Brain Stimulation xxx (2012) 1–6

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Research

Differential effects of left parietal theta-burst stimulation on order and quantity processing

Gordon L.F. Cheng [a,b,*,2], Joey Tang [a], Vincent Walsh [b], Brian Butterworth [b], Marinella Cappelletti [b,1,2]

[a] Department of Psychology, Knowles Building, University of Hong Kong, Hong Kong
[b] Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK

ARTICLE INFO

Article history:
Received 17 January 2012
Received in revised form
5 April 2012
Accepted 10 April 2012
Available online xxx

Keywords:
Number processing
Order and quantity
Theta-burst stimulation
Intraparietal sulcus
Parietal cortex

ABSTRACT

Numbers can be used to represent different meanings, including order information ('Steve lives at house number 24') and quantity ('Steve is paid 24 pounds'). The few previous neuroimaging studies that investigated order and quantity processing reported conflicting evidence as to whether same or partially overlapping brain systems are engaged in these processes. Such inconsistencies may be related to the use of neuroimaging techniques which do not allow causal inference regarding brain-behaviour relationships. To overcome this problem, the present study employed continuous theta-burst stimulation (TBS) to investigate whether interference to either the left or right parietal regions affected order and quantity in similar or different ways. Results revealed that following TBS to the left intraparietal sulcus, quantity processing was impaired and order facilitated; TBS to the contralateral brain region led to no specific effects in either order or quantity processing. These findings suggest that there are at least partially different neuronal populations involved in order and quantity processing, and that the left parietal cortex is critical for both processes.

Introduction

In everyday life we effortlessly use different meanings of numbers, including *quantity* (e.g. 'Steve is paid 24 pounds') and *order*, sometimes called rank (e.g. 'Steve lives at house number 24'). Very few studies have explored order processing and in particular the issue of whether this is distinct from quantity or not. Findings from these studies are in support of either one of the following not mutually exclusive positions: (1) order and quantity are processed in similar ways [1–3] or (2) processing order and quantity information require at least partially distinct cognitive mechanisms [4–7].

A common representation for order and quantity has been suggested by studies reporting similar brain regions activated by processing order and quantity information. For instance, the bilateral intraparietal sulci (IPS) have been reported to be activated by both a numerical quantity task and an order task that used letters of the alphabet as stimuli [1]. Similarly, it was found that both order and quantity processing involve left IPS activation, although they showed different numerical distance effects which may suggest independent cognitive mechanisms being used [2]. On the other hand, evidence supporting distinct representations for order and quantity comes from an event-related potentials (ERPs) study. This reported only partially overlapping neural courses for order and quantity, the latter associated with brain signals in the left parietal cortex, the former with bilateral and delayed parietal signal [6]. Support for separable order and quantity processes also comes from a few single-case studies of neurological patients showing double dissociations between these processes [8–10]. The inconsistencies between studies supporting common or distinct representations between order and quantity may be methodological. It is possible that some early functional imaging studies claiming common brain regions involved in order and quantity processing may have used methods that did not allow us distinguishing between order and quantity-related areas. Indeed, based on a more sophisticated method such as multivariate pattern recognition [11], a recent re-analysis of the data reported in a previous study which supported the 'common' position [1] has in fact identified separable sets of voxels within the IPS for order and quantity processing [7].

Functional imaging is essential to identify the brain regions involved in order and quantity processing, but it does not allow us

* Corresponding author. Department of Psychology, Knowles Building, University of Hong Kong, Pokfulum, Hong Kong. Tel.: +852 2859 2381.
E-mail addresses: glfcheng@hku.hk (G.L.F. Cheng), m.cappelletti@ucl.ac.uk (M. Cappelletti).
[1] Tel.: +44 020 7679 5430.
[2] This research was supported by a Wellcome Trust Scholarship awarded to GC, and the Royal Society Dorothy Hodgkin Fellowship to MC.

1935-861X/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.brs.2012.04.005

Table 1
Examples of the experimental trials used and corresponding answers for the order and quantity tasks. (For interpretation of the references to colour in this table, the reader is referred to the web version of this article.)

