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Research report

A brain for numbers

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ABSTRACT

Healthy human brains come equipped with several circuits that contribute to number processing. Nature and nurture interact to produce a unique combination of core skills and more sophisticated abilities, by building on a handful of auxiliary routes (e.g., verbal language, body knowledge and visuospatial attention). Transcranial magnetic stimulation (TMS) studies on number processing will be here succinctly reviewed, in light of their most stimulating and challenging contributions. New research directions will be pointed out, that might enhance their theoretical impact.

> The great glory of mathematics is its durative nature; that is one of humankind's longest conversations; that it never finishes by answering some questions and taking a bow. (Barry Mazur (2003) – ''Imagining Numbers'', p. 225)

Number processing is an essential part of our culture (Bynner and Parsons, 1997). Numbers are used for counting, measuring, comparing, ordering, identifying objects, calculating. Even people who do not deal professionally with numbers use their number skills in everyday life, and acquired impairment of numerical skills is a severe handicap in working life (Butterworth, 1999). Severe difficulties in learning about numbers (dyscalculia) are probably as widespread as disorders of literacy development (dyslexia), and the best prevalence estimates for each lie between 3.6 and 6.5% (Butterworth, 2005). A deeper understanding of normal numerical skills is a necessary requirement for studying the impairment itself. TMS studies in mathematical cognition are aimed precisely to clarify the relation between the mental operations involved in normal number processing and specific brain circuits.

Within mathematical cognition, certain topics have attracted more attention (e.g., core quantity representation, the relation between finger pointing and counting or between numbers and spatial attention) probably also due to the fact that they are methodologically easier to investigate with TMS than others (e.g., complex arithmetic). Existing studies have met their objectives with mixed success and different protocols (see Table 1 for an overview), revealing the necessity of different cortical regions for number skills. Going beyond the virtual lesion metaphor, moreover, is perhaps the most intriguing open challenge in this field.

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Table 1 – Summary of reviewed TMS studies including stimulation parameters and results

Study	TMS parameters			Sites and behavioural effects				
	Frequency	Intensity	Duration	Stimulation sites	Localization method	Critical area	Task	TMS effect
Göbel et al. (2001) Exp 1	10 Hz	105% of active MT[a]	rTMS delivered pseudo-randomly, 500 ms, 100 ms before stimulus onset	PPL: X = ±42, Y = −58, Z = 52	Functional and Brainsight™	Left PPL	Comparison with 65	Slower RTs for numbers larger than and close to 65
Exp 2				SMG: X = ±52, Y = −46, Z = 44				No effect
Exp 3				PPL			Comparison with 65 (reversed response)	Generalized slowing of RTs
Sandrini et al. (2004)	15 Hz	110% of resting MT[a]	225 ms from stimulus onset	1 cm lateral to CP3 vs. 1 cm lateral to CP4 (SMG) vs. sham X = ±48, Y = −47, Z = 52	10/20 EEG system and SofTaxic	Left SMG	Comparison of two digits	Generalized slowing of RTs
Oliveri et al. (2004)	1 Hz offline	90% of resting MT[b]	5 min followed by 30–60 min rest before the next session	P3 vs. P4 vs. baseline	10/20 EEG system	P4	Comparison of two numerical intervals	Elimination of pseudoneglect
Rusconi et al. (2005) Exp 1	1 Hz offline	90% resting MT[a]	10 min, 20–25 min pause in between blocks	AG vs. SMG	Brainsight™	Left and Right AG	Finger gnosis task	Symmetric interference with the finger schema task from left AG; asymmetric (contralateral > ipsilateral) interference from right AG
Exp 2	10 Hz	60%[c]	rTMS delivered pseudo-randomly, 500 ms from stimulus onset	AG		Left AG	Magnitude matching + arithmetic prime	Slower RTs in trials with unrelated primes
Andres et al. (2005)	Single pulse	130% of resting MT[a]	Pulses at 150, 200, 250 ms after stimulus onset	P3 vs. P4 vs. P3+P4 (bilateral stimulation) vs. sham	10/20 EEG and TMS navigator (Noirhomme et al., 2004)	P3, P4 and P3+P4	Comparison with 5	Slower RTs to numbers close to 5 with TMS on P3 and P3+P4; slower RTs to far numbers with TMS on P3+P4
Göbel et al. (2006a)	5 Hz	110% of active MT[a]	rTMS delivered pseudo-randomly, 1000 ms from stimulus offset	AG/adjacent posterior part of the IPS left: X = −34, Y = −62, Z = 50; right: X = 38, Y = −65, Z = 48; vs. OCC X = 1, Y = −98, Z = 18	Functional and Brainsight™	Right AG/adjacent posterior part of the IPS	Mental number bisection	Reduction of pseudoneglect
Göbel et al. (2006b)	10 Hz	100% of active MT[a]	rTMS delivered pseudo-randomly, 500 ms from the onset of the inter-stimulus interval	AG/adjacent posterior part of the IPS X = ±40, Y = −61, Z = 54 vs. SMG/adjacent anterior part of the IPS X = ±45, Y = −40, Z = 58	Functional and Brainsight™	Left AG/adjacent posterior part of the IPS AG and left SMG/adjacent anterior part of the IPS	Selection of the correct result for addition problems	Increases RTs

