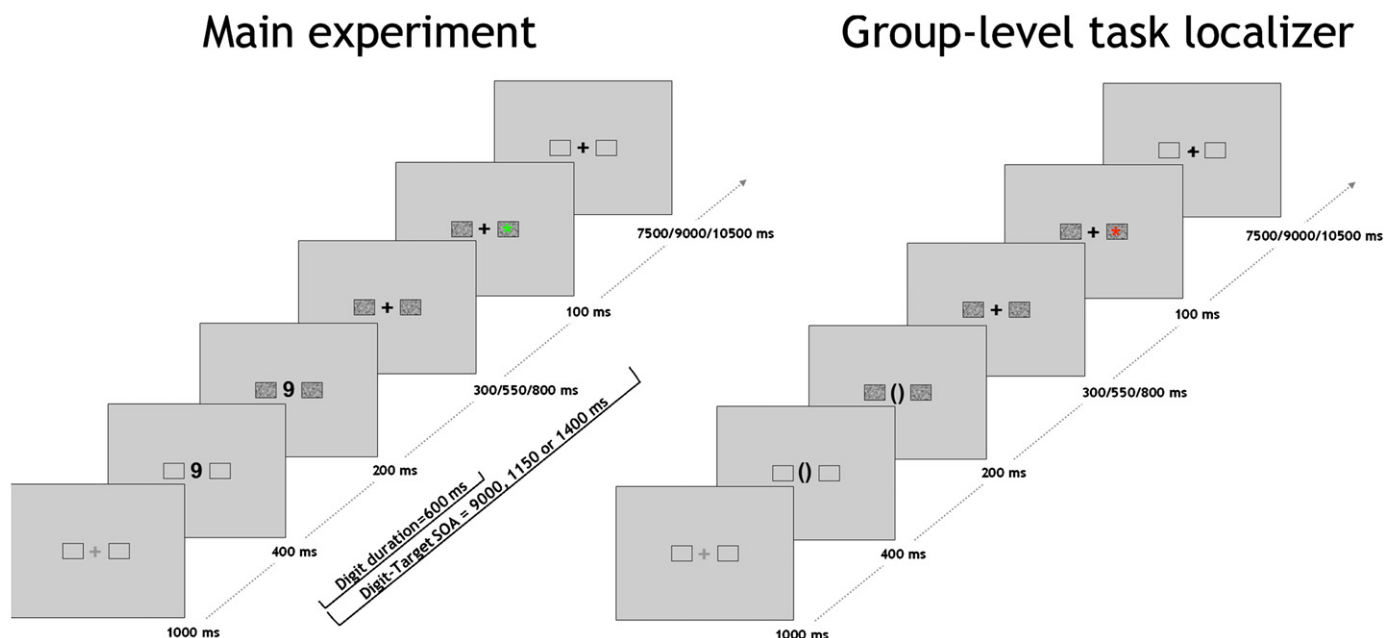


Fig. 1. Sequence of example trials in the main experiment (left) and the group-level task localizer (right). In both tasks participants had to discriminate the color of a lateral target. During the main experiment, targets were preceded by digits whereas they were preceded by neutral bracket symbols in the group-level task localizer. Note: Stimuli are not drawn to scale.

task localizer. We designed this localizer in order to map the cortical regions activated by the main experiment.

In order to define the visual regions responding to the lateral targets at the single-subject level, participants further performed a *subject-level visual localizer* consisting of 24 blocks of 13,200 ms. Participants viewed a similar display with central fixation cross and lateral rectangles as in the main experiment and the group-level task localizer. However, we used a blocked design to obtain a high signal to noise ratio and reach the statistical power necessary to localize occipital ROI at the individual level. Single-level approach was preferred because the localization of functional activations is known to vary across individuals (Saxe, Brett, & Kanwisher, 2006; Nieto-Castañón & Fedorenko, 2012). Depending on the block condition (unilateral-left, unilateral-right, bilateral or blank), one, both or no rectangle(s) were filled with white noise of variable duration (200, 300, 400 ms). As in the other experiments, a white noise array comprised 16×12 squares of 4.5×4.5 average size in pixel. Within a block, there were 12 trials of 1100 ms on average. A fixation pause (i.e., central cross flanked by empty rectangles) separated trials (variable duration: 700, 800, 900 ms) within a block. In one third of the trials, a blue asterisk (0.7×0.7 degrees of visual angle) appeared at the centre of each rectangle 100 ms prior to rectangle stimulation offset. Participants had to detect the asterisk by pressing the response button with their right index finger. There were 6 blocks per condition and blocks were interleaved with twelve seconds of fixation pauses (i.e., central cross flanked by empty rectangles).

The order of experiments was the same for all subjects but runs within experiments were counterbalanced across subjects. The session began with one run of the main experiment, followed by one group-level task localizer run, and then came the anatomical run. After the anatomical run, subjects performed the second main experiment run, followed by the second run of group-level task localizer. Response keys were counterbalanced after the anatomical run. The scanning session ended with the subject-level visual localizer.

2.4. fMRI data analyses

Functional and anatomical images were analyzed using BrainVoyager QX (version 1.10, Brain Innovation, Maastricht, The Netherlands). The first four volumes were skipped to avoid T1 saturation effect. Functional runs then underwent several pre-processing steps: correction of inter-slice scan time differences, linear trend removal, temporal high-pass filtering (to remove frequencies lower than three cycles per time course), smoothing with a Gaussian kernel of 6 mm full width at half maximum, and correction for interscan head motion (translation and rotation of functional volumes to align them to a reference volume). Anatomical and functional data were spatially normalized to Talairach coordinate system (Talairach & Tournoux, 1988) with a resolution of $3 \times 3 \times 3$ mm using trilinear interpolation. The data of one subject was discarded due to excessive movement during scanning.

The predictor time courses for stimulation events/blocks were constructed as box-car functions filtered through a general linear model (GLM) indirectly relating neural activity and BOLD response (Boynton, Engel, Glover, & Heeger, 1996). Predictor time courses were obtained by the convolution of a box-car time course with two-gamma hemodynamic response function. In the main experiment, eight predictors were entered in the GLM: left versus right target sides by small versus large digit magnitudes, plus two predictors encompassing the small versus large magnitude catch trials and two predictors to cover the longer digit-target SOA trials (separately for 1150 and 1400 ms digit-target SOAs). In the group-level task localizer, we used five predictors: left versus right target sides, plus one predictor encompassing all catch trials and two predictors for the longer digit-target SOA trials (separately for 1150 and 1400 ms digit-target SOAs). Finally, in the subject-level visual localizer, we used four predictors (unilateral-left, unilateral-right, bilateral, and blank conditions). In all experiments, the box car function covered the whole trial (in the main experiment and the group-level task localizer) or block (in the subject-level visual localizer). In the main experiment and the group-level task localizer, predictors encompassed the interval running from the onset of the warning cue to the offset of the target. In the subject-level visual localizer, predictors ran from the onset of the warning cue to the offset of rectangle stimulation.