Order Correct order?	Correct response?	Quantity More red or green Xs?	Correct response?
← X4XXXXX3X	Yes	↔ XX3XX6XXX	Green
→ X4XXXXX3X	No	↔ X4XXXXX3X	Red

to establish whether these regions are also critical for those processes. Transcranial magnetic stimulation (TMS) has been successfully used to establish the causal involvement of a brain region in a cognitive function. For instance, the IPS has been shown to be critical for number quantity processing [12], but so far no study investigated whether this is also the case for order processing. The aim of the present study was therefore to investigate the interplay between order and quantity processing by testing the brain regions that may be critical for them. To achieve this, TMS in the form of continuous theta-burst stimulation (TBS) was used to investigate the extent to which the IPS may be equally critical for order and quantity processing. The bilateral IPS were chosen as target regions since: (i) previous functional imaging studies indicated that this region to be most consistently associated with order processing [1,2]; and (ii) previous transcranial magnetic stimulation studies revealed the IPS to be critically involved in quantity [12]. If order and quantity processing indeed rely on the same neuronal resources, then IPS-TBS should affect performance on both tasks. Conversely, if order and quantity involve different brain areas, then IPS-TBS may result in different effects.

Methods and materials

Participants

Twenty-one neurologically healthy adults participated in the present study. A screening was conducted to ensure that all participants were TMS-compatible, i.e. that they had no history of neurological conditions, seizure, loss of consciousness, or serious illness, and currently not taking any form of medication, suffer from frequent or severe headaches, or having family members with epilepsy. As an additional safety precaution, only one of the targeted brain areas (LIPS, RIPS, vertex) was stimulated per day for participants who were able to come back for more than one testing session. Specifically, 4 participants attended three sessions on three separate days, 5 attended two sessions on two separate days, and 12 attended one session only. For each of the three targeted areas there was an equal number of 11 participants; data from one participant who attended one session only was discarded as he obtained abnormally high error rates (i.e. higher than 40% error). Participants were initially randomly assigned to one of three targeted areas: (i) left IPS (mean age 24.2 $\pm$ 5.20, 2 males); (ii) right IPS (mean age 24.0 $\pm$ 5.39, 3 males); and (iii) vertex (mean age 22.6 $\pm$ 5.20, 2 males). For participants who attended more than one session, the order of stimulation sites was counterbalanced such that the targeted areas were not stimulated in the same order. All participants reported normal or corrected-to-normal vision. The factors that influence individual variability in neuroplasticity induction are becoming increasingly well-established. These factors include age, gender, level of physical exercise, time of day, attention, etc. [13]. Our participants across the different conditions were matched in some of these factors (i.e. age and gender), and other factors were assumed to be matched based on the randomization procedure. The Ethics Committee of the Institute of Neurology, University College London, approved the present study which was performed in accordance with the standard TMS safety procedures [14].

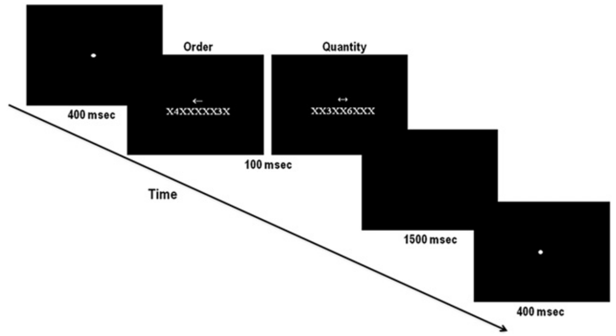

Figure 1. Timeline of a single experimental trial.

Stimuli and tasks

The current experimental tasks were adapted from a previous study that also investigated order and quantity processing [5]. Each stimulus consisted of an array of nine items presented side-by-side at the centre of a computer screen on a black background. Two of these nine items were single-digit numbers (ranging from 1 to 7); the other seven items were ‘X’s. Some of the items were presented in red, others in equiluminant green. The array subtended a visual angle of approximately 11.9° (width) and 0.96° (height). For the order task, a white arrow pointing either left- or right-ward was presented directly above and at the same time as the stimulus. For the quantity task, a similar arrow pointing simultaneously at both left and right was presented; this aimed to match the visual presentation of the order task.

In the order task, participants decided whether the two numbers in the array were in the correct ascending order according to the direction of the arrow. Prior to the beginning of this task, participants were instructed to ignore the ‘X’s in the array. In the quantity task, participants decided whether there were more green ‘X’s or red ‘X’s in the array. Participants were instructed to ignore the arrow and the two numbers in the array. One number was always presented in green while the other in red so the correct answer did not change even if participants included the numbers in their judgements. The larger number was always in the colour of the larger set so that any incongruent numerical Stroop effect could be avoided [15,16]. The numerical distance of stimuli was manipulated [17]. In the order task, the distance between the two presented numbers referred to the numerical difference between them. There were two possible distances: 2 (i.e. 1–3; 3–5; 4–6) and 4 (i.e. 1–5; 2–6; 3–7). In the quantity task, the manipulation of distance referred to the difference between the number (or numerosity) of green and red ‘X’s. The distances were always 1 (small) or 3 (large), namely, for each array there were always either 3 ‘X’s in one colour and 4 ‘X’s in the other colour (for distance 1); or 2 ‘X’s in one colour and 5 ‘X’s in the other colour (for distance 3). The range of numerosity chosen (i.e. 2–5) was within the canonical subitizing range, so that answers were likely to be based on processing discrete items, rather than continuous quantity, i.e. amount of colour [18]. However, since the discrete and continuous quantity correlated in the quantity task, it is not possible to identify the precise quantity strategy used by participants to perform the task. See Table 1 for example trials of each task.

