

## Chapter 32

# Mapping the Brain for Math

*reversible inactivation by direct cortical electrostimulation  
and transcranial stimulation*

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### Introduction

In the study of mathematical functions, as in other domains within human cognitive neuroscience, traditional anatomo-clinical correlation, electrophysiology, and various, more or less advanced, methods of neuroimaging have been complemented by different localization methods aimed at seeking for converging evidence. These methods include Transcranial Magnetic Stimulation (TMS) and intraoperative DCE. These two methods, while very different in several respects, share the property of deactivating brain functions safely and, crucially, in a quickly reversible way.

Intraoperative DCE is a very powerful method for investigating the location of brain functions (Duffau et al. 2008; Mandonnet et al. 2010). Brain mapping conducted with this method offers tremendous clinical value. Particularly when operating in the dominant hemisphere, it helps to limit the risk of personal and professional disturbances caused by acquired cognitive disorders in patients undergoing surgery for brain tumors or epilepsy. The purpose of this procedure is to gather precise information about the brain localization of functions that must be spared while removing tissues affected by pathology. Therefore, when possible (unfortunately, in a limited number of cases), neurosurgeons check the functions that they know might depend upon the area that is being operated. They do this by applying electrodes directly to the cortex, after removing part of the skull bone under local anesthesia. Because the brain lacks pain receptors, it is possible for the patient to be alert during the operation in order to interact with the operating team. He or she will commit errors in tasks sustained by stimulated areas, revealing the location of these certain functions. These areas will be spared in the operation, when possible. Despite several limitations (Duffau 2011; Karnath and Steinbach, 2011; Shallice and Skrap, 2011; Borchers et al. and 2012), this methodology seems to provide surprisingly consistent results. DCE is most often used in order to preserve sensory processing, motor functions, and speech. Only recently have mathematical skills received some attention in this respect. There are very good reasons to expect further research in this particular domain, however. The parietal areas have been singled out as critical for number and calculation skills since the first clinical studies on acquired calculation disorders (e.g., Henschen 1919; Hecaen et al. 1961). Mathematical functions in the parietal lobe have been further investigated and understood by means of neuroimaging, showing that numerical tasks involve a distributed network of areas, including the frontal cortex and left and right parietal lobes (e.g., Dehaene et al. 2003; Pinel et al. 2004; Eger et al. 2003; Cantlon et al. 2006; Ansari et al. 2006; Price et al. 2007; Emerson and Cantlon 2012). Neurosurgeons, therefore, need to take these findings into account in their intraoperative procedures. A safe surgery in the parietal areas must include proper testing of number processing and calculation. They must want, in fact, to limit damage to functions that are important in everyday life. Researchers in cognitive neuroscience can also benefit from findings with direct cortical stimulation. As argued in this chapter, these findings are not only interesting insofar as the method allows for direct interference with brain activity that can be quickly reversed. Additionally, a reasoned comparison with findings obtained using other techniques, such as TMS, may provide valuable insights, potentially leading to significant progress in the field.

Like DCE, TMS complements neuroimaging with causality. The question is whether all of the regions identified with functional neuroimaging are necessary for the performance of a given

task (Robertson et al. 2003; Walsh and Cowey 2000). Essentially, fMRI findings reflect correlations between brain activations and a functional hypothesis in the experimental design. The fact that an fMRI study shows activations in a certain area does not imply that the area is crucial for a specific function. The basic idea of most TMS experiments is that if the temporary disruption of a brain area impacts accuracy and/or reaction times in a task or experimental condition, then this area is considered critical for the function behind the task. In other words, TMS is employed to test whether or not a region in which change in neural activity is associated with a given task is also *necessary* for the performance of this task. TMS has, thus, been used in the investigation of areas that have previously been linked with number processing, with the goal of determining their necessity for certain mathematical functions. Given the amount of neuroimaging evidence suggesting that core number representations reside in the intraparietal sulcus (IPS), the goal was to determine the essentiality of the IPS in core magnitude processing. Another important area of focus has been determining which brain areas are behind space-number relations, and just a few works have been dedicated to the mapping of calculation. While TMS and DCE have been used for the temporary disruption of brain activity, a pair of recent studies employed another non-invasive stimulation technique, Transcranial Direct Current Stimulation (TDCS) (Utz et al. 2010), to improve numerical competence (Cohen Kadosh et al. 2010b; Iuculano and Cohen Kadosh 2013). TDCS consists of the delivery of a constant, low current (e.g. 1–2 mA). Saline-soaked surface electrodes supply the current through the anodal or cathodal end. Depending on the direction of the current, the effect is enhancing cortical functions (anodal) or temporarily disrupting cortical function (cathodal). The effects of TDCS are persistent due to modifications in postsynaptic connectivity. In the study by Cohen Kadosh et al. (2010b), anodal stimulation led to a specific improvement in the learning of artificial number symbols during anodal TDCS excitation of the right parietal lobe. The improvement was manifested in adult like numerical effects (linearization in quantity representation and numerical Stroop effects). In a recent study (Iuculano and Cohen Kadosh 2013), adult participants were administered TDCS on the posterior parietal cortex (PPC) and over the dorsolateral prefrontal cortex (DLPFC) areas, which are believed to be used in numerical understanding and learning, respectively. The authors showed a double dissociation: stimulation over PPC led to a better and faster overall learning of a new numerical notation, while automaticity, as measured by a numerical Stroop task, was impaired; stimulation over DLPFC enhanced automaticity while impairing numerical learning. Still another study (Snowball et al. 2013), combined near-infrared spectroscopy (NIRS) with transcranial random noise stimulation (TRNS). TRNS is a technique that alters cortical excitability in a polarity-dependent manner, in which an alternating current is applied over the cortex at random frequencies (see Terney et al. 2008 for an introduction to TRNS). Snowball and colleagues found that TRNS increased the learning rate for calculation and drill learning and decreased RTs for drill learning. Stimulation also had an effect on the amplitude and timing of the haemodynamic response. Behavioral and neurophysiological effects for calculation were still present in a follow-up test conducted six months later. This approach complements TMS and DCE, and, importantly, extends brain mapping to the treatment of numerical processing anomalies.

In what follows, we will report the (so far) relatively limited amount of work conducted with TMS and DCE methodologies in the mapping of brain for math, in an effort to understand the most robust findings and whether a direct comparison between the obtained results could lead to valuable conclusions and a significant advancement of research in this area.

## Transcranial Magnetic Stimulation

TMS is based upon Faraday's principles of electromagnetic induction: an electrical current produces a magnetic field, and changing magnetic fields induce a secondary electric current in nearby conductors, such as human tissue. A TMS stimulator delivers a fast and large current that produces a magnetic field for about a millisecond. The magnetic field passes through the scalp and skull, inducing an electrical field sufficient to alter neuronal activity. A single pulse of TMS can modulate neurons up to a few hundred milliseconds. Different coil types exist, with changes in their focality and the depth of the effect. For example, a figure-of-eight coil targets an area about 1–2 cm<sup>2</sup> of cortex under the junction. It must be noted, however, that while TMS stimulates a particular cortical area, the effect is not restricted to that area. Even with the most focal coils, changes in activity can spread through several centimeters, and affect distant brain regions that

are connected to the stimulated brain region (e.g. Ruff et al. 2006). Additional sources of variability in a TMS design come from the intensity, frequency, duration, and time point of stimulation, as well as the actual TMS paradigm and site localization method. When cognitive functions are under study, the location and timing of stimulation is determined using other brain imaging techniques (ERPs, MEG, PET, or fMRI). In a less precise approach, the researcher can use the 10–20 EEG positions, for example using P3 and P4 sites). Another way to carry out a functional search would be to apply TMS on proximal sites until maximum effects on related tasks (i.e. a visual search) are achieved, and then marking the relevant sites on MRI scans. But perhaps the most powerful way of localizing a site, for either an individual or a group, is to obtain an MRI for each subject and localize coordinates of interest. These coordinates can come from a previous fMRI study on the same participants, from similar fMRI studies on different participants or from a meta-analysis. During TMS application, frameless stereotaxic systems permit the on-line interactive navigation of the site of interest in the individual T1, allowing researchers to monitor the position of the coil during the experiment. When individual T1s are not available, a template image can also be used. Finally, the chosen intensity for stimulation can be fixed, or based on individual motor threshold (minimum intensity needed to generate visible hand movements or motor evoked potentials when stimulating primary motor cortex) or phosphene threshold (minimum intensity needed to generate stationary or moving phosphene perception when stimulating V1 or V5), albeit the correlation between these parameters is questionable (Stewart et al. 2001).