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Knops et al. (2006)	1 Hz offline	60%[c]	10 min, 15 min rest before the next session	Left IPS vs. vertex and no stimulation	LOCALITE TMS Navigator	Left IPS	Comparison task (two-digit). Numbers pairs were presented above each other	Gender-mediated effects. Males: distance effect decreased after TMS over IPS; females: distance and compatibility effect increased
Cohen Kadosh et al. (2007)	10 Hz	60%[c]	200 ms, 220 ms after stimulus onset	IPS (individual fMRI data) vs. sham	fMRI-Guided TMS navigation Brain Voyager TMS navigator	Right IPS	Number-Stroop task: indicate the larger (either in physical or numerical size)	Disappearance of facilitation (no interaction with type of comparison). Interference remains.
Rusconi et al. (2007)	10 Hz	62%[c]	rTMS delivered pseudo-randomly, 500 ms from stimulus onset	Anterior portion of PPL $X = \pm 60$, $Y = -32$, $Z = 44$; posterior portion of PPL $X = \pm 36$, $Y = -64$, $Z = 36$	SofTaxic and Brainsight™	Left and right posterior portion of PPL	Parity judgment	Reduction of SNARC interference
Cappelletti et al. (2007) Exp 1	1 Hz offline	65%[c]	10 min, different days and 30 min rest before the next session	IPS vs. AG vs. Sham (site between IPS and AG)	Brainsight™	Left and right IPS	Comparison with 65	Slower RTs after TMS over left IPS: effect greater for comparisons of close numbers; generalized facilitation of RTs after TMS over right IPS
Exp 2							Comparison with the reference display of 65 dots	
Exp 3				IPS vs. Sham		Right IPS	Judging whether each ellipse was more elongated than a circle (never presented)	Slower RTs: greater effect with more difficult stimuli
Sato et al. (2007) Exp 1A	Single pulse	120% of resting MT[b]	TMS applied 200 ms after stimulus	Left vs. right M1	MEP: APB, ADM	Left M1	Parity judgment orally	Larger MEPs (right hand only) observed only for small numbers as compared to larger numbers
Exp 1B			TMS applied also at the onset of the stimulus					Larger MEPs (right hand only) only for small numbers (for TMS applied at 200 ms)

(continued on next page)

Table 1 (*continued*)

Study	TMS parameters			Sites and behavioural effects				
	Frequency	Intensity	Duration	Stimulation sites	Localization method	Critical area	Task	TMS effect
Andres et al. (2007) Exp 1	Single pulse	120% of resting MT[b]	TMS applied 200 ms after small arrays and either 200 or 1700 ms after large arrays	Left M1	MEP: FDI	Left M1	Counting task using either numbers or letters. Control task: respond if two contiguous dots had the same colour	Larger MEPs for both numbers and letters.
Exp 2			TMS applied 1700 ms after stimulus display		MEP: FDI, BB, TA		Counting task with numbers (large numerosities) and control task	Larger MEP only for FDI in the numerical task.
Exp 3			Half trials, TMS applied 1000 or 1500 ms after stimulus; in the other half, 3500 or 4000 ms		MEP: FDI		To recite mentally either number series or the alphabet. Dimming task was used as a control	MEP amplitude was not influenced by task
Exp 4							Counting task, using either numbers or letters. Control task: detecting two successive dots of the same colour	Larger MEPs during number and letter enumeration. MEP amplitude was larger when TMS was delivered after 3500–4000 ms than after 1000–1500 ms
Kansaku et al. (2007) Exp1	Paired TMS pulses (second 50 ms after the first)	160% of resting MT[b]	TMS delivered randomly, 50 ms	vPM $X = \pm 48$, $Y = -2$, $Z = 28$ vs. SMA vs. Sham	Brainsight™	Left vPM	Enumeration of successive stimuli (visual shapes)	Effects on accuracy during large but not small number counting
Exp 2							Enumeration of number words instead of visual shapes	No effect
Exp 3		70%[c]					Counting successive stimuli (Counting task) or recite letters alphabetically in concert with each stimulus (Letter task)	Effect on accuracy only in the Counting task
Dormal et al. (2008)	1 Hz offline	65%[c]	15 min, different days	Left IPS $X = -39$, $Y = -52$, $Z = 55$, right IPS $X = 35$, $Y = -55$, $Z = 56$ vs. vertex	TMS navigator (Noirhomme et al., 2004)	Left IPS	Comparison of pairs of series/dots	Slowing on RTs only for numerosity: larger effect for small distances