The timeline of a single trial is illustrated in Fig. 1. Following a 400 msec fixation point, each stimulus was presented for

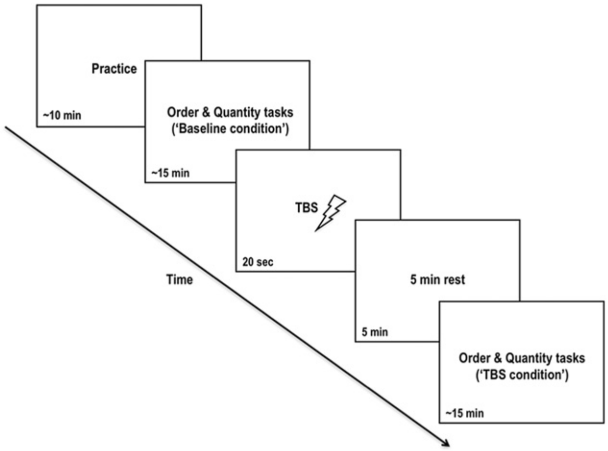

Figure 2. Timeline of events in TBS experiment.

100 msec, after which a blank screen appeared. Once a response was made, 1500 msec elapsed before another fixation dot appeared for 400 msec, after which the next stimulus was presented. The brief presentation of the stimuli was used to avoid the possibility of parietal-TMS affecting saccadic movements [19]. There were 160 experimental trials, 80 of which contained stimuli with a small distance and 80 with a large distance. In the order task and independent of distance, half of the trials had the arrow pointing left-ward; the other half pointing right-ward. There was also an equal number of correct-key presses for the two assigned keys. The trials were presented in a pseudo-random fashion so that (1) for the quantity task, there were no more than three consecutive trials with the same numerical distance or the same correct-key assignment; (2) for the order task, there were no more than three consecutive trials with the same numerical difference and the same correct-key assignment; additionally, (3) in both tasks trials with the same combination of numbers were never presented consecutively. The order in which participants completed the two tasks (order or quantity) was counterbalanced.

TBS procedure

In each session, participants received continuous TBS to either a control brain region (the vertex) or one of the two intraparietal regions (left or right IPS, MNI coordinates: −42, −40, 42, and 38, −44, 40 respectively). The coordinates were obtained from a previous fMRI study that revealed activation of these regions in a quantity task [20] and were also shown to be critically involved in quantity processing in a previous TMS study [21].

For each session, participants first received training in both the experimental tasks, and then completed the tasks without TBS. This condition served as a baseline to be compared with performance following TBS on the same day. Once the baseline task was completed, participants received TBS stimulation at one of the three aforementioned brain areas, and then performed the tasks again. See Fig. 2 for timeline of events in a single testing session.

Prior to the experiment, high-resolution structural brain images were obtained for each participant. These images were skull-stripped and normalized against a standard template (FSL, Oxford, UK). The resulting mathematical description of this transformation was then used to obtain the coordinates to be targeted in the untransformed space. These new coordinates were marked on each participant's structural image using Brainsight (Rogue Research, Montreal, Canada), a frameless stereotactic system that allows precise localization to the areas of interest for each participant. Visually available external landmarks, i.e. tip and bridge of the nose, and the tragus of the ears, were also marked on the structural image. The 3-D locations of these landmarks were registered using an optical tracking system based on an infra-red camera that detects reflectors attached to the participant's forehead. The same optical tracking system was then used to precisely locate the areas of interest (see Fig. 3). Repetitive TMS in the form of continuous theta-burst [22–24] was applied using a figure-of-eight coil measuring 70 mm in diameter and connected to a Magstim Rapid biphasic stimulator (Whitland, Magstim, UK). Specifically, stimulation in chains of 3 pulses with a 20 msec inter-pulse interval was applied every 200 msec at 40% of the machine power output, at frequency of 50 Hz for 20 s, totalling 300 pulses. Power output was fixed rather than tailored for each individual since the parietal