Magnetic stimulation can be applied in single pulse (spTMS) or repetitive pulse mode (rTMS). With spTMS, a single pulse is applied at a specific point in time. In rTMS, stimulation is delivered as a train of pulses of variable frequency, up to 50 Hz and for tens, hundreds, or thousands of ms. Thus, spTMS provides a good temporal resolution, which is useful when the experimenter knows when a certain process should occur. When used to disrupt performance, cognitive processes are better targeted with rTMS to produce an increase in errors and longer-lasting effects; however, when other dependent measures other than errors (i.e. RTs) are considered, spTMS can be successfully used in the study of cognition. Theta burst stimulation (TBS) is a form of rTMS in which brief trains of pulses are delivered at 5 Hz (theta frequency). One advantage of this technique is that the effect of 20 seconds of stimulation has been shown to last for 20 minutes. In turn, when TMS is used to disrupt the function of a targeted cortical site through a 'virtual brain lesion', information about the *where* and the *when* of that function can be obtained.

TMS designs require different means in order to assure specificity. Firstly, control tasks are required whose functions are not altered when a target area is stimulated, in contrast to the function of study. Secondly, control sites are required, the stimulation of which does not result in any change of the target function. Finally, a double dissociation can also be targeted: when Site 1 is stimulated, Task A is altered, but not Task B, whereas when Site 2 is stimulated, Task A is spared, and Task B is altered. Proximity can also be explored by stimulating proximal areas, thus possibly circumscribing effects to the target site. Dissociations in time are also possible: the role of functional areas can be explored through, for example, the inclusion of several Stimulus Onset Asynchronies (SOAs) for the pulse. This allows any differential effects at different time points to be detected. Finally, this technique can differentially affect functionally distinct neural populations, depending on their initial state of activity. This fact can be incorporated into the experimental design (state dependent TMS), greatly enhancing its functional specificity. As such, TMS is a very versatile technique, which has more to offer than simply 'disrupting site X alters function Y'. (More extensive reviews on the use of TMS in cognitive neuroscience can be found in Walsh and Rushworth 1999; Walsh and Cowey 2000; Pascual-Leone et al. 2000; Sandrini et al. 2011.)

## TMS in The Study of Quantity

A number of studies have used TMS to investigate the crucial areas for number quantity processing, and almost all of them have focused on whether left and/or right parietal areas are crucial for quantity. While more convergence is being found among experiments into the link between space and numbers, lateralization for the processing of magnitude has not yielded such consistent results. There is now little doubt that the IPS is a locus for quantity processing: findings from fMRI (where bilateral IPS activations are found—see Dehaene et al. 2003), patient data (e.g. Cipolotti et al. 1991; Dehaene and Cohen 1991), physiological studies in monkeys (e.g. Nieder and Miller 2004), or studies in developmental dyscalculia (Price et al. 2007; Rotzer et al.

2008) all converge to support this. Divergence arises between (and within) TMS and fMRI research with regard to the differential involvement of the left and right IPS.

It is important to note that, apart from necessary differences in experimental paradigms, the above-mentioned TMS versatility is also found in the study of math cognition. Studies vary in site localization procedures, if participants' MRIs, or an initial fMRI, are not available, the use of a stereotactic system with a template image may not take into account the variability across subjects (Sack et al. 2009). On the other hand, the task used in a previous fMRI experiment should be measuring very similar processes to the process under study (i.e. distance or size effects and not just activations to a number comparison task). The selection of a stimulation pattern differs across studies (e.g. single pulse, repetitive—and Hz—triple pulse TMS, theta burst stimulation) and so does TMS effect. Selection of timing parameters often varies, as well: for example, SOAs are often used for single pulse or for the time locking of rTMS or TBS in relation to the stimuli. These are sources of variability that can explain discrepancies of findings. For these reasons, a correct approach might be to reconcile the positive results from the different studies. It is important to observe in which of these works the distance effect (by which faster and more accurate responses occur when comparing two numbers, if the numerical distance separating them is relatively large) or other effects that stem from the numerical representations are impaired (i.e. disturbing a certain site of interest with a higher cost for closer numerosities would be the relevant outcome if one wants to show that magnitude processing has been targeted). Otherwise, a delay in RTs or decrease in accuracy could result from processes that occur earlier or later than the access to magnitude. In any case, the number comparison is generally taken as a task that activates the quantity code. However, only some of the studies below have based their choice of the pulse timing on the available ERP studies that had shown distance effects of around 200 ms (Libertus et al. 2007; Dehaene 1996; Pinel et al. 2001; Turconi et al, 2004). ERP effects may certainly occur later than the optimal time of choice in a TMS design (Walsh and Rushworth 1999), but when single neuron studies in monkeys, more accurate in timing (e.g. Ashbridge et al. 1997), are not available with comparable experimental designs, ERP effects can orient the TMS starting point and duration.

The first study that used magnitude comparison was the carried out by Göbel et al. (2001). They showed delayed comparison times between a reference number (65) and two-digit numbers under rTMS stimulation of both the left and right angular gyrus (AG), but only a stronger effect for closer distances for numbers larger than the reference 65 in the left AG was shown.

Sandrini et al. (2004) used rTMS on the inferior parietal lobule (IPL) during a comparison between two single-digit numbers presented at the same time. Stimulation started during the presentation of digits and lasted 225 ms. They used sham stimulation as a comparison and the supramarginal gyrus as the control site. They found a general interference from the left IPL stimulation and no interaction with distance. The authors considered the possibility of having interfered before the magnitude was accessed—in turn, this would slow down the processing sequence from input to number semantics.

Andres et al. (2005) stimulated the posterior parietal cortex (PPC) using spTMS (150, 200, 250 ms after stimulus onset) on either one hemisphere or both (double pulse). They used sham stimulation as a comparison. Participants were required to compare one-digit numbers to the reference (5). Interestingly, a comparison of close distances was disrupted after bilateral and left PPC stimulation. A comparison on far distances was delayed only after bilateral PPC stimulation. The authors explain these effects as reflecting a fine discrimination in the left PPC, whereas each hemisphere could be able to perform the task by itself. There is, nevertheless, a stronger predominance of the left PPC in this study, as the sole stimulation of the right PPC produced no effect on far or close distances.

