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Use of transcranial magnetic stimulation for studying the neural basis of numerical cognition: A systematic review

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ABSTRACT

Complex numerical cognition is a crucial ability in the human brain. Conventional neuroimaging techniques do not differentiate between epiphenomena and neuronal groups critical to numerical cognition. Transcranial magnetic stimulation (TMS) allows defining causal models of the relationships between specific activated or inhibited neural regions and functional changes in cognition. However, there is insufficient knowledge on the differential effects of various TMS protocols and stimulation parameters on numerical cognition. This systematic review aimed to synthesize the evidence that different TMS protocols provide regarding the neural basis of numerical cognition in healthy adults. We included 21 experimental studies in which participants underwent any transcranial magnetic stimulation such as a single pulse TMS, repetitive TMS, and theta-burst stimulation. The primary outcome measures were any change in numerical cognition processes evidenced by numerical or magnitude tasks, measured with any independent variable like reaction times, accuracy, or congruency effects. TMS applied to regions of the parietal cortex and prefrontal cortex has neuromodulatory effects, which translate into measurable behavioral effects affecting cognitive functions related to arithmetic and numerical and magnitude processing. The use of TMS for the study of the neural bases of numerical cognition allows addressing issues such as localization, timing, lateralization and has allowed establishing site-function dissociations and double site-function dissociations. Moreover, this technique is in a moment of expansion due to the growing knowledge of its physiological effects and the enormous potential of combining TMS with other techniques such

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Abbreviations: aMT, Active motor threshold; AG, Angular gyrus; BOLD, Blood oxygenation level-dependent; CT, Computerized tomography; cTBS, Continuous theta-burst Stimulation; DLPFC, Dorsolateral prefrontal cortex; EEG, Electroencephalogram; ERSP, Event-related spectral perturbation; ERP, Event-related potential; FEF, Frontal eye field; fMRI, Functional magnetic resonance imaging; HD-tDCS, High-definition transcranial direct current stimulation; HIPS, Horizontal segment of the intraparietal sulcus; IFG, Inferior frontal gyrus; IPC, Intraparietal cortex; IPS, Intraparietal sulcus; iTBS, Intermittent theta-burst stimulation; LTD, Long-term depression; LTP, Long-term potentiation; MEG, Magnetoencephalography; MEP, Motor evoked potential; MNL, Mental number line; MRI, Structural magnetic resonance imaging; MSO, Maximum stimulator output; MT, Motor threshold; NFA, Number form area; NIBS, Non-invasive brain stimulation techniques; NIRS, Near-infrared spectroscopy; PET, Positron emission tomography; PPC, Posterior parietal cortex; PT, Phosphene threshold; pTMS, Paired pulses transcranial magnetic stimulation; PSPL, Posterior superior parietal lobe; rCBF, Regional cerebral blood flow; rMT, Resting motor threshold; rTMS, Standard repetitive transcranial magnetic stimulation; SMG, Supramarginal gyrus; SNARC, Spatial numerical association of response codes; SPECT, Single-photon emission computed tomography; spTMS, Single-pulse transcranial magnetic stimulation; SSVEP, Steady-state visually evoked potential; TBS, Theta-burst stimulation; tDCS, Transcranial direct current stimulation; tES, Transcranial electrical stimulation; TMS, Transcranial magnetic stimulation; TMSA, Transcranial magnetic stimulation adaptation; tTMS, Triple pulses transcranial magnetic stimulation; VIPS, Ventral portion of the right intraparietal sulcus.

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as electroencephalography, functional magnetic resonance imaging, or near-infrared spectroscopy to reach a more precise brain mapping.

1. Introduction

Complex numerical cognition is a relatively recent emergent ability in the brain's evolution (Cantlon, 2018). Intuitively recognizing small numbers is a skill common to all cultures and has been present since prehistoric times. Also, some higher mammals can display numerical cognition (Ardila, 2010). Even invertebrates can successfully discriminate different quantities (Bortot et al., 2020). However, other advanced functions, such as arithmetic, are unique to humans and arose with the first historical civilizations (Butterworth, 2005). Number sense and computational operations involve recognizing quantities (visually or verbally) and applying a series of logical sequences to reach a result (Butterworth, 2010). These abilities involve an extensive bilateral brain network with left hemisphere dominance. The most critical areas are the posterior parietal lobe and the dominant hemisphere's prefrontal cortex.