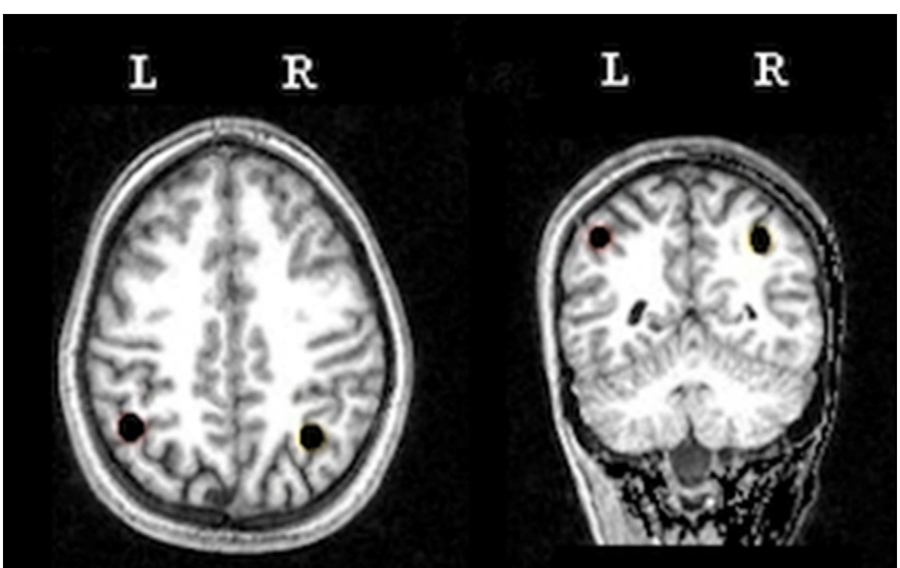

Figure 3. Brain areas targeted with TBS. Axial and coronal views of the brain of a representative participant. The horizontal segments of the left (red) and right (yellow) intraparietal sulci (IPS) were targeted (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

cortex does not have a proxy for testing excitability similar to that of resting motor threshold and phosphene threshold for the motor and visual cortex, respectively [25]. Moreover, the current fixed parameters have been successfully used for stimulating areas outside the motor and visual cortices [23]. Twenty seconds of TBS was delivered as this was shown to be equally effective in reducing cortical excitability compared to the more common 40 s protocol, albeit for a shorter duration of 20 min [22], which was sufficient for completing the present experimental tasks. The centre of the coil was firmly held tangentially to the participant's scalp and with the handle pointing backwards and approximately 45% lateral to the sagittal plane. This led to current flow in the posterior–anterior direction. Based on previously observed time course of TBS effects on the motor cortex [22], participants were asked to rest for five minutes after stimulation before starting the experimental tasks.

Data analysis

Mean accuracy and reaction times (RTs) were calculated for each participant in each condition. In accordance with previous TMS studies on number processing [21,26–28], trials with RTs below 200 msec (anticipatory responses) and 2 SDs above the mean were removed and not used in further analyses (4.5% of total trials removed). Since each participant took part in a different number of experimental sessions, a multi-level mixed model using maximum likelihood estimation was used as it tolerates missing data [29]. Dependent variables were accuracy and RT (in separate models) following TBS. The random effect factor was the difference in baseline intercepts between participants. Fixed factors were task (order and quantity), numerical distance (small and large), and site (LIPS, RIPS, vertex). Baseline performance was incorporated as a covariate in order to take into account potential differences in baseline across stimulation sites. Interaction terms between the covariate (i.e. baseline performance) and fixed factors (i.e. task, distance, and site) were initially included, and only removed if these interactions proved non-significant. When there were significant interaction effects, simple main effect analyses were carried out. Where appropriate, Bonferroni-corrected post-hoc comparisons with estimated marginal means were also performed. If the factor site was involved in the interaction, then vertex performance was used as the reference to be compared with.[3]

Results

Table 2 provides descriptive statistics (accuracy and RTs) for each condition, broken down by task, distance, and site.