For anatomical reference, the statistical maps were overlaid on Talairach-normalized individual anatomical volumes.

2.5. Subject-level visual localizer

The present study explored whether the attentional shifts induced by the central presentation of digits would modulate neural activation to targets presented laterally in the occipital regions. Following the tradition of spatial attention studies (e.g., Murray, 2008; Ress, Backus, & Heeger, 2000; Silver, Ress, & Heeger, 2007; Huddleston & DeYoe, 2008), occipital regions were mapped at the single-subject-level based on the localizer block experiment. To map the visual regions responding to the stimulation of the left and right rectangular portions of visual hemifields, the occipital areas responding preferentially to white noise in the left vs. the right lateral rectangles were defined independently for each participant. A fixed effect (FFX) GLM was first computed for each individual. The positive and negative voxel clusters ($q(\text{FDR}) < .05$; cluster size threshold: 4 voxels), which were significantly activated by the [Unilateral-Left minus

Unilateral-Right] contrast, were then selected in each subject as ROIs for further analysis. The data of one out of the twenty-one subjects were discarded for the group ANOVA, because of excessive noise in this region. We also had to discard one run of the main experiment in one subject because of excessive motion.

We extracted the activity time course in each individual ROI for each condition of the main experiment. We averaged the signal time course across trials in each condition and converted these time courses to percent signal change (PSC) relative to fixation baseline activity (baseline interval: 2 TR of fixation prior to warning cue onset). PSC time course was then averaged over time for each participant in each condition (from 0 to 12 TR post warning cue onset). These intervals were selected to monitor the BOLD response to experimental trials. The so-obtained PSC values were subjected to a repeated-measure ANOVA with Hemisphere (Left versus Right), Magnitude (Small versus Large) and Target side (Left versus Right) as within-subject factors. Paired-sample *t*-tests were used to perform planned comparisons between conditions (significance levels were Bonferroni-corrected (α/n) to counteract the problem of multiple comparisons). When the effect of Hemisphere was not significant, data from the two hemispheres were collapsed.

To further assess how digit magnitude affects lateral target discrimination, we computed the difference in neural activity induced by left and right targets (dPSC, i.e., PSC for left target minus PSC for right target) for each digit magnitude separately. Hence, a positive value denotes a stronger BOLD response to left targets whereas a negative value denotes stronger responses to right targets. Subsequently, the computed dPSC were entered in a regression analysis with magnitude as predictor per subject. This method allows capturing in a regression equation and slope value how digit magnitude influenced the BOLD response to lateralized visual targets. Based on the mental number line hypothesis, we expected a significant *negative* slope between dPSC values and digit magnitude (Lorch & Myers, 1990; see Fias, Brysbaert, Geypens, & d'Ydewalle, 1996; van Galen & Reitsma, 2008), resulting in a negative slope. Slope values were compared to zero using a paired-sample one-tailed *t* test. In addition, we also report our results in terms of cue-target compatibility effects and contrast the BOLD response of compatible (small magnitude – left targets and large magnitude – right targets) and incompatible (large magnitude – left targets and small magnitude – right targets) trials. Both types of methodological approaches were used because they provide complementary information on the neuronal correlates of attention orienting induced by uninformative digit cues.

2.6. Group-level task localizer

Parietal, occipital as well as the other regions that were activated by the color discrimination of the lateral target were disclosed using a random effect (RFX) whole brain analysis of the task localizer data including the last seventeen subjects. Based on the [(Left target + Right target) minus fixation] contrast at an *q* (False Discovery Rate, or FDR) $< .05$ and a voxel cluster size threshold of 4, cortical regions in and outside the occipital cortex that were activated by the target color discrimination task were highlighted. To highlight the ROIs related to target discrimination, we used group rather than individual analyses because single-subject activations were not reliable enough across subjects with the latter approach due to a lack of statistical power (probably related to the use of a SER design).

3. Results

3.1. Behavior

Accuracy ($88 \pm 8\%$ on average) and response times for the main experiment were submitted to a repeated-measure ANOVA with digit magnitude (large, small), and target side (left, right) as within-subject factors. None of the main effects or interactions were significant ($ps > .21$) and there was no significant linear relationship between dRT (i.e., RT for left target minus RT for right target) and digit cue magnitude ($p > .5$) and no cue-target compatibility effects ($t(20) = 1.17$, $p = .26$). The observed activation pattern could thus not be accounted for by differences in behavioral performance across experimental conditions.

3.2. fMRI results

3.2.1. Subject-level visual ROIs

The bilateral occipital regions responding to the lateral rectangles were localized individually based on block-localizer data of each participant (Fig. 2a). The activation time course of these ROIs was then extracted in the main experiment in each of the 19