The only TMS study that uses non-symbolic stimuli (Cappelletti et al. 2007) explored the possible difference between symbolic and non-symbolic quantity processing using a comparison task between two-digit numerosities and a reference (65). They applied rTMS for 10 min before each task. TMS was delivered to the left and right IPS and the AG as a control site, in a between-subjects design for site vs. sham stimulation. They used a control task in which the orientation of ellipses had to be judged. The results showed left IPS involvement both in symbolic and non-symbolic comparisons. These effects were modulated by numerical distance with greater impairment for close numbers. Facilitation emerged after stimulation of the right IPS. The authors concluded that the left IPS is crucial both for symbolic and non-symbolic comparisons. In a recent study, Sasanguie et al. (in press) investigated the role of right and left IPS in the processing of symbolic and non-symbolic magnitude using rTMS. They used sham stimulation

as control and selected the targeted sites based on the average activation reflecting a distance effect in the same paradigm from a previous study (Notebaert et al. 2011). A priming paradigm was used in two experiments and stimulation was delivered on the presentation of the prime. Participants had to compare the second number of a pair to a reference 5. In a first experiment primes and targets were symbolic numerosities (Arabic or verbal). In a second experiment, primes and targets were symbolic and non-symbolic numerosities (dots or Arabic digits). The results showed that stimulation to right or left IPS was not enough to reduce the priming distance effect (PDE) between two symbolic numerosities. In contrast, left IPS stimulation tended to reduce the PDE between symbolic and non-symbolic numerosities. The authors conclude that the left hemisphere has a crucial role in the mapping between symbols and quantities. These data also reflect a differential brain basis in the processing of symbolic and non-symbolic magnitude.

A new approach to the study of magnitude with TMS was taken by Cohen Kadosh and collaborators (Cohen Kadosh et al. 2007; Cohen Kadosh et al. 2012). They used a size-congruity paradigm (numerical Stroop task) and asked subjects to attend to the physical size of a pair of digits while ignoring their numerical value, or in different blocks to attend the numerical value and ignore the physical size. Healthy participants, unlike dyscalculic participants, are faster in judging congruent trials (i.e. the numerical value matches the physical dimension (e.g. 2 4)), than in judging incongruent trials (e.g. 2 2). The authors used event-related triple pulse TMS to simulate dyscalculic-like behavior by disrupting right or left IPS in healthy participants. Another group of dyscalculics underwent the same paradigm without TMS. The results showed that healthy participants under sham stimulation and stimulation on right IPS or left IPS, as well as the dyscalculic group, all showed a cost in RTs for incongruent trials in comparison to neutral trials (e.g. 2 2) (interference). However, only after sham and left IPS stimulation, the facilitation effect (faster RTs for congruent compared to neutral) appeared. The facilitation effect was absent after right IPS stimulation and in the dyscalculic group. The authors concluded that the right IPS is crucial for the automatic, task-irrelevant processing of magnitude. More recently, Cohen Kadosh et al. (2012) provided the results from the other part of the task. They analyzed trials wherein healthy participants were requested to judge the numerical value of the number pairs, while ignoring the physical sizes of these pairs—that is, a number comparison task where the processing of magnitude was intentional. The results paralleled those of automatic processing: distance effects were significantly reduced after right IPS stimulation compared to sham and left IPS stimulation. No effect was found for physical size comparison in these sites. Thus, the study also implies some conclusions about the contrast between physical and a numerical magnitude: namely, that they might at least partially overlap in right IPS. The computation of congruency between physical and numerical magnitude appeared to rely on the right IPS, a site that was revealed to compute numerical distance during that size-congruity paradigm.

## Numerical and Non-Numerical Quantities

Recent studies explicitly explore different types of non-numerical magnitude with the aim of dissociating or finding common neural substrates. It has been assumed that the adult brain has a *partially* shared magnitude system for time, space, and numbers (Walsh 2003). More generally, the parietal lobe could work within a broader network of areas that are involved in non-numerical magnitude representations (Fink et al. 2000; Pinel et al. 2004; Dormal et al. 2010; Holloway et al. 2010; see Cohen Kadosh et al. 2008 for a review). The few TMS studies addressing this issue—described below—have shown both overlap and dissociations between numeracy and non-numerical magnitude tasks (e.g. length, duration, time, categorical, and order information).

Dormal et al. (2008) tested this possible neural overlap in IPS by asking participants to compare the *duration* between flashed single dots in one task. In another task, participants judged the difference in numerosity of groups of flashing dots presented for a fixed interval. These tasks were performed prior to and after the application of one Hz rTMS for 15 minutes. The sites for stimulation were left or right IPS, and vertex was chosen as the control site, based on T1-weighted MRIs and using a frameless stereotactic system. The results showed a disruption of the numerosity task for close numerosities, after disrupting the left IPS. Specifically, RTs were always faster after rTMS application except after left IPS stimulation, for close numerosities, both compared to large distances and to vertex stimulation. Some facilitation was found (i.e. the fastest second block RTs) for the left IPS in duration processing, but this facilitation was not

statistically significant. The authors concluded that there is at least one cerebral site wherein numerosity and duration processing dissociate.

Similarly, a recent study by Dormal et al. (2012) studied a possible overlap between the discrimination of *length* and numerosities in the IPS. The tasks for the TMS study were, again, comparable tasks that implied different functions: arrays with different numbers of dots constant in length, to which the participant had to give either a 'few' or 'many' response, compared with a continuous rectangle that varied in length, to which the participant had to give a 'short' or 'long' response. Therefore, a numerical vs. non-numerical size effect, was evaluated for the two dimensions, instead of a distance effect. rTMS was applied to the right or the left IPS. For localization, the study used another fMRI study (Dormal and Pesenti 2009). The IPS coordinates for stimulation were individually determined by subtracting the activations to a color detection task from those obtained by a numerosity task. Average coordinates were similar to the averages used in Dormal et al.'s study (2008), although standard deviations, especially in the left hemisphere, were twice as much. Vertex stimulation was used as the control site. The results showed significant disruption for numerosity *and* length processing after right IPS stimulation. Nevertheless, and although left IPS disruptive effect showed a tendency to differ from the vertex condition, this tendency was not significant. The authors concluded that the integrity of the right IPS is necessary both in numerosity and in length discrimination.

In an extensive study, Cappelletti et al. (2009) contrasted the crucial role of IPS in the processing of numerical quantity and *quantity processing with non-numerical stimuli*. Participants had to: (1) compare the magnitude of two numbers (e.g. 12.07 vs. 15.02) in a numerical quantitative task; (2) decide which of two dates referred to a summer month or to time (12.07 vs. 15.02 or time 11.01 vs. 12.06) in a numerical non-quantitative task; (3) decide which of two objects was larger (bikini vs. coat) in a categorical quantitative task; (4) decide whether an object was a summer object or not (bikini vs. coat) in a categorical non-quantitative task. As control tasks, the authors manipulated the color of the two types of stimuli, and a judgment of color was requested. A similar fMRI study identified the stimulation IPS sites as the common areas for the quantitative task on numbers and the quantitative task on object names (Cappelletti et al. 2010). A unique area in the left and right IPS was stimulated with 10 Hz rTMS for 500 ms at stimulus onset. Sham stimulation was used on the same areas as control sites. Results showed that quantitative and non-quantitative tasks on digits (e.g. numbers and months) were impaired after left or right IPS stimulation, with larger disruption after left IPS stimulation only during numerical comparison. Judgments on objects were disrupted after left or right IPS stimulation, but only when the task was quantitative (e.g. in determining which is the larger object). Again, disruption was larger after left IPS stimulation, in comparison to right IPS stimulation. No effects were found in the perceptual task on color. Importantly, only judgments of time implied larger impairment for close distances. A main effect of distance (but no site by distance interaction) appeared in the rest of conditions. No main effect or interaction implying distance was found in the color judgment task on objects or numbers. The authors concluded that bilateral IPS is crucial in performing quantitative or non-quantitative conceptual operations with numbers, as well as that these areas are crucial for quantity processing of numbers or objects. However, IPS is not critical in perceptual decisions based on numbers or in conceptual tasks not involving quantity in non-numerical stimuli.