Accuracy

For accuracy, the initial multi-level mixed model with interactions between baseline (covariate) and other fixed factors (task, distance, and site) were not significant [baseline-by-task: $F(1,131) = .077$, $P = .78$, *ns*; baseline-by-distance: $F(1,125) = .032$, $P = .86$, *ns*; baseline-by-site: $F(2,131) = 1.92$, $P = .15$, *ns*; task-distance-baseline: $F(1,122) = .09$, $P = .76$, *ns*; baseline-task-site: $F(2,125) = .41$, $P = .66$, *ns*; baseline-distance-site: $F(2,126) = .10$, $P = .37$, *ns*; 4-way interaction: $F(2,126) = .18$, $P = .84$, *ns*]. Therefore, another model was run without the interaction terms. In this subsequent model, the random effect that tested for individual differences in baseline intercepts was not significant [Wald's $Z = .349$, $P = .73$, *ns*]. As for fixed effects, the 3-way interaction between task, distance, and site was non-significant [$F(2,107) = .27$, $P = .76$, *ns*]. The task-by-site interaction [$F(2,107) = 1.37$, $P = .26$, *ns*], distance-by-site interaction [$F(2,109) = .098$, $P = .91$, *ns*], and main effect of site [$F(2,97) = 2.57$, $P = .082$, *ns*] were also not significant. However, the main effects of covariate (i.e. baseline performance), task, distance, and task-by-distance interaction were significant [baseline: $F(1,88) = 34.5$, $P < .001$; task: $F(1,127) = 6.43$, $P = .012$; distance: $F(1,126) = 12.9$, $P < .001$; task-by-distance: $F(1,126) = 12.1$, $P = .001$]. Post-hoc analyses revealed that for the quantity task, there was a simple main effect of distance [$F(1,114) = 15.8$, $P < .001$] such that small distance trials were responded less accurately relative to large distance trials, reflecting a classic numerical distance effect. The simple main effect of distance in the order task was not significant [$F(1,107) = .013$, $P = .91$, *ns*].

Table 2
Reaction time (msec) and accuracy (%) and for each condition broken down by distance.

			LIPS	RIPS	Vertex
O	Baseline	Small	808 (93%)	716 (93%)	758 (91%)
		Large	799 (91%)	703 (93%)	739 (92%)
	TBS	Small	738 (92%)	703 (91%)	727 (91%)
		Large	715 (93%)	700 (91%)	718 (91%)
Q	Baseline	Small	804 (72%)	823 (70%)	834 (67%)
		Large	694 (92%)	702 (92%)	664 (93%)
	TBS	Small	887 (76%)	796 (73%)	755 (74%)
		Large	724 (93%)	658 (91%)	614 (94%)

O = order task; Q = quantity task; LIPS = left intraparietal sulcus; RIPS = right intraparietal sulcus.

Response times

For RTs, in the initial model that included interaction terms between covariate and other fixed factors revealed that the 4-way interaction [$F(2,109) = .26$, $P = .77$, *ns*], baseline-distance-site interaction [$F(2,109) = .87$, $P = .42$, *ns*], baseline-task-distance interaction [$F(1,109) = .70$, $P = .41$, *ns*], baseline-by-distance interaction [$F(1,109).78$, $P = .38$, *ns*], and baseline-by-site interaction [$F(2,125) = 1.21$, $P = .30$, *ns*] were non-significant. However, there was a significant 3-way interaction between baseline, task, and site [$F(2,118) = 22.4$, $P < .001$], as well as a significant 2-way interaction between baseline and task [$F(1,119) = 8.01$, $P = .005$]. Therefore, the baseline-by-task and baseline-task-site interactions were retained in the second model for testing the fixed effects (i.e. task, distance, and site). In this model, the random effect revealed that individual differences in baseline intercepts were significant [Wald's $Z = 2.48$, $P = .013$]. The baseline fixed effect covariate was also significant [$F(1,132) = 386.6$, $P < .001$], as were its 2-way interaction with task [$F(1,120) = 8.11$, $P = .005$] and 3-way interaction was task and site [$F(4,122) = 16.0$, $P < .001$]. For fixed effect factors, there were significant main effects of task [$F(1,119) = 10.3$, $P = .002$] and distance [$F(1,111) = 9.47$, $P = .003$], though not for site [$F(2,125) = 1.64$, $P = .20$, *ns*]. In terms of interaction effects, the site-by-distance [$F(2,110) = .56$, $P = .57$, *ns*] and task-distance-site [$F(2,109) = .59$, $P = .56$, *ns*] interaction were not significant. However, there were significant task-by-site [$F(2,118) = 13.9$, $P < .001$] and task-by-distance [$F(1,110) = 10.7$, $P = .001$] interactions.

To tease apart these interactions, post-hoc analyses were carried out. First, in the quantity task there was a simple main effect of distance, such that small distance trials took longer to perform than large distance trials [$F(1,113) = 18.7$, $P < .001$], reflecting a classic distance effect. There was no significant difference between small

[3] The data was also analyzed in a $2 \times 2 \times 2 \times 3$ ANOVA with task, numerical distance, and condition as within-subjects factors and treating stimulation site as a between-subjects factor, as suggested by an anonymous reviewer. This analysis yielded consistent results to the multi-level mixed model. However, the statistics of this ANOVA analysis is not presented due to space constraint.