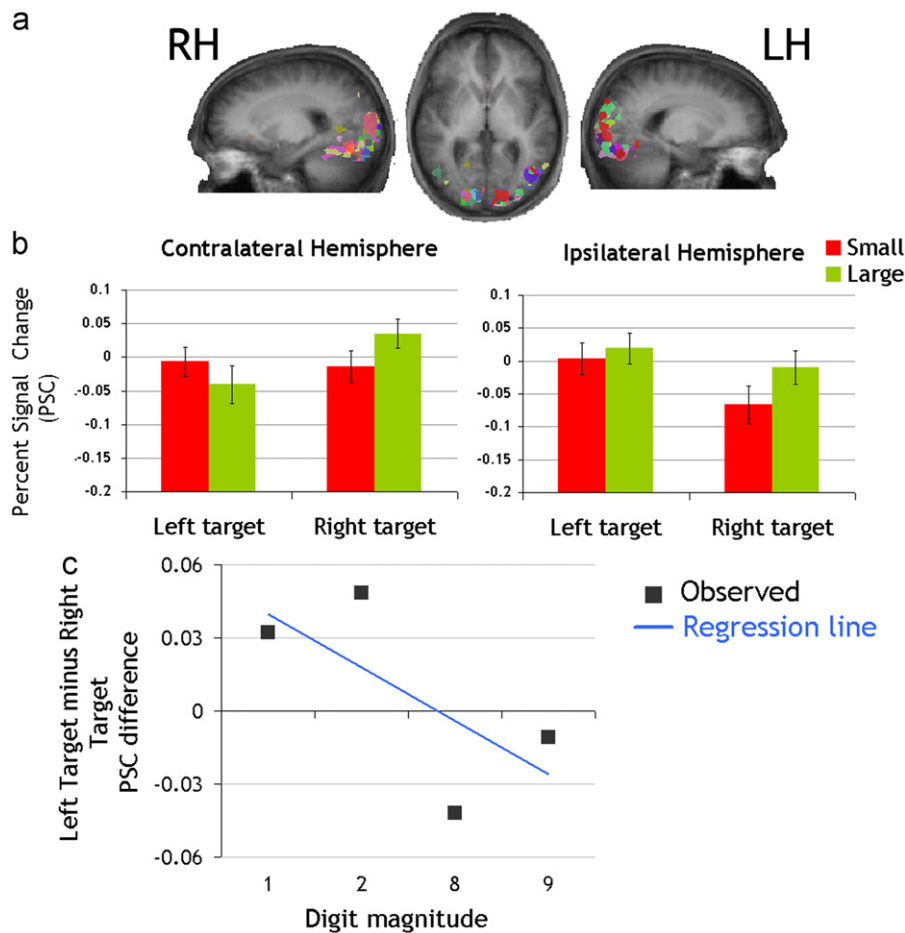


Fig. 2. (a) Occipital cortical regions responding to the lateral rectangles were defined in each individual participant based on subject-level visual localizer (i.e., positive and negative voxel clusters activated by the [Unilateral-Left minus Unilateral-Right] contrast). Examples of individual ROIs are displayed on the average of individual 3D volumes. Different colors highlight the ROIs of different subjects randomly selected from the sample. (b) Averaged PSC values of these ROIs are plotted for each condition of the main experiment. Statistical analyses revealed that digit magnitude significantly modulated BOLD response to lateral targets. Activation pattern in contralateral and ipsilateral hemisphere ROIs are illustrated separately. Error bars represent the standard errors of the means. (c) To further substantiate the role of uninformative digit cues in attentional orienting the activation difference between left and right target trials was computed in each individual ROI. We show that the average Left–Right difference in BOLD response decreases linearly as a function of digit magnitude.

subjects included in the analyses. The ANOVA revealed a significant interaction between number magnitude and target side factors in the bilateral occipital ROIs ($F(1,18)=4.5$, $p<.048$). Hence, although the digits preceding target appearance were irrelevant to the colour discrimination task, this pattern of results indicates the presence of a compatibility effect between digit magnitude and target side ($t(18)=2.5$, $p<.024$). There was no other significant main effect or interaction ($ps>.08$). Because the factor hemisphere was not significant and did not interact with any other factors, data from each hemisphere was collapsed in these analyses. However, results are displayed separately for contra- and ipsilateral hemispheres, for the sake of completeness (Fig. 2b). It is interesting to note that “digit magnitude–target side” compatibility effects were significant in the individually defined ROIs of the contralateral ($t(18)=2.8$, $p<0.01$) but not ipsilateral hemisphere ($t(18)=1.4$, $p<0.175$), as expected from the visuo-spatial attention literature (e.g., Martínez et al. 1999).

Furthermore, we compared the activity of each individual ROI to left and right targets, and estimated whether left–right target differential PSC decreased linearly as function of digit magnitude. Across hemispheres, the effect of digit magnitude on lateral target processing was captured in a regression equation ($dPSC=0.0616-0.0219(\text{digit magnitude})$; Fig. 2c). Statistical analyses of the individual slope values disclosed a significant contribution of digit magnitude (two-tailed t test, $t(18)=-2.1$, $p<.05$).

3.2.2. Group-level task ROIs

Beside occipital cortex, other cortical regions were involved in the discrimination of the lateral targets. In order to localize them, we ran a multi-subject whole brain RFX analysis of the task localizer data. Based on the [(Left target+Right target) minus fixation] contrast ($q(\text{FDR})<.05$; voxel cluster size >4), we delineated target-related activations in bilateral intraparietal, inferior parietal, occipital and sub-cortical cortices as well as in right precuneus and medial superior frontal gyrus. Other regions were also activated by the target discrimination of the task localizer experiment but did not show any modulation across experimental conditions of the main experiment (in ANOVA or regression analysis). Coordinates of all regions resulting from the task localizer are listed in Table 1.

Targets induced significant activity in bilateral occipital regions (Fig. 3a). Note that these occipital activations were situated anterior to those observed with the individual ROI analysis. The ANOVA did not reveal any significant effects or interactions of hemisphere, target side, or magnitude in the main experiment ($ps>.08$). There was no compatibility effect between digit magnitude and target side ($t(16)=1.55$, $p=.14$). But $dPSC$ (Left minus Right target PSC difference in the main experiment) was found to decrease linearly as a function of digit magnitude (regression equation: $dPSC=y=0.0509-0.02(\text{digit magnitude})$; significant contribution of magnitude: two-tailed t test $t(16)=-2.7$, $p<.016$).

Table 1

Talairach coordinates (in x, y, z) of the cortical regions that were activated by the target discrimination task of the SER localiser experiment.

Talairach coordinates	X	Y	Z	Size (in voxels)
Left cerebellum	−32	−48	−27	273
Left inferior parietal lobule	−41	−26	52	2848
Left intraparietal sulcus	−34	−55	49	1197
Left occipital gyrus	−37	−68	−7	5955
Left precentral gyrus	−45	−4	35	152
Left putamen	−23	1	4	2263
Left thalamus	−12	−19	1	2940
Medial cerebellum	5	−59	−18	790
Medial superior frontal gyrus	−2	−2	46	4336
Right cerebellum	25	−45	−23	3590
Right inferior parietal lobule	38	−43	43	144
Right insula	30	20	7	120
Right intraparietal sulcus	23	−63	45	139
Right occipital gyrus	34	−72	−7	9474
Right precentral	16	−65	34	113
Right putamen	17	4	4	942
Right superior frontal gyrus	−26	−14	59	344
Right thalamus	7	−18	3	1944

Besides occipital activations, targets activated bilateral *intraparietal sulci* extending into the superior parietal lobule on the right side (Fig. 3b). There was a main effect of digit magnitude ($F(1,16)=7.8$, $p<.013$) as large digits induced more activity than small digits. No other main effect or interaction reached significance in these regions ($ps>.5$), neither was there a significant linear relationship between dPSC and digit magnitude (regression equation: $y=0.03740-0.0111(\text{digit magnitude})$; $t(16)=-1.1$, $p=.3$) nor was the global effect of compatibility significant ($t(16)=.83$, $p=.42$). Additional spots of activation were located in the bilateral *inferior parietal lobe* (Fig. 3b). In these regions, there was also a main effect of digit magnitude with large digits inducing larger responses than small digits ($F(1,16)=9.5$, $p<.007$). There was no significant linear relationship between dPSC and digit magnitude (regression equation: $y=0.0472-0.0142(\text{digit magnitude})$; $t(16)=-.46$, $p=.4$). Digit-target compatibility had no significant influence on IPL activation ($t(16)=.95$, $p=.36$).