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Rusconi et al. (2008)	12 Hz	110% MT[a]	400 ms, from stimulus onset	Right/leftFEF MNI: R 31 −4.5 51 L −32.3 −4.4 49.8 and IFG MNI: ±50 22 22 vs. vertex	Brainsight™	right/left FEF and right IFG	Parity judgment, magnitude comparison	In magnitude comparison only: elimination of SNARC interference for small numbers on the FEF; for both small and large numbers on IFG; Interference on large numbers from left FEF stimulation

When cells are empty, see cell above. Coil type: 70-mm figure-of-eight coils were used in all studies but one. Rusconi et al. (2008) used 50-mm figure-of-eight coils. ADM, abductor digit minimi; AG, angular gyrus; APB, abductor pollicis brevis; BB, biceps brachialis, FDI, first dorsal interosseus, FEF, frontal eye field; IFG, inferior frontal gyrus; IPS, intraparietal sulcus; M1, primary motor cortex; MEP, motor evoked potential; PPL, posterior parietal lobe; OCC, occipital cortex; SMA, supplementary motor area; SMG, supramarginal gyrus; TA, tibialis anterior; vPM, ventral premotor cortex, CP3, CP4, Cz, P3, P4, localization according to the international 10/20 EEG system (Herwig et al., 2003). TMS Neuronavigation systems: SofTaxic: http://www.emsmedical.net/; Brainsight™: http://www.rogue-research.com/; BrainVoyager TMS Navigator: http://www.brainvoyager.com/; LOCALITE TMS navigator: http://www.localite.de

a Motor threshold (MT), the lowest intensity of stimulation capable of producing changes in a muscle, using visible inspection (Pridmore et al., 1998).

b MT using electromyography (Rossini et al., 1994).

c Fixed intensity is reported as percent of maximum stimulator output.

2. The number sense

Data from brain-damaged patients, single-cell recordings and functional neuroimaging have implicated the bilateral parietal lobes (intra-parietal sulci and neighbour areas, with an emphasis on the left hemisphere) as the neural substrate of number magnitude processing (see review by Ansari, 2008).

Much research today relates to an influential paper by Moyer and Landauer (1967), reporting that reaction time is inversely related to the distance between numbers when adults perform relative magnitude comparisons. The ‘‘distance effect’’ has become a marker for basic representations of numerical quantity. Functional magnetic resonance imaging (fMRI) studies have shown that intraparietal sulcus (IPS) activation is modulated by numerical distance during comparison tasks (Pinel et al., 2001) and even passive viewing (e.g., Piazza et al., 2007). Such distance-related activation is thought to reflect the properties of numerosity-selective neurons, as recorded in the monkey putative homologue of IPS (Nieder and Miller, 2004).

One intriguing discrepancy between lesion and imaging studies concerns the lateralization of the core quantity circuit. In quantity-related acalculia, lesions are often restricted to the left hemisphere, whereas imaging studies show bilateral parietal activation in quantity tasks. The exact role of the right hemisphere in number processing is therefore still unclear.

Sandrini et al. (2004) found that repetitive TMS (rTMS) applied over the left supramarginal gyrus (SMG) slowed down reaction times (RTs) when subjects were asked to select the largest digit amongst a pair, whereas right-SMG rTMS had no effect. However, rTMS did not interact with numerical distance. This result could therefore be interpreted as evidence that there is interference before accessing magnitude (i.e., operations between input and semantics are slowed down). Another possible explanation is interference on motor response selection, a process in which the left SMG is thought to play a fundamental role (e.g., Rushworth et al., 2001). Such alternative accounts do not hold for Andres et al.’s study (2005), in which TMS did interact with both hemisphere and numerical distance. In that study, single-digit numbers were compared to digit five. TMS was delivered 150, 200 or 250 ms after stimulus onset on the left IPS, right IPS or both simultaneously. When the distance between target and reference numbers was small, responses were significantly slower in unilateral left and bilateral stimulation conditions than in unilateral right stimulation and sham conditions. When numerical distance was large, responses were significantly slower in the bilateral stimulation only. Left and right parietal cortices, therefore, showed a different resolution in single-digit comparison, the left being necessary for fine discrimination, and both right and left being able to support coarser comparisons. What remains unclear is whether, by having a larger range of TMS timings, effects could be modulated. Event-related potentials (ERPs) studies indicate that number semantic processing from Arabic input occurs between 170 and 240 ms, and optimal TMS timing should either precede or follow this ERP peak (Walsh and Cowey, 2000). Introducing TMS timings beyond the +150/250 ms window might thus reveal a more complex picture of the interaction between left and right IPS.