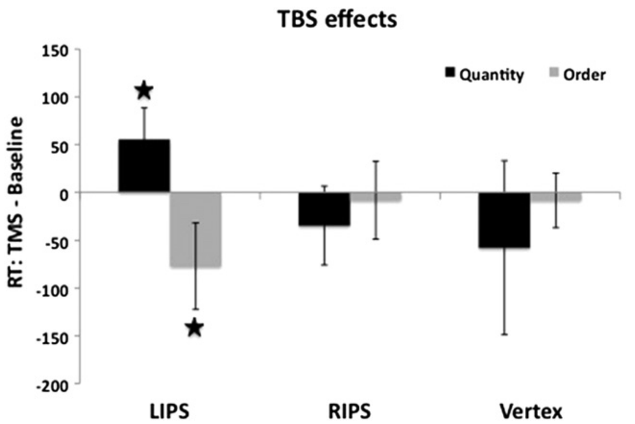

Figure 4. Reaction times (RTs) mean difference (with standard error) between each stimulation area and its baseline. Asterisks indicate significant TBS effect. Following LIPS-TBS, quantity was slower (longer RTs) and order was faster (shorter RTs). Note that actual RTs before and after TBS (rather than the difference in RT before and after TBS) were used for analyses. RTs mean difference shown on the *y*-axis is for clarity in presentation only.

and large distance trials in the order task [$F(1,108) = .017$, $P = .90$, *ns*]. Second, there was a simple main effect of site in both the order [$F(2,126) = 9.81$, $P < .001$] and quantity [$F(2,125) = 16.2$, $P < .001$] tasks. Bonferroni-corrected pairwise comparison using estimated marginal means revealed that, having adjusted for baseline differences, LIPS-TBS led to faster RTs in the order task ($P < .001$) and slower RTs in the quantity task ($P < .001$), relative to vertex-TBS. On the other hand, there was no difference in RTs between vertex-TBS and RIPS-TBS (both order and quantity: $P = 1$, *ns*). These results suggest that LIPS-TBS impaired performance in the quantity task, consistent with previous TMS studies [21,26,28]. However, the novel finding was that stimulation to the same area facilitated order processing (see Fig. 4).

In summary, by using the multi-level mixed modelling analyses, we showed that LIPS-TBS led to faster RTs in order processing and slower RTs in quantity, whereas RIPS-TBS led to no specific effects in either order or quantity task.

Discussion

The aim of this study was to investigate order and quantity processing by testing the brain regions that may be critical for these processes. This was achieved by examining the effects of temporary de-activation of the left and right parietal lobes using theta-burst stimulation on order and quantity processing. Three main results emerged: (1) left IPS-TBS impaired quantity processing (slower RTs); (2) it facilitated order processing (speeded RTs); and (3) right IPS-TBS had no specific effect on either order or quantity processing.

TBS over LIPS impairs quantity processing

Our evidence of impaired quantity processing following left parietal-TBS reinforces previous findings that this area is critically involved in number comparison [21,26–28,30–32]. These findings extend neuroimaging evidence by showing that the left IPS is not just involved in but also critical for quantity processing, even when this area is only temporary de-activated. Therefore, present and past studies have firmly established that quantity processing relies on the integrity of the brain regions surrounding the LIPS.

We also found that there was no effect of right parietal-TBS on quantity processing, suggesting no causal role of this region in number quantity. This is consistent with some previous studies [28,32], but not in line with others that showed either impairment [21,31,33] or facilitation [27] following RIPS-TMS. The inconsistent findings of the RIPS may be related to the kind of quantity information that was investigated. It seems that the RIPS and LIPS are involved in the processing of continuous quantities (e.g. physical size) and discrete or symbolic quantities (e.g. dots or number comparison) respectively [12,27,30,34]. Since the present experimental task likely involved the processing of numerosity (or discrete quantity), the finding that LIPS-TBS but not RIPS-TBS affected discrete quantity seems therefore compatible with the proposal of the LIPS being involved in discrete quantity processing.

TBS over LIPS facilitates order processing

A facilitation in the order task emerged following LIPS-TBS, which contrasted with impaired quantity processing following the TBS manipulation on the same area. This novel result suggests that order and quantity processing may dissociate, in line with some recent findings [7]. Although some previous neuroimaging studies report common brain regions involved in order and quantity processing [1,2], these and the present findings are not necessarily in conflict. Neuroimaging studies indicate that order and quantity processing engage largely overlapping brain areas especially within the parietal regions [1,2]. Our finding that LIPS-TBS is differently critical for order and quantity processing refines the role of this parietal region, and shows that these processes are at least partially dissociable, rather than 'both sides of the same coin' [3]. This can be further reinforced by the observation of lack of numerical distance effect in the order task. This finding has been reported by previous behavioural studies and may be suggestive of independent strategies involved in processing order and quantity [35].