Significant main effects of magnitude were observed in the *medial superior frontal gyrus* ($F(1,16)=7$, $p<.018$) and *right precuneus* ($F(1,16)=7.3$, $p<.016$) that were found to be activated by lateral targets in the group-level task localizer experiment

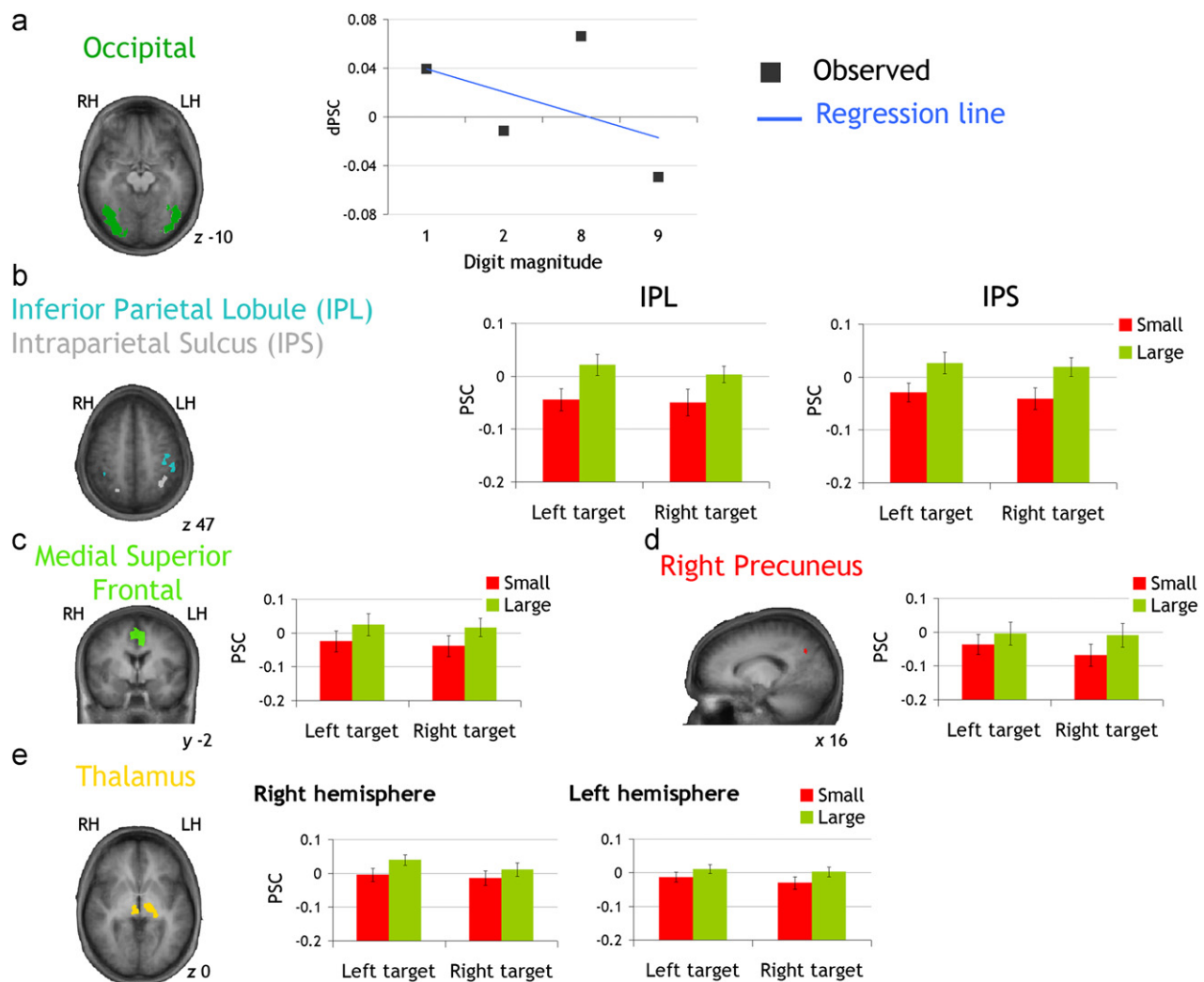


Fig. 3. Analyses of the regions being involved in the lateral target discrimination task. These ROIs were defined based on the group-level task localizer. Average PSC values are plotted for each target side, digit cue magnitude, and hemisphere separately. Error bars represent standard errors of the means. (a) In occipital ROIs, there was a significant modulation of dPSC as a function of digit magnitude. Squares represent the observed dPSC and lines illustrate fitted regression slopes. (b) In the parietal ROIs IPS and IPL analyses revealed that large digits (8, 9) induced higher BOLD signal than small digits (1, 2). (c) and (d) The main effect of digit magnitude was also significant in medial Superior Frontal and right Precuneus ROIs. (e) Bilateral thalamus responded more to large than small digit magnitudes. Moreover, the activity of these regions was stronger in the right than the left hemisphere. Error bars represent standard errors of the means.

(Fig. 3c–d). Large magnitudes elicited stronger responses than small magnitudes in these regions. There was no significant linear relationship between dPSC and digit magnitude in these regions ($ps > .14$) and no global effect of digit-target side compatibility ($t(16) < 1.16$, $ps > .26$).

Bilateral *thalamus* also responded strongly to lateral targets in the group-level task localizer. The ANOVA revealed significant main effects of hemisphere and of magnitude in these regions (Hemisphere: $F(1,16)=7$, $p < .018$; magnitude: $F(1,16)=4.6$, $p < .05$; Fig. 3e). Thalamic activation was indeed stronger in the right than the left hemisphere, and for large than small magnitudes. There was no significant linear relationship between dPSC and digit magnitude (regression equation: $y = 0.0407 - 0.0099 \times (\text{digit magnitude})$; $t(16) = -1.4$, $p = .17$) and no overall effect of digit-target compatibility ($t(16) = .95$, $p = .36$).

4. Discussion

The present fMRI findings reveal, for the first time, the neuronal correlates of visuo-spatial attention shifts associated with non-predictive central number cues. Participants had to discriminate the color of a lateral target. Before target appearance, a task-irrelevant digit of small or large magnitude (1, 2, or 8, 9, respectively) was briefly presented at fixation. We report that target-related BOLD response in occipital visual regions was modulated by the compatibility of digit magnitude (small/large) and target side (left/right). Targets appearing in the hemifield congruent with respect to digit magnitude (i.e., “8”—right target) induced larger neuronal responses in extrastriate visual areas than those presented on the incongruent side (i.e., “8”—left target). The occipital effects of number-space interactions were robust as they were observed irrespective of whether ROIs were defined based on individual data in a visual localizer or on group data in a task localizer. Observing selective attentional enhancements in visual cortex following the presentation of a non-predictive digit cue provides evidence that numerical and spatial information are integrated at early stages of semantic processing.