Knops et al. (2006) presented pairs of two-digit numbers in a comparison task and tested left-IPS rTMS effects on distance between target decades. The distance effect decreased in male participants and increased in female participants after left-IPS rTMS. Gender effects were attributed to transcallosal transfer (hence, to simultaneous interference with right IPS) in female participants. However their groups were not matched (e.g., by age), and an overall increase in the distance effect was also reported by Andres et al. (2005) and Cappelletti et al. (2007), with only 60% of their participants being female. On the whole, studies reviewed so far point to the left IPS as a necessary substrate for processing symbolic representations of numerical magnitude.

In fact, imaging studies in humans and cell-recording in primates indicate that, besides the comparison of symbolic stimuli, parietal regions are involved in quantity processing of non-symbolic numerosities (e.g., Castelli et al., 2006; Nieder and Miller, 2004; Piazza et al., 2004). Cappelletti et al. (2007) investigated the causal role of parietal regions in processing both two-digit numbers and dots: in either case, performance was slower following left-IPS rTMS, and faster following right-IPS rTMS (attributed to disinhibition of the homologous region in the left hemisphere). No rTMS effects were found when stimulating the angular gyrus (AG). With participants judging ellipse orientation, instead, slower RTs were found after right- but not left-IPS rTMS, and the authors suggested that right IPS may be involved in the processing of continuous (as opposed to discrete) quantities. Dormal et al. (2008) tested directly the specialization of left vs. right IPS in the processing of continuous vs. discrete quantities. Left-IPS rTMS slowed down comparisons between numerosities of flashed-dot sequences, not between durations of single-dot displays, whereas right-IPS rTMS affected neither tasks.

Cohen-Kadosh et al. (2007) applied neuronavigated TMS in a Stroop-like task in which numerical values and physical sizes varied orthogonally. Participants had to compare either the numerical or the physical size of two Arabic numerals varying along both dimensions. Bilateral IPS activations were related to the size-congruity effect for each individual separately and used to guide a successive rTMS experiment. No effect was found with left-IPS rTMS, whereas right-IPS rTMS eliminated the facilitation component of the effect, independent of the task-relevant attribute (i.e., numerical or physical size). This may suggest a role for right IPS in early processing and integration of numerical and continuous quantities.

In conclusion, neuroimaging studies suggest the involvement of both the left and right IPS in quantity representation. In contrast, TMS data show that the left IPS is critical for processing of symbolic and non-symbolic numerosity, whereas the right IPS seems involved in the processing of continuous quantities.

3. Making space for numbers

Whether the mental representation of numbers is intrinsically spatial or is a cultural achievement is still open to debate. However, in Western cultures people are thought to implicitly represent numbers spatially, with small numbers toward the left of mental space and large numbers toward the right. Traces of number magnitude processing may be found in visuospatial attention and response selection circuits. Behavioural studies show that right (or left) targets are detected faster than left (or right) targets after exposure to large (small) numbers (Fischer et al., 2003), and responses to small numbers are faster when the effector is in left space, while responses to larger numbers are faster when the effector is in right space (Spatial-Numerical Association of Response Codes or SNARC effect; Wood et al., in press).

Göbel et al. (2001) found increased RTs when rTMS was applied over posterior parietal lobe (PPL) (on the same site on which rTMS interferes with visual search) during comparison of two-digit numbers to 65. RTs increase following left PPL stimulation was specific to numbers close to and larger than 65, whereas a trend for a more generalized effect was observed after right PPL stimulation. No effect was found when participants were stimulated on either left or right SMG and it was suggested that posterior PPL might play a fundamental role in the spatial representation of number magnitude, with the left hemisphere containing a spatiotopic representation (i.e., the mental number line). Rusconi et al. (2007) reduced the SNARC effect by applying rTMS over left and right posterior, but not anterior portion, of PPL. The effect was attributed to disruption of the link between numbers and visuo-spatial attention rather than to interference with core number representations. Subsequently, Rusconi et al. (2008) found that the interaction between numbers and spatial attention extends beyond the parietal cortex, since right- and left-FEF rTMS interferes with the processing of contralateral number space. A right-lateralized circuit (Corbetta and Shulman, 2002) is also thought to intervene in numerical processing, as suggested by the rightward biases found by Oliveri et al. (2004) and Göbel et al. (2006) in number bisection with rTMS over right PPL, and the suppression of the SNARC effect during right inferior frontal gyrus (IFG) rTMS (Rusconi et al., 2008). Regarding the involvement of the posterior PPL in the visuospatial representation of numbers, the data seem to suggest a different hemispheric contribution that could be attributed to task specificities (only right in quasi-spatial interval bisections and bilateral in symbolic comparison tasks).