In a recent study, Cheng et al. (2012) contrasted the role of IPS for *order vs. quantity processing*. They applied TBS for 20 seconds on right and left IPS and vertex for five minutes, then order and quantity tasks were performed. In the order task, a line of Xs and digits in either correct (XXX3XX4X) or incorrect order (XXX4XX3X) was presented, and a judgment on the correctness of the order was given. Numbers and Xs were always in two different colors; thus, a numerical task on the same stimuli consisted of judging which of the colors contained more Xs. After left IPS stimulation, a disruptive effect was shown for the quantity task, while the order task showed a facilitatory effect, with respect to sham stimulation. Neither the right IPS nor the vertex appeared as crucial for these tasks. The authors interpreted the results as evidence for, at least, partially different neuronal populations involved in order and quantity processing.

## Use of Fingers during Early Arithmetic

The importance of fingers as an aid in the early stages of arithmetic is something evident. It is perhaps not a coincidence that the ten fingers have left us with a base ten system for math (see Andres and Pesenti, this volume). But have they left a trace in our brain? The skilled use of fingers has been found to be a predictor of math achievement (Fayol et al. 1998). The presence of Gerstmann syndrome (Gerstmann 1940) after a lesion in the left AG has been taken as evidence of an association between finger gnosis and numeracy (Butterworth 1999). Some TMS studies have examined this association in the posterior parietal lobe. Rusconi et al. (2005) used a magnitude matching task with related or unrelated primes. Five hundred ms of 10 Hz rTMS to the left AG impaired magnitude judgment in numbers with unrelated primes. Identification of hand finger after opposite finger stimulation also impaired after bilateral AG stimulation. Thus, the authors suggested that an association existed between finger and number tasks in the left AG, demonstrating a relationship in the left AG between numbers and body knowledge in skilled adults who no longer use their fingers for solving simple arithmetical tasks. Sato et al. (2007) showed increased amplitude in motor-evoked potentials for the right hand muscles specific for smaller numbers, suggesting a close relationship between hand and finger numerical representations.

In conclusion, all of the reported TMS studies have found sites surrounding the IPS as crucial for the representation or manipulation of magnitude. Many succeed in finding a larger disruption in the comparison between close numbers (i.e. disruption of the distance effect). Thus, taking into account all of the positive effects, the described research supports the idea that left and right IPS are crucial for magnitude processing. Figure 32.1 and Table 32.1 display brain sites that have been shown to be involved in the processing of quantity in the above described studies, with a focus on effects related to magnitude processing (i.e. distance or size effects disrupted). More recurrently, findings showed left IPS involvement in magnitude, which was often related to distance effects. On the other hand, an explanation of the divergences between studies should be found in a dissection of TMS parameters (including site localization), task and stimuli, overall design, etc. In both the studies of Cohen Kadosh et al. (2007) and Dormal et al. (2012), the only two studies that do not show left IPS as critical, size is used as a dimension in their tasks. The study of Cappelletti et al. (2009) implies a much more complex numerical decoding than the rest, and again, uses size, albeit representational.

More TMS studies are needed in order to understand the necessary areas for non-numerical quantities and their possible overlap with numerical quantities. They should use different tasks, implying the same non-numerical dimensions. Overall, it appears that

**Figure 32.1** Reported brain sites whose stimulation through TMS has led to disruption in *quantity*. More overlap or sites with effect are found in left parietal areas. When Talairach coordinates had been reported, they were transformed to MNI coordinates. A sphere of a 5.25 mm radius and MNI coordinates as center was generated (Table 32.1). *Left*: General distribution of sites; yellow means overlap between the loci with effects in two or more experiments. *Right*: A different color is assigned to the locus/loci with effect for each experiment.

both overlaps or dissociations can be found, but why, in which tasks (i.e. processes), and why some dimensions show overlap while others do not, needs of further research. On the other hand, although being valuable in the study of crucial areas, the study of the overlapped vs. separate numerical and non-numerical dimensions using TMS is faced with the question of the inherent monolithic TMS effect. Because the hypothesis is about a partiality of overlap, no study showing dissociation between numerical and non-numerical areas will exclude the possibility that they can also overlap. In fact, as it is acknowledged in these studies (Dormal et al. 2008; Cheng et al. 2012), the most that can be stated is that there is at least a site where those representations dissociate. In this sense, special care has to be taken with focality and with the variability in the targeted brain locus. As an example, the overlap between length and numerosity found by Dormal et al. (2012) might be explained by the variability in the exact site location across subjects. Ideally, studies should look for loci that double dissociate, showing overlap and separation in the same study, depending on the chosen brain locus. It is possible that the best way for the study of this issue would be the use of state-dependent TMS (Silvanto et al. 2008). As an example, putative neurons for one dimension could be adapted. If behavior on the deviant

values of the same vs. a different dimension does not change after stimulation of Site A, then overlapped representations would have been detected. On the contrary, if after stimulating Site B, behavior to the deviant differed between the adapted vs. non-adapted dimension, then TMS would have detected an overlapped but distinct neural population for the two dimensions. Variations in proximity along parietal areas could be added to the design. Cohen Kadosh et al. (2010a) used this TMS adaptation paradigm for the study of format dependencies vs. number-specific parietal neurons. Segregated neurons for digits vs. verbal formats were found in the left IPS, but not in the right IPS. In turn, state-dependent use of TMS allows for the study of the functional role of distinct neural populations, an approach that should be fruitful in the study of the neural locus of numerical and non-numerical magnitude.

## Space in Numbers

Many mathematicians report the intuition of using space in the manipulation of numerical concepts, and space is explicit in the use of math concepts many times. Spatial components in mathematics have, thus, a role in the curricula (e.g., using blocks or the mental number line (MNL) to introduce calculation or numerical concepts to first-learners). Cohen Kadosh and Gertner (2010) offer an explanation of this link between numbers and space (including time) in terms of synesthesia. The association is implicit for most people, as a sort of lower synesthetic proficiency, whereas number-space synesthetes vividly experience explicit associations between time, space and number in a sort of over-binding (Robertson 2003). Up to one out of five people experience this form of synesthesia consciously, but it is implicit for the rest of the population (Sagiv et al. 2006; Cohen Kadosh and Henik 2007). Nevertheless, the exact nature of the relationship between numbers and space, and the origin of this relationship are still unknown. It could be that it emerges over the course of education, giving rise to a MNL, but the representation of numbers could be intrinsically spatial (Dehaene 1997; Walsh 2003). In any event, a link between space and numbers is shown in many studies, even in congenitally blind participants (Castronovo and Seron 2007; Salillas et al. 2009, see Castronovo, this volume). Empirically, the spatial characteristic of numbers is almost always addressed through the study of the so-called 'MNL'. In this MNL, numbers have been proposed to be represented along a horizontal left-to-right oriented mental line, with small numbers on its left and high numbers on its right portion (see van Dijck et al., this volume). A first index for this MNL was the Spatial Numerical Association of Response Codes (SNARC) effect, by which small numbers are responded to more quickly with a left lateralized response, and large numbers are responded to more quickly with a right lateralized response (Dehaene et al. 1993). However, other effects, which include a link between numbers and space in their explanation, have been reported since then. For example, Fischer and colleagues (Fischer et al. 2003) attained the orienting of spatial attention by the central presentation of numbers, and Calabria and Rossetti (2005) showed that a biased number strings bisection to the right or left, depending on the number repeated in a string. Even the visual field in which a number is presented determines the speed of response, with a preference for small numbers in the left visual field and large numbers in the right visual field (Lavidor et al. 2004).

Neuropsychological studies show a relation between number and space: Gerstmann's syndrome involves dyscalculia, spatial problems, finger agnosia, and dysgraphia, while hemispatial neglect patients show a bias in the bisection of number intervals, just as they show in line bisection (Zorzi et al. 2002; Vuilleumier et al. ), which implies the use of a MNL in a representational side of neglect (but see Fias et al. 2010).