So far the cerebral substrates of attentional shifts induced by non-predictive number cues had only been investigated using ERP studies (Salillas et al., 2008; Salillas, Graná, El-Yagoubi, & Semenza, 2009; Ranzini et al., 2009). They provided evidence that number cues evoke cue-locked ERP modulations reflecting the spatial orienting likely operated by parietal and frontal regions, as well as early and late target-locked modulations. It was proposed that early (P1) target-locked effects reflect excitability changes in visual areas and provide neural evidence that number cues can affect visuo-spatial attention to external locations. The late (P3) effects were interpreted as revealing different cognitive requirements as a function of number-space compatibility. But event-related potential evidence has very limited spatial resolution. The present data, for the first time, provide unequivocal evidence that number-induced attentional shifts modulate the response of visual areas, as observed in more conventional attention paradigms on voluntary visuo-spatial orienting (e.g., Brefczynski & DeYoe, 1999). This is all the more remarkable since, contrary to other central symbolic cues like eye gaze or arrows (Thiel, Zilles, & Fink, 2004; Hietanen, Nummenmaa, Nyman, Parkkola, & Hämäläinen, 2006; Engell et al., 2010), Arabic digit stimuli provide no spatial information whatsoever. Consequently, the number-space association must arise at a purely semantic level related to long-term memory traces (Hubbard et al., 2009) and/or working memory rehearsal (van Dijck & Fias, 2011; Fias, van Dijck, & Gevers, 2011) of the central uninformative number cues. Together with the ERP data, these findings clearly support the existence of an early locus of number-space integration (for convergent fMRI evidence from a numerical landmark task see also Koten et al., 2011).

Visuo-spatial attention orienting has long been known to enhance neural processing in visual cortex (Moran & Desimone, 1985; McAdams & Maunsell, 1999). The attentional enhancement of information within a circumscribed region of visual space is evoked by the theoretical concept termed spotlight of attention. Brefczynski and DeYoe (1999) for instance showed that when attention was voluntarily directed to a specific target location in the visual field it produced multiple foci of cortical enhancement in occipital visual cortex. The position of these foci within the cortex corresponded precisely with the cortical representation of the attended target. Compatible with the results of the present experiment, Brefczynski and DeYoe (1999) found the largest attentional effects in the ventral occipito-temporal cortex. In the present study we observed increased BOLD signal during spatio-numerical compatible trials in occipital regions encoding the lateral target areas in visual cortex. This indicates that non-predictive, centrally presented digit cues induce visuo-spatial attention shifts, which result in amplified visual response to right and left visual field stimulation depending on the numerical value of the digit cue.

The attentional spotlight is thought to be regulated by top-down attentional control signals in the parietal cortex, which has direct neural connections to occipital cortex (Brefczynski & DeYoe, 1999; see also Silver et al., 2007; Lauritzen, D'Esposito, Heeger, & Silver 2009). Because of its well-known role in magnitude processing, the parietal cortex is also one of the favorite candidate regions from which the attentional shifts associated with numerical symbols might originate in the present paradigm. Indeed bilateral parietal regions, and especially the intraparietal sulcus (IPS), play a pivotal role in numerical processing in non-human (for a review see Nieder, 2004) and human primates (for a review see Cohen Kadosh et al., 2008). Neuropsychological studies have shown that lesions in parietal areas often impair number processing (Cipolotti, Butterworth, & Denes, 1991; Delazer & Benke, 1997; Delazer, Karner, Zamarian, Donnemiller, & Benke, 2006). Cipolotti et al. (1991) for instance described a patient with Gerstmann's syndrome due to parietal lesions who lost the access to numbers above 4, whereas her semantic abilities with other categories and her reasoning skills were intact. Over and above its contribution to complex quantity processing such as comparison or calculation, the parietal cortex thus also plays a core role in automatic processing of number semantics. Basic tasks on numbers that do not require access to their magnitude (e.g., the detection of visual numerals or number words) indeed activate the IPS significantly more than when the same basic tasks are performed with non-numerical stimuli (e.g., detection of letters or colors Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003; but see Chochon, Cohen, Moortele, & Dehaene, 1999). These results indicate that numerical magnitude representations are automatically accessed in IPS whenever numerals are detected. Accordingly, the parietal cortex might host the attentional top-down control of the occipital BOLD signal enhancements we observed in response to targets presented after uninformative digits.

To date few studies systematically explored the differential neuronal response to small and large number symbols. Here, we observed a significant effect of digit magnitude bilaterally in the parietal cortex. The two bilateral parietal regions (IPS and IPL) identified using an independent localizer yielded a higher BOLD response following large (8, 9) compared to small (1, 2) digits. The posterior right IPS activation is close to a region activated conjointly in symbolic and non-symbolic number magnitude comparison (Holloway, Price, & Ansari, 2010; for symbolic comparison only see also Pesenti, Thioux, Seron, & Volder, 2000; Pinel, Dehaene, Rivière, & LeBihan, 2001; Ansari, Garcia, Lucas, Hamon, & Dhital, 2005). Ranzini et al., (2009) also recently reported larger ERP amplitudes over parietal electrode sites for

large compared to small digit magnitude (see their Fig. 3). The high spatial resolution of the present data allows confirming that activity modulations related to magnitude arise in parietal cortex. As digit magnitude was non-informative in the present study, magnitude effect on parietal activity is likely to result from differences in the automatic semantic processing of large vs. small numbers.

It is important to note that bilateral activations in the IPS and IPL were identified using the group-level task localizer, which was designed to highlight sensori-motor regions activated by the lateral target discrimination task and did not contain any numerical stimulus material or processing requirement. Consequently, magnitude-related activity changes in these regions provide indirect evidence for interactions between visuo-spatial and numerical processing in parietal cortex. However, neither the ANOVA nor the regression analyses testing for a direct interaction between digit magnitude and target side yielded significant interactions in IPS and IPL. This observation is in line with the findings of *Koten et al. (2011)*, who also failed to observe number-space interactions in the parietal cortex when participants performed a numerical landmark task and the BOLD response was analyzed using univariate statistics as done here. Only using a more fine-grained multi-voxel pattern analysis could this interaction be demonstrated. Future studies using an appropriate fMRI design should address whether this methodological approach would provide similar results with the present attentional cueing paradigm (*Fischer et al., 2003; Posner, 1980; Posner, Cohen, & Rafal, 1982*).