Future TMS studies should address timing issues, with an eye to the interplay between numbers and other cues, in getting access to the spatial attention system. Clarifying how development and enculturation tune the circuitry for number–space interactions, is certainly one of the most intriguing issues to be dealt with in the future, perhaps in combination with complementary imaging techniques.

4. The body of numbers

Body parts, such as hands and fingers, are natural means for counting and representing numbers in human cultures (Menninger, 1969). The acquisition of arithmetic skills passes through the stage of counting (Fuson, 1988), tests of finger knowledge are good predictors of later mathematical achievement (e.g., Noël, 2005), and classical studies on developmental and acquired deficits suggest common representations for numbers and fingers (Butterworth, 1999). So far,

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TMS studies have addressed the issue by taking two different perspectives. Rusconi et al. (2005) found that left AG rTMS disrupted both the use of a high-level finger task (possibly implying the use of a finger schema) and number magnitude processing. By contrast, it did not disrupt arithmetic priming, parity processing or a lower-level finger task. Other studies, instead, focused on primary motor and pre-motor cortices and serial counting. Kansaku et al. (2007) found that left ventral premotor cortex (vPM) rTMS (but not supplementary motor area, SMA) interferes with serial cumulative counting of large numbers and not with recursive counting of small numbers, or letter reciting. Andres et al. (2007) employed TMS as a correlational method and found right first dorsal interosseus (FDI) motor evoked potentials (MEPs) increase during serial counting, irrespective of the use of numbers or letters to keep track of items, but no increase in arm and foot MEPs. They suggested that hand motor circuits are active above baseline whenever a correspondence is to be drawn between items and ordered series. Sato et al. (2007) measured abductor pollicis brevis (APB) and abductor digit minimi (ADM) MEPs from both right and left hands in a parity judgement task, and found an increase in MEPs for the right hand only during small number processing, a modulation they relate to their participants' counting habits. Since changes in resting MEPs, as measured with single-pulse TMS are not a univocal measure of activity in cortical areas (Di Lazzaro et al., 2001), the use of paired-pulse TMS (Kujirai et al., 1993), a technique that provides a more reliable index of motor cortical activation (Oliveri et al., 2004), is to be preferred in future studies. In conclusion, the relationship between numbers and hand/finger representations seems to be confined to the left hemisphere.

5. What's next?

All the studies described above exemplify nicely how TMS can be used to investigate a variety of issues in cognitive neuroscience, including the location, timing, lateralization and functional relevance of the neuronal correlates underlying number processing.

However, any conclusions on the causal structure–function relationships described in classical TMS studies are indirectly inferred on the basis of TMS induced changes in behavioural performance. Most of these conclusions rely on the implicit assumption that TMS-induced behavioural impairments are caused by TMS-induced disruptions of local neural activity at the stimulation site of TMS. However, it is also known that the neural consequences of focal TMS are not restricted to the site of stimulation (see review by Ruff et al., this issue).

Moreover, an important issue in cognitive neuroscience is how neural populations within a region interact to originate behaviour. It is potentially possible to enhance the functional specificity of TMS by measuring its differential effects on neural populations, based on their initial state of activation. Indeed, TMS has recently been shown to perceptually and behaviourally facilitate the attributes encoded by less active neurons relative to those encoded by more active neurons (Silvanto et al., 2007). In order to clarify the critical contribution of the left and right IPS in the abstract coding of numerical representation (see Ansari, 2007), for example, it could be possible to use adaptation to suppress neural activity of neurons tuned to either symbolic (Arabic numerals) or non-symbolic (arrays of dots) representations, before the application of TMS. If the numerical representation in the IPS is abstract, application of TMS after adaptation to the Arabic numerals (e.g. 17) should behaviourally modulate detection of the same quantity (17 dots). Otherwise, it should only modulate the quantity represented in the same stimulus format. In conclusion, this TMS-adaptation paradigm could better inform about functions and properties of specific neural populations in the stimulated region.

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