There are three possible reasons for the facilitatory effect in the order task following LIPS-TBS. First, numerical processing might be regulated by inhibitory connections between homologous areas of the cortex [27,36]. Therefore, it might be possible that LIPS-TBS interfered with these inhibitory connections which in turn led to more efficient processing of contralateral areas, such as the right IPS. However, these inhibitory processes would have impaired order processing following RIPS-TBS, which was not the case. Secondly, it is possible that facilitation in order processing was a result of increased general cognitive resources available for order within the LIPS. This would be consistent with the idea that the IPS might be involved in both order and quantity processing [7]. It is therefore possible that TBS temporarily 'switched off' quantity processing, leaving extra resources for order processing, although it remains to be explained why stimulation to IPS affected quantity-sensitive neurons only. The third possibility is that there are inhibitory connections between the LIPS and surrounding area(s) of the parietal cortex of the same hemisphere [37]. Once these areas are released from inhibitory connections, for instance from the IPS in this case, they may result in more efficient processing of order information. It is possible that the angular gyrus, one of the three 'parietal circuits' for number processing proposed by Dehaene and colleagues [38], may be the area within the parietal lobe to be released from IPS inhibitory connections. This is supported by two sets of evidence. Firstly, there have been reports that the left angular gyrus (posterior to the IPS) is activated during learning of an ordered sequence irrespective of the stimulus used [39,40]. Secondly, temporary interference by means of TMS to the same region can lead to impairment in direction discrimination [41]. Therefore, it is possible that the result of speeded responses in the order task following LIPS-TBS was due to release of inhibitory connections from the IPS to nearby areas, possibly including the left angular gyrus. Our data, however, cannot provide direct evidence for it, and the role of the angular gyrus in order processing remains to be tested in future studies.

The different LIPS-TBS effects in terms of a facilitation of order processing and impairment of quantity may depend on the format used for these tasks (symbolic for order and non-symbolic for quantity). Although the present study could not exclude the use of strategy based on the format of the stimuli, we note that facilitation simply driven by symbolic strategies would be incompatible with previous TMS findings that reported an impairment of symbolic numerical tasks following left parietal-TMS [21,26–28,31,32].

Conclusions

Order information is an important and pervasive part of our life: 'Let's catch the second train'; 'Who came first in the race' are just a few examples of how we need to process order in daily life. However, it is still unclear whether processing order and quantity are 'both sides of the same coin' [3] and which are the brain regions critical for these processes. The present study reveals that LIPS-TBS led to facilitated order processing and impaired quantity processing, whereas RIPS-TBS had no effect to either order or quantity. These findings suggest that order and quantity processes are independent ways of using numbers requiring at least partially distinct demands on the parietal lobe.

Acknowledgment

We wish to thank Dr. Cheung Sing-Hang for advice on data analysis.