Considering that (*Koten et al. (2011)*) report late response-related, as well early semantic number-space interactions, one could have expected further attentional effects in the other regions highlighted by the group-level task localizer. Given its role in response selection (*Kurata, Tsuji, Naraki, Seino, & Abe, 2000; Dux, Ivanoff, Asplund, & Marois, 2006*) especially the medial superior frontal gyrus would seem an ideal candidate for response-related number-space interactions. However, the main effect of digit magnitude we observed in this region only provides indirect evidence in this direction. The discrepancy with the results of *Koten et al. (2011)* might be due to the use of different behavioral paradigms and/or analysis methods.

In the present study numerals were task-irrelevant and passively viewed. Consequently the visuo-spatial attention effects we observed in occipital regions are in line with the mental number line view proposing that numbers “automatically elicit task-, modality- and effector-independent spatial representations, even when these spatial representations are not strictly relevant to the task” (*Hubbard et al., 2009*). According to this approach, spatial-numerical interactions arise at a central level of semantic representation of numbers in long term memory and are an example of “neuronal recycling” (*Dehaene, 2005*). It is proposed that the same spatial attention mechanisms are being used to shift attention between positions in physical space and the mental number line (*Hubbard et al., 2009*).

On the other hand, and despite the fact that number cues were task-irrelevant and passively viewed, it cannot be excluded that the lateral target discrimination task itself created a spatial context for the semantic processing of the central digit cues, entailing the observed attentional modulations. If this reasoning is correct, attentional effects should not be observed when participants are passively viewing the same attentional cueing paradigm, i.e., without performing a task on the lateral targets. According to this view, spatio-numerical interactions would not be intrinsic properties of semantic representations triggered automatically by numbers, but arise as a function of task context. This proposal is in line with the observation that number-related attentional effects are highly sensitive to task instructions and context (*Galfano et al., 2006; Ristic et al., 2006*). More generally, it

also fits with the recent observation that even basic number-related effects such as the distance effect are task-related and only arise if number semantics need to be accessed for successful task performance (*Goldfarb, Henik, Rubinsten, Bloch-David, & Gertner, 2011*).

In summary the present study demonstrates that number-related attentional shifts are associated with modulations of visual responses to subsequently presented lateral targets in occipital cortex. The digit magnitude effect observed in the bilateral parietal cortex supports the hypothesis that the attentional effect originates in this cortical region known to play a critical role in number representation (*Cohen Kadosh et al., 2008; Ansari, 2008; Nieder & Dehaene, 2009*).

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References

- Andres, M., Seron, X., & Olivier, E. (2005). Hemispheric lateralization of number comparison. *Cognitive Brain Research*, 25, 283–290.
- Ansari, D. (2008). Effects of development and enculturation on number representation in the brain. *Nature Reviews Neuroscience*, 9, 278–291.
- Ansari, D., Garcia, N., Lucas, E., Hamon, K., & Dhital, B. (2005). Neural correlates of symbolic number processing in children and adults. *Brain Imaging*, 16, 1769–1773.
- Ashkenazi, S., & Henik, A. (2010). A disassociation between physical and mental number bisection in developmental dyscalculia. *Neuropsychologia*, 48, 2861–2868.
- Boynton, G. M., Engel, S. A., Glover, G. H., & Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 16, 4207–4221.
- Brefczynski, J. A., & DeYoe, E. A. (1999). A physiological correlate of the ‘spotlight’ of visual attention. *Nature Neuroscience*, 2, 370–374.
- Calabria, M., & Rossetti, Y. (2005). Interference between number processing and line bisection: a methodology. *Neuropsychologia*, 43, 779–783.
- Casarotti, M., Michielin, M., Zorzi, M., & Umiltà, C. (2007). Temporal order judgment reveals how number magnitude affects visuospatial attention. *Cognition*, 102, 101–117.
- Cattaneo, Z., Silvanto, J., Battelli, L., & Pascual-Leone, A. (2009). The mental number line modulates visual cortical excitability. *Neuroscience Letters*, 462, 253–256.
- Cattaneo, Z., Silvanto, J., Pascual-Leone, A., & Battelli, L. (2009). The role of the angular gyrus in the modulation of visuospatial attention by the mental number line. *NeuroImage*, 44, 563–568.
- Chochon, F., Cohen, L., Moortele, P. F. V. D., & Dehaene, S. (1999). Differential contributions of the left and right inferior parietal lobules to number processing. *Journal of Cognitive Neuroscience*, 11, 617–630.
- Cipolletti, L., Butterworth, B., & Denes, G. (1991). A specific deficit for numbers in a case of dense acalculia. *Brain: A Journal of Neurology*, 114(Pt 6), 2619–2637.
- Cohen Kadosh, R., Lammertyn, J., & Izard, V. (2008). Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. *Progress in Neurobiology*, 84, 132–147.
- Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, 58, 306–324.
- Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, 3, 201–215.
- de Hevia, M., Girelli, L., Bricolo, E., & Vallar, G. (2008). The representational space of numerical magnitude: illusions of length. *Quarterly Journal of Experimental Psychology* 2006, 61, 1496–1514.
- de Hevia, M., Girelli, L., & Vallar, G. (2005). Numbers and space: a cognitive illusion? *Experimental Brain Research*, 168, 254–264.
- de Hevia, M. D., Vallar, G., & Girelli, L. (2008). Visualizing numbers in the mind’s eye: the role of visuo-spatial processes in numerical abilities. *Neuroscience and Biobehavioral Reviews*, 32, 1361–1372.
- Dehaene, S. (1997). *The number sense: how the mind creates mathematics*. USA: Oxford University Press.
- Dehaene, S. (2005). Evolution of human cortical circuits for reading and arithmetic: The neuronal recycling hypothesis. In: *From monkey brain to human brain. From monkey brain to human brain*. Cambridge, MA: MIT Press pp. 133–158.
- Dehaene, S., Bossini, S., & Giraux, P. (1993). The mental representation of parity and number magnitude. *Journal of Experimental Psychology: General*, 122, 371–396.
- Delazer, M., & Benke, T. (1997). Arithmetic facts without meaning. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior*, 33, 697–710.