In a review about the space-number relationship, Hubbard et al. (2005) identified human homologues of spatial cognition areas in monkeys. They proposed that numerical-spatial interactions arise from common parietal circuits for attention to external space and internal numerical representations. Nonetheless, the main approach to the study of the brain basis of the space and number link has been through the use of MNL. Using TMS, the approach has been diverse: from findings that relate to MNL in number comparison tasks to direct tackling of the MNL through the study of the number bisection or spatial priming by numbers. Last, studies have extended their target areas to the frontal lobe, and others have incorporated motion perception as a part of the spatial quality of numbers. rTMS, spTMS, or triple pulse TMS has been used in the study of the MNL, but the exact timing for the studies was not inferred from previous ERPs studies.

As mentioned earlier, Göbel and collaborators (2001) used a number comparison to a reference number (65) while stimulating left and right AG with the supramarginal gyrus as the control site. Sites were studied as between-subjects variables. The parietal site at which the rTMS was delivered was identified through a visual search task. The authors found a greater disruption with rTMS over left AG for numbers greater than 65, which was even larger for numbers closer to the standard. rTMS over right AG disrupted the comparison of numbers larger and smaller than 65. The distance effect was not affected by stimulation. The authors concluded that within the left AG, the representation of numbers appears to be spatial in nature, differing from the right AG. Attention over the MNL has been studied through biases in the bisection of lines occurring in pseudoneglect or hemispatial neglect (Zorzi et al. 2002, Rossetti et al. 2004). The anatomical basis of this approach was explored by Göbel et al. (2006a). The focus was on attention over a mental spatial representation—the MNL, rather than on the representation, per se. Given auditory number intervals (e.g. 117 166), participants were asked to provide the center of that interval without calculating. Left AG/adjacent posterior part of left and right IPS were stimulated with rTMS. The central occipital cortex was used as a control site, and trials without TMS were used as a control task. Interestingly, no significant disruption was found in the RTs, but bisection errors appeared: a systematic right displacement of the center (i.e. correction of pseudo-neglect in control trials) was found after right PPC stimulation. Although based, again, in a between-subjects comparison, this pseudo-neglect correction also seemed to appear after left PPC stimulation, compared to the control site. In any case, the effect after the right PPC stimulation was, indeed, larger. The authors concluded that the right PPC is crucially involved in the spatial representation of numbers.

The presentation of numbers has been shown to bias attention in space depending on their position in the MNL. Fischer and collaborators (2003) showed that the simple central presentation of a small number entails a faster detection of targets in the left visual field, and the presentation of a large number implies faster detection times of targets in the right visual field. This is something that could be taken as spatial priming by numbers. The critical brain basis of this effect was studied with a triple pulse TMS on the left and right AG by Cattaneo et al. (2009a). Cattaneo et al. (2009a) presented large or small numbers and subsequently asked participants to report the longer side of a bisected line. Trials with asterisks, instead of numbers and trials without TMS, served as controls. Without TMS, higher accuracy in 'left side is longer' responses after small numbers, and higher accuracy in 'right side is longer' responses after large numbers were reported. They stimulated during the interval between the prime and the line, and they found that when the number was small, a right AG stimulation made the higher rate of accuracy for 'left side is longer' disappear. For large number primes and after stimulation of the left AG, the higher rate of accuracy for 'right side is longer' disappeared. Right AG also had an effect with large number primes, with lower accuracy for 'right side is longer' responses. The authors explained the results by conventional attention accounts (e.g. right hemisphere processes information from both hemifield and left hemisphere processes information from the right hemifield only (Mesulam 1981)). As for the number domain, the authors explain the results as the AG being part of a network that mediates the impact of the MNL on visuospatial representations, rather than implying number processing, per se. The same network includes the visual cortex (V3, V4), as demonstrated by the effects of presentation of numbers from the low or high end of the MNL on visual cortex excitability. Namely, Cattaneo et al. (2009b) showed that small numbers increased the proportion of trials, on which phosphenes were induced from stimulating the right visual cortex. High numbers decreased the proportion of trials on which phosphenes were induced from stimulating the right visual cortex. The opposite pattern of effects was found during the stimulation of the left visual cortex. In turn, as the authors pointed out, the numbers magnitude modulates spatial attention; subsequently, these shifts induce changes in the excitability of both the left and right visual cortex.

The SNARC effect has been studied using TMS disruption, both within and outside of the parietal lobe. Rusconi et al. (2007) studied possible dissociations between the SNARC and Simon effects in the posterior parietal lobe (PPL), finding that the bilateral posterior part of PPL had a causal role in the SNARC effect. In a parity task to numbers 1 to 9, presented lateralized to fixation, they found that the SNARC effect was reduced after posterior, but not anterior, rTMS. The Simon effect was reduced after anterior and posterior PPL stimulation. More recently, Rusconi et al. (2011) compared two tasks that differed in the relevance of number magnitude. Areas in the frontal lobe responsible for visual scene analysis and visual conjunction (right frontal eye fields—FEF—and right inferior frontal gyrus—rIFG) were critical for the SNARC effect only for number

comparison, where number magnitude is relevant, but not for a parity task, for which number magnitude is irrelevant. The authors explained the data as frontal regions, added to the parietal circuits as crucial for the representation and orienting to number space in humans. Besides, rFEF and rFIG rTMS effects were correlated, suggesting a common cognitive mechanism.

Another area in the PPC related to the perception of motion, but not space, has been studied using TMS (Salillas et al. 2009). Numerical processes have been found within the dorsal pathway (Fias et al. 2001; Izard et al. 2008). Salillas and collaborators (2009) hypothesized that the areas in the PPC with a role in motion perception could be sub-serving attentional processes over the MNL in a similar way that attention to motion operates over other visual images. In fact, a link between motion perception and approximate arithmetic processing had been proposed, perhaps with quantitative rules analogous to those characterizing movement in an internal continuum (McCrink et al. 2007). The motion area selected by Salillas and collaborators was the ventral IPS (VIPS), located in the occipital part of the IPS and reported as being connected to other motion responsive areas, such as MT or V3a (Orban et al. 2006; Vanduffel et al. 2002). The area was far enough to other areas classically implied as quantity responsive (Figure 32.2 and Table 32.2). In separate blocks, participants (a) compared numbers to a reference (5), responding only to numbers higher than the reference, (b) responded to numbers lower than the reference, (c) detected rightward coherent motion on random dot kinetograms (RDKs) with different proportion of dots moving coherently, (d) or detected leftward motion on RDKs with different proportion of dots moving coherently. Stimuli were presented lateralized to a central fixation point, in the left visual field or in the right visual field (RVF, LVF) while the contralateral VIPS was stimulated. spTMS was delivered at the right or left VIPS with varying SOAs (100, 150, 200 ms) from the presentation of the number or the RDK. A control task consisted of the presentation

**Figure 32.2** Reported brain sites whose stimulation through TMS has led to disruption in *spatial-numerical processes*. Similar number of sites with effect was found in left and right parietal areas. Frontal areas show to have a role in spatial-numerical processes when the task is number comparison. Figure 32.2 was built as Figure 32.1. See Table 32.2 with the MNI coordinates for each study.