References

[1] Fias W, Lammertyn J, Caessens B, Orban G. A processing of abstract ordinal knowledge in the horizontal segment of the intraparietal sulcus. J Neurosci 2007;27:8952–6.
[2] Franklin MS, Jonides J. Order and magnitude share a common representation in parietal cortex. J Cogn Neurosci 2009;21:2114–20.
[3] Jacob SN, Neider A. The ABC of cardinal and ordinal number representations. Trends Cogn Sci 2008;12:41–3.
[4] Dehaene S, Brannon EM. Space, time and number in the brain: searching for evolutionary foundations of mathematical thought. London: Elsevier; 2011.
[5] Tang J, Ward J, Butterworth B. Number forms in the brain. J Cogn Neurosci 2008;20:1547–56.
[6] Turconi E, Jemel B, Rossion B, Seron X. Electrophysiological evidence for differential processing of numerical quantity and order in humans. Cogn Brain Res 2004;21:22–38.
[7] Zorzi M, Di Bono MG, Fias W. Distinct representations of numerical and non-numerical order in the human intraparietal sulcus revealed by multivariate pattern recognition. Neuroimage 2011;56:674–80.
[8] Delazer M, Butterworth B. A dissociation of number meanings. Cogn Neuropsychol 1997;14:613–36.
[9] Turconi E, Seron X. Dissociation between order and quantity meanings in a patient with Gerstmann syndrome. Cortex 2002;38:911–4.
[10] Dehaene S, Cohen L. Cerebral pathways for calculation: double dissociation between rote verbal and quantitative knowledge of arithmetic. Cortex 1997; 33:219–50.
[11] Haynes JD, Rees G. Decoding mental states from brain activity in humans. Nat Rev Neurosci 2006;7:523–34.
[12] Sandrini M, Rusconi E. A brain for numbers. Cortex 2009;45:796–803.
[13] Ridding MC, Ziemann U. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol 2010;588: 2291–304.
[14] Rossi S, Hallett M, Possini PM, Pascual-Leone A, The Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39.
[15] Pavese A, Umilta C. Symbolic distance between numerosity and identity modulates Stroop interference. J Exp Psychol Hum Percept Perform 1998;24: 1535–45.
[16] Pavese A, Umilta C. Further evidence on the effects of symbolic distance on Stroop-like interference. Psychol Res 1999;62:62–71.
[17] Moyer RS, Landauer TK. The time required for judgements of numerical inequality. Nature 1967;215:1519–20.
[18] Piazza M, Izard V. How human's count: numerosity and the parietal cortex. The Neuroscientist 2009;15:261–73.
[19] Ryan S, Bonilha L, Jackson SR. Individual variation in the location of the parietal eye fields: a TMS study. Exp Brain Res 2006;173:389–94.
[20] Cappelletti M, Lee HL, Freeman ED, Price CJ. The role of the right and left parietal lobes in the conceptual processing of numbers. J Cogn Neurosci 2010; 22:331–46.
[21] Cappelletti M, Muggleton N, Walsh V. Quantity without numbers and numbers without quantity in the parietal cortex. Neuroimage 2009;49:522–9.
[22] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6.
[23] Kalla R, Muggleton NG, Cowey A, Walsh V. Human dorsolateral prefrontal cortex is involved in visual search for conjunctions but not features: a theta TMS study. Cortex 2009;45:1085–90.
[24] Vallesi A, Shallice T, Walsh V. Role of the prefrontal cortex in the foreperiod effect: TMS evidence for dual mechanisms in temporal preparation. Cereb Cortex 2007;17:466–74.
[25] Walsh V, Pascual-Leone A. Transcranial magnetic stimulation: a neurochronometrics of mind. Cambridge, Massachusetts: The MIT Press; 2003.
[26] Andres M, Seron X, Olivier E. Hemispheric lateralization of number comparison. Brain Res Cogn Brain Res 2005;25:283–90.
[27] Cappelletti M, Barth H, Fregni F, Pascual Leone A, Spelke E. rTMS over the left and the right intraparietal sulcus disrupts discrete and continuous quantity processing. Exp Brain Res 2007;179:631–42.
[28] Sandrini M, Rossini PM, Miniussi C. The differential involvement of inferior parietal lobule in number comparison: a rTMS study. Neuropsychologia 2004; 42:1902–9.
[29] Hox J. Multilevel analysis: techniques and applications. Mahwah, NJ: Erlbaum; 2002.
[30] Dormal V, Andres M, Pesenti M. Dissociation of numerosity and duration processing in the left intraparietal sulcus: a transcranial magnetic stimulation study. Cortex 2008;44:462–9.
[31] Göbel SM, Walsh V, Rushworth MFS. The mental number line and the human angular gyrus. Neuroimage 2001;14:1278–89.
[32] Rusconi E, Walsh V, Butterworth B. Dexterity with numbers: rTMS over left angular gyrus disrupts finger gnosis and number processing. Neuropsychologia 2005;43:1609–24.
[33] Oliveri M, Rausei V, Koch G, Torriero S, Turriziani P, Caltagirone C. Overestimation of numerical distances in the left side of space. Neurology 2004;11:2139–41.
[34] Cohen Kadosh R, Cohen Kadosh K, Schuhmann T, Kaas A, Goebel R, Henik A, et al. Virtual dyscalculia induced by parietal-lobe TMS impairs automatic magnitude processing. Curr Biol 2007;17:1–5.
[35] Franklin MS, Jonides J, Smith EE. Processing of order information for numbers and months. Mem Cogn 2009;37:644–54.
[36] Hilgetag CC, Theoret H, Pascual-Leone A. Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. Nat Neurosci 2001;4:953–7.
[37] Oliveri M, Caltagirone C, Filippi MM, Traversa R, Cicinelli P, Pasqualetti P, et al. Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex. J Physiol 2000;529:461–8.
[38] Dehaene S, Piazza M, Pinel P, Cohen L. Three parietal circuits for number processing. Cogn Neuropsychol 2003;20:487–506.
[39] Van Opstal F, Fias W, Peigneux P, Verguts T. The neural representation of extensively trained ordered sequences. Neuroimage 2009;47:367–75.
[40] Van Opstal F, Verguts T, Orban GA, Fias W. A hippocampal–parietal network for learning an ordered sequence. Neuroimage 2008;40:333–41.
[41] Hirnstein M, Bayer U, Ellison A, Hausmann M. TMS over the left angular gyrus impairs the ability to discriminate left from right. Neuropsychologia 2011;49: 29–33.