- Delazer, M., Karner, E., Zamarian, L., Donnemiller, E., & Benke, T. (2006). Number processing in posterior cortical atrophy—a neuropsychological case study. *Neuropsychologia*, 44, 36–51.
- Dodd, M. D., Van der Stigchel, S., Adil Leghari, M., Fung, G., & Kingstone, A. (2008). Attentional SNARC: there's something special about numbers let us count the ways. *Cognition*, 108, 810–818.
- Doricchi, F., Guariglia, P., Gasparini, M., & Tomaiuolo, F. (2005). Dissociation between physical and mental number line bisection in right hemisphere brain damage. *Nature Neuroscience*, 8, 1663–1665.
- Dux, P. E., Ivanoff, J., Asplund, C. L., & Marois, R. (2006). Isolation of a central bottleneck of information processing with time-resolved fMRI. *Neuron*, 52(6), 1109–1120.
- Eger, E., Sterzer, P., Russ, M. O., Giraud, A., & Kleinschmidt, A. (2003). A supramodal number representation in human intraparietal cortex. *Neuron*, 37, 719–726.
- Engell, A. D., Nummenmaa, L., Oosterhof, N. N., Henson, R. N., Haxby, J. V., & Calder, A. J. (2010). Differential activation of frontoparietal attention networks by social and symbolic spatial cues. *Social Cognitive and Affective Neuroscience*, 5(4), 432–440.
- Fias, W., Brysbaert, M., Geypens, F., d'Ydewalle, G. 1996. *The importance of magnitude information in numerical processing: evidence from the SNARC effect*. <http://cogprints.org/3444/>.
- Fias, W., & Fischer, M. (2005). Spatial representation of numbers. In: J. I. D. Campbell. (Ed.), *Spatial representation of numbers* (pp. 43–54). Psychology Press.
- Fias, W., van Dijk, J., Gevers, W. 2011. *How number is associated with space? The role of working memory*.
- Fischer, M., Castel, A., Dodd, M., & Pratt, J. (2003). Perceiving numbers causes spatial shifts of attention. *Nature Neuroscience*, 6, 555–556.
- Fischer, M. H. (2001). Number processing induces spatial performance biases. *Neurology*, 57, 822–826.
- Galfano, G., Rusconi, E., & Umiltà, C. (2006). Number magnitude orients attention, but not against one's will. *Psychonomic Bulletin and Review*, 13, 869–874.
- Göbel, S. M., Calabria, M., Farnè, A., & Rossetti, Y. (2006). Parietal rTMS distorts the mental number line: simulating '[spatial]' neglect in healthy subjects. *Neuropsychologia*, 44, 860–868.
- Goldfarb, L., Henik, A., Rubinsten, O., Bloch-David, Y., & Gertner, L. (2011). The numerical distance effect is task dependent. *Memory and Cognition*, 39, 1508–1517.
- Herrera, A., Macizo, P. 2011. When symbolic spatial cues go before numbers. *Psicologica*, 32, Psicologica.
- Hietanen, J. K., Nummenmaa, L., Nyman, M. J., Parkkola, R., & Hämäläinen, H. (2006). Automatic attention orienting by social and symbolic cues activates different neural networks: an fMRI study. *NeuroImage*, 33, 406–413.
- Hietanen, J. K., Leppanen, J. M., Nummenmaa, L., & Astikainen, P. (2008). Visuospatial attention shifts by gaze and arrow cues: an ERP study. *Brain research*, 1215, 123–136.
- Holloway, I. D., Price, G. R., & Ansari, D. (2010). Common and segregated neural pathways for the processing of symbolic and nonsymbolic numerical magnitude: an fMRI study. *NeuroImage*, 49, 1006–1017.
- Hubbard, E., Piazza, M., Pinel, P., & Dehaene, S. (2005). Interactions between number and space in parietal cortex. *Nature Reviews Neuroscience*, 6, 435–448.
- Hubbard, E. M., Piazza, M., Pinel, P., & Dehaene, S. (2009). *Numerical and spatial intuitions: a role for posterior parietal cortex? Cognitive biology: evolutionary and developmental perspectives on mind, brain and behavior*. MA: Cambridge.
- Huddleston, W. E., & DeYoe, E. A. (2008). The representation of spatial attention in human parietal cortex dynamically modulates with performance. *Cerebral Cortex New York, N.Y.*: 1991, 18, 1272–1280.
- Kanwisher, N., & Wojcikuli, E. (2000). Visual attention: insights from brain imaging. *Nature Reviews Neuroscience*, 1, 91–100.
- Kastner, S., & Pinsky, M. A. (2004). Visual attention as a multilevel selection process. *Cognitive, Affective & Behavioral Neuroscience*, 4, 483–500.
- Knops, A., Thirion, B., Hubbard, E. M., Michel, V., & Dehaene, S. (2009). Recruitment of an area involved in eye movements during mental arithmetic. *Science*, 324, 1583–1585.
- Koten, J. W., Jr, Lonnemann, J., Willmes, K., & Knops, A. (2011). Micro and macro pattern analyses of fMRI data support both early and late interaction of numerical and spatial information. *Frontiers in Human Neuroscience*, 5, 115.
- Kurata, K., Tsuji, T., Naraki, S., Seino, M., & Abe, Y. (2000). Activation of the dorsal premotor cortex and pre-supplementary motor area of humans during an auditory conditional motor task. *Journal of neurophysiology*, 84(3), 1667–1672.
- Lauritzen, T. Z., D'Esposito, M., Heeger, D. J., & Silver, M. A. (2009). Top-down flow of visual spatial attention signals from parietal to occipital cortex. *Journal of Vision*, 9(18), 1–14.
- Lindemann, O., Abolafia, J. M., Girardi, G., & Bekkering, H. (2007). Getting a grip on numbers: Numerical magnitude priming in object grasping. *Journal of Experimental Psychology: Human Perception and Performance*, 33, 1400–1409.
- Loetscher, T., Bockisch, C., & Brugger, P. (2008). Looking for the answer: the mind's eye in number space. *Neuroscience*, 151, 725–729.
- Loetscher, T., Bockisch, C. J., Nicholls, M. E., & Brugger, P. (2010). Eye position predicts what number you have in mind. *Current Biology*, 20, R264–R265.
- Longo, M. R., & Lourenco, S. F. (2007). Spatial attention and the mental number line: evidence for characteristic biases and compression. *Neuropsychologia*, 45, 1400–1407.
- Lorch, R. F., & Myers, J. L. (1990). Regression analyses of repeated measures data in cognitive research. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 16, 149–157.
- Martínez, A., Anillo-Vento, L., Sereno, M. I., Frank, L. R., Buxton, R. B., Dubowitz, D. J., et al. (1999). Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature Neuroscience*, 2, 364–369.
- McAdams, C. J., & Maunsell, J. H. (1999). Effects of attention on orientation-tuning functions of single neurons in macaque cortical area V4. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 19, 431–441.
- Moran, J., & Desimone, R. (1985). Selective attention gates visual processing in the extrastriate cortex. *Science New York, N.Y.*, 229, 782–784.
- Munneke, J., Belopolsky, A. V., & Theeuwes, J. (2012). Shifting attention within memory representations involves early visual areas. *PLoS One*, 7, e35528.
- Murray, S. O. (2008). The effects of spatial attention in early human visual cortex are stimulus independent. *Journal of Vision*, 8(2), 1–11.
- Müller, N. G., & Kleinschmidt, A. (2007). Temporal dynamics of the attentional spotlight: neuronal correlates of attentional capture and inhibition of return in early visual cortex. *Journal of Cognitive Neuroscience*, 19, 587–593.
- Nicholls, M. E. R., Loftus, A. M., & Gevers, W. (2008). Look, no hands: a perceptual task shows that number magnitude induces shifts of attention. *Psychonomic Bulletin and Review*, 15, 413–418.
- Nieder, A. (2004). The number domain—can we count on parietal cortex? *Neuron*, 44, 407–409.
- Nieder, A., & Dehaene, S. (2009). Representation of number in the brain. *Annual Review of Neuroscience*, 32, 185–208.
- Nieto-Castañón, A., & Fedorenko, E. (2012). Subject-specific functional localizers increase sensitivity and functional resolution of multi-subject analyses. *NeuroImage* [Epub ahead of print].
- Ogawa, S., Lee, T., Kay, A., & Tank, D. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, 87, 9868–9872.
- Pesenti, M., Thioux, M., Seron, X., & Volder, A. D. (2000). Neuroanatomical substrates of Arabic number processing, numerical comparison, and simple addition: a PET study. *Journal of Cognitive Neuroscience*, 12, 461–479.
- Pinel, P., Dehaene, S., Rivière, D., & LeBihan, D. (2001). Modulation of parietal activation by semantic distance in a number comparison task. *NeuroImage*, 14, 1013–1026.
- Posner, M. I. (1980). Orienting of attention. *The Quarterly Journal of Experimental Psychology*, 32(1), 3–25.
- Posner, M. I., Cohen, Y., & Rafal, R. D. (1982). Neural systems control of spatial orienting. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 298(1089), 187–198.
- Priftis, K., Zorzi, M., Meneghello, F., Marenzi, R., & Umiltà, C. (2006). Explicit versus implicit processing of representational space in neglect: dissociations in accessing the mental number line. *Journal of Cognitive Neuroscience*, 18, 680–688.
- Ranzini, M., Dehaene, S., Piazza, M., & Hubbard, E. M. (2009). Neural mechanisms of attentional shifts due to irrelevant spatial and numerical cues. *Neuropsychologia*, 47, 2615–2624.
- Ress, D., Backus, B. T., & Heeger, D. J. (2000). Activity in primary visual cortex predicts performance in a visual detection task. *Nature Neuroscience*, 3, 940–945.
- Ristic, J., Wright, A., & Kingstone, A. (2006). The number line effect reflects top-down control. *Psychonomic Bulletin and Review*, 13, 862–868.
- Rotzer, S., Loenneker, T., Kucian, K., Martin, E., Klaver, P., & von Aster, M. (2009). Dysfunctional neural network of spatial working memory contributes to developmental dyscalculia. *Neuropsychologia*, 47, 2859–2865.
- Rusconi, E., Bueti, D., Walsh, V., & Butterworth, B. (2011). Contribution of frontal cortex to the spatial representation of number. *Cortex*, 47, 2–13.
- Rusconi, E., Turatto, M., & Umiltà, C. (2007). Two orienting mechanisms in posterior parietal lobule: an rTMS study of the Simon and SNARC effects. *Cognitive Neuropsychology*, 24, 373–392.
- Salillas, E., El Yagoubi, R., & Semenza, C. (2008). Sensory and cognitive processes of shifts of spatial attention induced by numbers: an ERP study. *Cortex*, 44, 406–413.
- Salillas, E., Graná, A., El-Yagoubi, R., & Semenza, C. (2009). Numbers in the blind's "eye". *PLoS One*, 4, e6357.
- Salverda, A. P., & Altmann, G. T. M. (2011). Attentional capture of objects referred to by spoken language. *Journal of Experimental Psychology: Human Perception and Performance*, 37, 1122–1133.
- Saxe, R., Brett, M., & Kanwisher, N. (2006). Divide and conquer: a defense of functional localizers. *NeuroImage*, 30, 1088–1096; discussion 1097–1099.
- Schuller, A., Hoffmann, D., Schiltz, C. (2011) Shifts of spatial attention cued by irrelevant numbers: electrophysiological evidence from a target discrimination task. In: *The 18th annual meeting of the cognitive neuroscience society*, April 2–5, 2011, San Francisco, USA.
- Silver, M. A., Ress, D., & Heeger, D. J. (2007). Neural correlates of sustained spatial attention in human early visual cortex. *Journal of Neurophysiology*, 97, 229–237.
- Somers, D. C., Dale, A. M., Seiffert, A. E., & Tootell, R. B. (1999). Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Proceeding of the National Academy of Science USA*, 96(4), 1663–1668.
- Soto, D., Rotstein, P., Hodsoll, J., Mevorach, C., & Humphreys, G. W. (2012). Common and distinct neural regions for the guidance of selection by visuo-verbal information held in memory: converging evidence from fMRI and rTMS. *Human brain mapping*, 33(1), 105–120.
- Stoianov, I., Kramer, P., Umiltà, C., & Zorzi, M. (2008). Visuospatial priming of the mental number line. *Cognition*, 106, 770–779.
- Talairach, J., Tournoux, P. 1988. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. *Thieme*.
- Thiel, C. M., Zilles, K., & Fink, G. R. (2004). Cerebral correlates of alerting, orienting and reorienting of visuospatial attention: an event-related fMRI study. *NeuroImage*, 21, 318–328.
- Umiltà, C., Priftis, K., & Zorzi, M. (2009). The spatial representation of numbers: evidence from neglect and pseudoneglect. *Experimental Brain Research: Experimentelle Hirnforschung. Expérimentation Cérébrale*, 192, 561–569.