of shapes to which participants had to detect corners. The interhemispheric fissure, at the same Y and Z coordinates as VIPS, was used as control site. In the comparison task, results showed that at the shorter SOA, both right and left VIPS delayed RTs in responses to numbers higher than five. The effect remained at the 150 and 200 ms SOA, in the left VIPS/RVF only. Conversely, when responses to numbers lower than five were measured, a bigger disruption on the right VIPS/LVF was found at all SOAs, and only a tendency for the left VIPS/RVF was found at the shortest SOA. In the motion detection task, detection of coherent motion was slowed down when left or right VIPS was stimulated. Moreover, a displacement of the threshold (i.e. the proportion of coherent motion needed to clearly perceive it in more than 75% of the trials) was significantly increased when stimulating VIPS in comparison to central stimulation. The association between number comparison and sensitivity to motion coherence in random dot kinetograms was shown because of the impairment of both processes after the application of spTMS over VIPS. The authors concluded that bilateral VIPS was one of the possible areas within a functional network for the processing of quantity and that it was likely responsible for attention to motion over the MNL mental image continuum. Recently, another study by Renzi et al. (2011) used TMS-adaptation for the study of neuronal selectivity to quantity or motion in the PPC. In this study, adaptation was attained by the presentation of random dot kinetograms with coherent motion in rightward or leftward directions. Blocks of trials involving numerical magnitude judgment followed the adaptation blocks. The results showed that motion adaptation modulated in a direction-specific manner the initial state of neuronal representations causally involved in numerical magnitude judgments. This provided evidence for an overlap in neuronal representations of motion direction and numerical magnitude information. The exact nature of the link between attention to motion and number processes is not fully described to date. Nonetheless, and attending to the three described studies, commonalities between number manipulation and motion perception seems to occur in the space-in-time dimension. There might be processes entailing a moving focus of attention along space, which is what the perception of motion essentially entails from the perceiver. It also remains to be determined

whether the same mechanisms are behind arithmetic operations and number comparison or, in fact, if there is another common factor between quantity and approximate calculation (or even during exact calculation). It is worth noting here that Salillas et al. (2012) found right VIPS stimulation effects in exact multiplication facts (see below).

Overall, TMS studies succeed in demonstrating a link between numbers and space. They suggest spatio-numerical representations within parietal and frontal areas: bilateral posterior parietal sites, bilateral sites in the AG and right FEF and IFG, or even VIPS (Figure 32.2 and Table 32.2). The described research has remarkably extended the IPS mapping to more posterior sites (VIPS) and to frontal areas.

The main role of TMS is identifying the need of certain brain loci for certain functions.

Nonetheless, they must be put in a context of complex cognitive functions that imply functional segregation and integration of brain areas in time and possibly in hierarchies (e.g. Honey et al. 2007; Ioannides 2007; Varela et al. 2001). TMS studies have an important role in the study of the IPS within the mapping of numerical representations. Possibly, the use of TMS in math should also take connectivity into account. The goal would be to show double dissociations between processes, or even, ideally, within the same process at different time points. An example of such a functional connectivity fMRI study in the number domain is the recent work of Emerson and Cantlon (2012), which relates frontal and parietal areas during numerical tasks. spTMS at different time points in these two areas should distort behavior at different levels/times. As examples, two recent studies (Cohen Kadosh et al. 2011; Rusconi et al. 2013) have detailed functional numerical networks both within hemisphere, showing the contributions of rFEF and rIFG involvement in the SNARC effect using spTMS sampled between 0 and 400 ms (in Rusconi et al. 2013) and between the two parietal lobes, showing that the connectivity between both IPS is different depending on the numerical format (Cohen Kadosh et al. 2011).

## TMS in The Study of Calculation

The few TMS research that has been dedicated to explore calculation (Göbel et al. 2006b; Andres et al. 2011; Salillas et al. 2012) has addressed the question of lateralization, as it was proposed by the Triple Code Model (Dehaene et al. 2003). According to this model, the bilateral horizontal portion of the IPS (hIPS) is proposed to be the brain basis for the core quantity system; is active in mental arithmetic, numerical comparison, or subtraction; and is domain specific. The posterior superior parietal lobe (PSPL) is responsible for the attentional processes non-specific to the number domain (i.e. spatial attention and orienting). Finally, the left AG is part of a left-lateralized network, including also perisylvian and sub-cortical areas, and it is responsible for memory retrieval and exact calculation (i.e. number facts retrieval). The model states elsewhere (Dehaene et al. 2004) that the left AG network includes the left HIPS, however.

The studied operations through TMS have been addition (Göbel et al. 2006b; Salillas et al. 2012), subtraction (Andres et al. 2011), and multiplication (Andres et al. 2011; Salillas et al. 2012). The triple code model would predict that subtraction, which differs from addition and multiplication, is sub-served bilaterally. Exact multiplication and addition would, similarly, imply the language-dependent left lateralized network. Although the model was based

upon a compendium of some neuroimaging data, a discrepancy between the fMRI and TMS results emerged, similarly to what happens in quantity processing (see above). With the exception of Göbel et al. (2006a), the other two studies (Andres et al. 2011; Salillas et al. 2012) found the involvement of the bilateral hIPS in exact arithmetic.

Specifically, Göbel et al. (2006b) used additions that ranged from  $21 + 22$  to  $49 + 47$ , presenting the two numbers simultaneously. Then, participants had to judge whether a given solution was correct or not. The presented solution was always one unit larger or smaller than the correct solution to enforce exact calculation. 10 Hz rTMS was delivered on the left and right AG at the onset of the inter-stimulus interval until the response. The control site was the anterior IPL (supramarginal gyrus). Sites were chosen by TMS disruption in a visual search task. Although stimulation in the two sites on the left hemisphere produced a disruption in response latencies, the left AG stimulation had a non-significant tendency for greater disruption. No TMS effects were found in the problem size effect. Left hemisphere predominance was suggested for exact addition.

Using fMRI-guided rTMS, Andres and collaborators (2011) investigated the role of left hIPS in simple multiplication vs. PSPL in subtraction. Participants multiplied a digit by three or four, or subtracted a number from 11 or 13 in different blocks. Sites were determined from regions

showing increased activity in a subtraction and multiplication fMRI experiment by a conjunction analysis, obtaining coordinates in an individual basis. The vertex was used as a control site. Four 10 Hz rTMS pulse were delivered during 300 ms in each trial. Response latencies were slower after bilateral hIPS both in subtraction and multiplication in relation to the vertex condition. Multiplication errors in the verbal response increased after stimulation of hIPS, bilaterally. Interestingly, these effects were mainly operand-related errors (87%, i.e. the erroneous answer is a correct response for another problem which shares an operand, e.g.  $4 \times 8 = 24$ ), and a few table (the erroneous answer is a correct response for another problem but there is no operand shared; e.g.  $3 \times 8 = 28$ ) and non-table related errors (the erroneous answer is not a possible arithmetic response; e.g.  $4 \times 6 = 26$ ) appeared, suggesting that retrieval had been affected by bilateral stimulation.

Salillas and collaborators (2012) used spTMS with different SOAs (150, 200, 250, 300 ms) time-locked to the presentation of easy or hard addition and multiplication problems. Stimulation was delivered to right/left hIPS or right/left VIPS (Salillas et al. 2009) contralateral to lateralized problems. The interhemispheric fissure was used as a control site for measuring disruption. In a second experiment, ipsilateral stimulation was contrasted with stimulation delivered contralateral to the problem. The results of both experiments showed that addition and multiplication differed in hard problems: Addition involved bilateral hIPS, whereas multiplication relied on left hIPS but involved right VIPS in both experiments. Moreover, right VIPS disruption predicted problem size effects (note that the right VIPS in Salillas et al. 2008, 2012 has a similar location to Cohen Kadosh et al. 2007, 2012). Finally, the contrast between ipsilateral and contralateral stimulation along the different SOAs allowed to describe the temporal course for the involvement of the different sites: the left hIPS disruption appeared late in the 300 ms SOA, and it was preceded by an involvement of the right VIPS from 150 to 250 ms SOAs. The study, thus, provided a precise description of the hemispheric involvement in exact multiplication and suggested that multiplication is more verbally mediated than addition. Moreover, similar to Salillas et al. (2008), the results suggested that more occipital areas are likely involved in the automatic solution search and, in turn, that verbal and visuospatial processes interact in exact calculation.

**Figure 32.3** Scheme of the localization of calculation and language interference (reproduced from Figure 32.1 in Roux et al. 2009). Some of the areas overlapped and some were dissociated. C = number of specific calculation interferences found in the region tested; C + L = number of common calculation and language (naming and/or reading) interferences found; L = number of naming or reading interferences found (without calculation interference).

## Direct Cortical Electrostimulation

DCE entails the application of electrical stimulation on the cortical surface (see Duffau 2007 or Szelenyi et al. 2010 or Borchers et al. 2012, for a more extended introduction to methods). The use of a bipolar probe has become the standard method. In bipolar stimulation, when both anode and cathode electrodes are active, the structures located between the two electrodes are stimulated, receiving the maximum current density. Bipolar electrodes are usually spaced 5–10 mm and deliver current (60 Hz) for a duration of 1–4 ms at different intensities, depending, for example, on whether the patient is on local or general anesthesia. Preoperative imaging is often used to plan the operation. The specific electrode position can be tailored (Figures 32.3 and 32.4), in which case, the precise number of electrodes can be determined in the operating room. Sterile tags with numbers or letters on stimulation-positive spots helps the visualization of the cortical areas involved in the function. Electrodes can also come in linear arrays or in grids. More specifically, the required intensity entails a trade-off with the duration of the pulse, depending also on the fiber speed. The spatial resolution of DCE is five mm, which is how far the actual DCE diffuses. There are, as in other stimulation techniques, diffusions caused by physiological propagation—that is, the sub-circuits or networks to which the stimulated cortical tissue is connected. Ideally, concurrent electrophysiological recordings (through electrocorticography-ECOG) can

**Figure 32.4** Examples of two patients reproduced from Figure 32.1 in Roux et al. (2003) showing the proximity of different sites in left AG where Gerstmann symptoms were observed C = acalculia site; CN = color-naming procedure; F = finger agnosia site; G = Gerstmann symptoms; H = hesitation during object-naming, color-naming, or reading procedure; L = language mapping: object naming- or color naming-interference site; N = areas negative for functions tested in this study; R = reading—interference site; W = agraphia site.

measure the real physiological diffusion at the same time, which serves to monitor the excitability threshold in the avoidance of seizures. The topography of the tumor is delimited using a MRI, and functional neuroimaging can provide a first estimation of the location of the eloquent areas.

DCE has the advantage of not causing false negatives: eloquent structures with any role in a brain function that are disturbed by DCE will necessary induce a functional consequence. This is why, in the relative short time available for mapping, the assessed functions must be optimized. Nevertheless, a false negative would occur obviously, if the function was not included in the protocol or if the chosen intensity did not reach the excitability parameters of the tissue. DCE can cause false positives for different reasons: tiredness of the patient, partial seizures that look like positive effects, or by physiological spreading within a network that is wider than the tested area. Finally, DCE's positive effects cannot predict whether that function can be compensated, owing to brain plasticity. In fact, a tracking of postoperative outcomes is necessarily included in the protocols, with the aim of tracking the effects of surgery in a matching between intra-surgical positives and negatives and post-operative actual cognitive functioning.

## DCE in The Study of Calculation

A limited amount of studies conducted with DCE are available so far, and they will be summarized hereafter, grouped by the different goals of the studies reported. They all concern calculation and have dealt with the differentiation and overlap between operations within the left parietal lobe, but they have also attempted the study of the differing right and left hemispheres' roles on calculation. Given the tradition of testing the dominant hemisphere for language before operation, most of the studies were only focused on the left parietal lobe, and only three cases of right hemisphere stimulation are reported in the literature. Association and dissociation of Gerstmann syndrome symptoms in the left AG have also been reported. Stimulated sites through DCE have covered the AG and the IPS, and one study so far has studied the middle frontal gyrus.

## Dissociations Between Operations

In a first, single-patient investigation, Whalen et al. (1997) provided evidence as to how the production of one-digit multiplications solutions was disturbed by left anterior parietal stimulation in two consecutive sites in the AG (28% correct) to a much larger extent than single digit addition (87% correct responses). Twenty-seven trials were commission errors (vs. 19 trials without a response within the 7-second stimulation period), but the errors were not qualitatively analyzed. This pattern was not explained by the disruption of speech production or from impairment in attention. They ruled out possible differences between the difficulty of operations by comparing multiplication and addition problems that have the same answers (e.g.,  $9 + 7$ ;  $8 \times 2$ ); also, the two operations differed significantly in impairment. Stimulation on other sites (i.e. medial parietal, frontal) or other electrodes adjacent to the two positive anterior parietal sites did not impair any task. The authors explained the results as impairment in multiplication of arithmetic facts that are stored separately from addition facts, although an alternative explanation, in terms of over-learned additions, was considered.

Duffau et al. (2002) used both a multiplication and subtraction task in a single case of left parietal glioma. Multiplication consisted of simple single-digit problems with one operand < six. Subtraction consisted of subtracting seven from one- or two-digit numbers. Patients were requested to give an 'I don't know' response when they could not arrive to the solution to rule out speech arrest confound. Three positive sites were found in the AG: one site in the inferior part of the AG and similar in location to Whalen et al. (1997) showed disruption only in multiplication (100% errors); stimulation to one site in the superior part of AG and immediately

below the IPS, disturbed only subtraction. In the area between these two sites, stimulation of another site disturbed both operations. The authors suggest a 'calculotopy' for calculation based on a well-ordered distribution of specific calculation sites, with overlapping permitting functional organization. The authors did not control for solution size.

Another, less detailed, single case study (Kurimoto et al. 2006) detected common addition and subtraction areas in the left AG.

Roux et al. (2009) combined a language and a calculation task to DCE, with the intention of sparing both language and calculation functions in their surgical procedures (Figure 32.3).

Simple two-digit plus two-digit additions were used in the test of calculation functions.

Interestingly, these authors argued that they chose complex addition (e.g.  $26 + 43$ ) instead of simple addition ( $2 + 2$ ) or multiplication tables ( $7 \times 3$ ) because these latter tasks are generally solved in a completely automatic fashion. Discarding patients who presented preoperative acalculic symptoms, data were obtained from 16 patients. By stimulating brain areas possibly involved in calculation (the AG, intraparietal fissure, and dorsal premotor cortex-F2 in the left hemisphere), they caused various patterns of calculation interference. From 79 sites found with interference, 26 were naming- or reading-specific, 23 were calculation-specific, and 30 were common naming and calculation sites. Twelve out of 15 calculation specific areas were found in AG, six out of six were found in the intraparietal fissure, and four out of 12 were found in F2. Another was found in the supramarginal gyrus. From the 23 sites, 10 were 'single sites', in the sense that stimulating the surrounding  $1 \text{ cm}^2$  area did not show calculation interference. The authors analyzed errors, as well, with 11 omissions, five wrong answers, two hesitations, and five mixed responses distributed across sites (Figure 32.3). Importantly, the proximity of the localized calculation areas to the corticectomy (removed or less than 2 cm) predicted postoperative acalculia.

Yu et al. (2011), described below, found a differentiation in the right parietal and temporal cortex between multiplication and subtraction. Stimulation of the right IPL and of the right AG impaired performance on simple subtraction but not on multiplication. Della Puppa et al. (2013) found different sites for addition and multiplication (see below). Thus, differentiation between operations can also be detected in the right hemisphere.

## Right vs. Left IPS for Calculation

Pu et al. (2011) was the first DCE study contrasting the right and left hemispheres in different patients. They administered a numeric task to five patients: four were treated in the left hemisphere, and one was treated in the right hemisphere. Patients performed one-digit subtraction from a two-digit number and multiplications, wherein at least one of the operands was  $< 6$ .