- van Dijck, J., & Fias, W. (2011). A working memory account for spatial-numerical associations. *Cognition*, 119, 114–119.
- van Galen, M. S., & Reitsma, P. (2008). Developing access to number magnitude: a study of the SNARC effect in 7- to 9-year-olds. *Journal of Experimental Child Psychology*, 101, 99–113.
- Walsh, V. (2003). A theory of magnitude: common cortical metrics of time, space and quantity. *Trends in Cognitive Sciences*, 7, 483–488.
- Zago, L., Petit, L., Turbelin, M., Andersson, F., Vigneau, M., & Tzourio-Mazoyer, N. (2008). How verbal and spatial manipulation networks contribute to calculation: an fMRI study. *Neuropsychologia*, 46, 2403–2414.
- Zago, L., & Tzourio-Mazoyer, N. (2002). Distinguishing visuospatial working memory and complex mental calculation areas within the parietal lobes. *Neuroscience Letters*, 331, 45–49.
- Zorzi, M., Priftis, K., Meneghello, F., Marenzi, R., & Umiltà, C. (2006). The spatial representation of numerical and non-numerical sequences: evidence from neglect. *Neuropsychologia*, 44, 1061–1067.
- Zorzi, M., Priftis, K., & Umiltà, C. (2002). Brain damage: neglect disrupts the mental number line. *Nature*, 417, 138–139.