While no interference was found in the right hemisphere, the authors found interferences with subtraction and multiplication in the left AG, in the left HIPS, and, with multiplication only, in the left supramarginal gyrus. Similar to the single case study by Duffau et al. (2002), the overlap between subtraction and multiplication was only partial, and sites were also detected where stimulation interfered with only one of the two types of operations. Solution size was not controlled in their operations. Rather than interpreting the results as a possible calculotopy, the author emphasized the differences between hemispheres, with the right hemisphere possibly implied in a more complex processing sequence or cognitive constituents of arithmetic, but not essential for it.

Yu et al. (2011) found in a single case study that multiplication was not affected by DCE of the right parietal and temporal cortex, while stimulation of the right IPL and of the right AG impaired performance on simple subtraction problems. They used subtractions where both of the operands were no more than 10 and single-digit multiplication with at least one operand  $< 6$ . It is remarkable that the pre- and post-operative evaluation used fine measures, such as a numerical Stroop paradigm, apart from subtraction tasks. The authors explained the right parietal involvement in subtraction by the involvement of quantity processing, rather than verbal numerical processing, which was more relevant for multiplication. They also implied the role of spatial representation of numbers: spatial attention, visual imagery, and visuospatial working memory in the selected parietal sites.

Finally, Della Puppa et al. (2013) evaluated the clinical impact of simple calculation in DCE of right-handed patients affected by a right parietal brain tumor. Overall, numerical processing interferences were found in four parietal regions explored by electro-stimulation: three interferences (three multiplication) in the AG, three interferences (two multiplication and one

addition) in the SMG, two interferences (two multiplication) in the HIPS, one interference (one multiplication) in the Superior lobule. This is the first DCE study that shows non-dominant right hemisphere involvement in multiplication and addition.

## Gerstmann Syndrome and The Left AG

Roux et al. (2003) performed the first case series study with the double goal of characterizing the left AG sites behind the Gerstmann syndrome and possibly sparing the proposed as associated writing, finger gnosis and calculation, plus language functions. The authors found, in five patients, that different symptoms of Gerstmann syndrome can be found during DCE to the left AG, which may or may not be associated with language interference sites. According to the authors, the pattern of specific cortical stimulation findings explains the rarity of finding all of the Gerstmann syndrome symptoms at once, as only the distributed lesions within the AG would lead to manifestation of the complete syndrome (Figure 32.4).

## Qualitative Analysis of Errors in DCE

We will briefly mention here, therefore, some preliminary findings from our own laboratory that seem to add important information. The role of the left AG was explored through simple addition and multiplication in one patient suffering from low-grade left parietal glioma. While interference for simple addition was found in the posterior portion of the left AG, interference with simple multiplication was found in the anterior portion. Crucially, errors arising during simple multiplication were retrieval errors, while errors with a response close to the correct solution were given during addition, suggesting approximation errors. Thus, because different processes implied in different operations were disrupted, the effects cannot be described simply as a calculotopy. These results are exposed with the aim of highlighting the interest of the analysis of commission errors: in a possible case, if stimulating an area elicits an approximation error for addition, but stimulation in another area elicits retrieval errors (i.e. operand errors), the different contribution of the two stimulated sites could be inferred. In turn, the pattern of errors suggests different roles for each area. Similarly, the analysis of response latencies could follow a pattern, albeit a noisy one. While only two of the TMS studies studying calculation have reported effects in errors (Andres et al. 2011; Göbel et al. 2006b), the proportion of errors was the dependent variable mostly analyzed in DCE studies.

Overall, DCE succeeds in finding dissociations between operations. Interestingly, some studies, albeit not precisely compared, seem to converge in specific areas (e.g. left AG in Whalen et al. 1997 and Duffau et al. 2002 for multiplication). It is of interest that the pattern of overlap and separation between tasks appears in these two studies. Perhaps the hypothesis of calculotopy is too extreme, especially taking into account that size effect has not been fully controlled. They mainly show that addition and multiplication somehow differ, and they are not just two instances of arithmetic fact retrieval.

With regard to the differential involvement of right and left IPS, not much can be concluded so far from this technique, as only two patients with different results have been evaluated. Nonetheless, positive results have been shown for subtraction and even for arithmetic facts, in not always overlapped sites, in the right IPS. Also remarkable is the calculation impairment found in F2 for complex addition. Again, further characterization is needed for frontal areas using DCE in the study of math.

## Discussion

So far, TMS studies in the research of math converge about the key role of parietal sites in the representation of numerical and some non-numerical quantities, in the link between space and numbers and in calculation. Bilateral posterior parietal sites are needed in spatio-numerical processes. IPS is essential during the access to magnitude, although stronger left IPS involvement appears. Conversely, calculation processes tend to be bilateral, contrary to the left lateralization that would be expected from fMRI studies or patient data. Consequently, TMS effects suggest that processes proposed to rely on a left lateralized verbal network could be also dependent on non-verbal components in the non-dominant hemisphere. Conversely, representations that are

proposed to be bilateral may rely later on in the left hemisphere, as representations of numerosity link up with language (Rivera et al. 2005).

DCE studies show, on the one hand, that multiplication is specifically disrupted with respect to addition and subtraction in the left AG. They also show that areas in the left intraparietal fissure, AG, and medial prefrontal and supramarginal gyrus, all contribute to complex addition. Finally, in one occasion, subtraction disruption is found in the right hemisphere. Most of the DCE studies were not so detailed about distinct locations within the parietal lobe. With two exceptions, where the right hemisphere was stimulated, they all concerned the left hemisphere, and in no case was information about the nature of errors provided. An analysis of the type of errors after the surgery, although of no value for the surgeon, can inform the researcher about the part of the process that has been disrupted.

## Tms and DCE in Numerical Cognition

What can be concluded at present from the convergent results in DCE and TMS, attending to the fact that DCE has only addressed calculation processes, is as follows: (1) The dissociation between arithmetic operations in different brain loci. DCE has shown also within-area dissociation and overlap. Note that this pattern of dissociation and overlap is precisely what is predicted between numerical and non-numerical quantities, thereby showing the sensitivity of DCE to this network pattern; (2) the common involvement of left parietal areas in subtraction and multiplication, associated in the left HIPS. Less can be concluded at this point for the right hemisphere by contrasting these two techniques; and (3) symptoms in Gerstmann syndrome are associated in the left AG.

Both TMS and DCE are techniques that imply a reversible disruption of functional brain areas allowing the mapping of brain functions, although both electrical stimulation and TMS are thought to silence all cortical areas that receive direct input from the fibers of the stimulated neurons (Borchers et al. 2012). Therefore, it is better to talk about networks, rather than areas. Despite the fact that they are similar, these techniques entail different experimental approaches. Given the pragmatic advantages of TMS (i.e. that there is no need of a between-subjects design, as well as that there are much lower restrictions in time or reaction time analysis), it can, and has, complemented these few DCE studies. This, on the other hand, allows for the avoidance of false negatives (Mandonnet et al. 2010) and allows for direct stimulation of the brain tissue. It is worth noting that DCE implies stimulation in patients with brain damage or epilepsy, and brain reorganization and compensation might have occurred previously to stimulation. Nonetheless, TMS could facilitate a more precise task design in DCE studies. On the other hand, DCE, in the study, as well as prevention of damage to math functions, needs of an 'omnibus' but simple task that really predicts relatively more complex future math performance in the patient, such as complex calculations, in order to assure more than an isolated preservation of arithmetic facts. Such a pertinent task—or, rather, group of tasks—still needs to be offered to the patient. In conclusion, a truly meaningful comparison can hardly be made at the present time. However, this chapter is a first attempt to make a reasoned comparison between the results of two methods, implying temporary inactivation in the study of math processing. More is bound to follow.

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