Beyond the areas traditionally involved in numerical cognition, such as the angular gyrus (AG) and the intraparietal sulcus (IPS) of the dorsal parietal system (Dehaene et al., 2003), the construction of numerical representations also involves the ventral temporal-occipital system. (Menon, 2015). Arithmetic ability also requires multiple cognitive systems, including working memory, episodic, semantic memory, and executive control functions. Furthermore, neuroimaging studies show a change in the brain regions recruited during the acquisition of arithmetic expertise. The progressive improvement of arithmetic skills is accompanied by a shift in the frontoparietal network activity to specific parietal regions, with more significant activity in the AG than in the IPS, as arithmetic ability improves. This fact suggests a process of progressive automation. Furthermore, subjects with exceptional mathematical abilities involve a much broader network of structures (Zamarian et al., 2009).

Current Non-Invasive Brain Stimulation (NIBS) techniques have significantly contributed to understanding different cognitive processes. The most common NIBS types are transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). One of the applications of NIBS is the modulation of critical areas for cognitive processes such as working memory, executive functions, language, or numerical cognition (Sela and Lavidor, 2014). Moreover, the use of NIBS has resulted in reported therapeutic applications within clinical settings (Parkin et al., 2015; Di Lazzaro et al., 2021; Ekhtiari et al., 2019). Using NIBS facilitates identifying causal links between specific brain structures supporting cognitive, affective, sensory, and motor functions (Amidfar et al., 2019; Begemann et al., 2020; Kuo and Nitsche, 2012; Miniussi and Ruzzoli, 2013; Pitcher, 2021; de Graaf and Sack, 2014). NIBS also provide insight into local and global brain network organization, dynamics, and experience-dependent plasticity (Dayan et al., 2013). For instance, TMS and its combination with electroencephalography (TMS-EEG) help elucidate the neurochemical basis underlying the electrophysiological correlates of neural plasticity and connectivity in physiological brain aging and other neurological and neuropsychiatric disorders (Guerra et al., 2021).

TMS applies a magnetic field through a coil placed on the skull (Walsh and Cowey, 2000). The TMS stimulator delivers a large current in a short period, and the current flowing in the coil produces a magnetic field that lasts for only about a millisecond (Dayan et al., 2013). A rapidly changing magnetic field that easily penetrates the scalp and skull is generated when the appropriate stimulation parameters are selected. It induces an electrical field sufficient to stimulate neuronal activity and change the pre-stimulus dynamics of neuronal firing in the stimulated region. Although its precise action mechanisms are still far from clear, TMS activates neuronal axons in the cortex and subcortical white matter rather than cortical neurons' cell bodies (Ridding and Rothwell, 2007). TMS focality is currently expressed in square centimeters as a measure of the cortical surface and can be optimized by combining two circular coils to form a figure-of-eight or butterfly coil. TMS may suppress neural signals or generate random neuronal noise; however, its effects might be activity-dependent; TMS can suppress the most active neurons and change the balance between excitation and inhibition (Sandrini et al., 2011).

Historically, research in cognitive neuroscience used structural and functional neuroimaging to map active areas related to cognitive processes topographically. Diverse neuroimaging techniques such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Magnetoencephalography (MEG) have provided correlational maps of cognitive processes in the adult brain. These techniques record changes in blood oxygenation level-dependent (BOLD) signals, regional cerebral blood flow (rCBF), or evoked potential changes (EEG and MEG), which covary with the mental process of interest (Walsh and Cowey, 2000). These techniques do not differentiate between epiphenomena and neuronal groups whose activity is critical to the cognitive function in question(Parkin et al., 2015). However, suprathreshold application of TMS on specific regions can disrupt (cause interference) the ongoing activity affecting the cognitive function of interest (Pascual-Leone et al., 2000). When TMS application generates measurable behavioral changes, it helps establish causal models of the relationship between cognitive functions and specific brain regions (Sandrini et al., 2011). For this reason, TMS is widely useful for studying cognitive functions (Beynel et al., 2019; Cohen Kadosh et al., 2015; Lage et al., 2016; Neggers et al., 2015; Pascual-Leone et al., 2002; Robertson et al., 2003).

In contrast, TMS allows defining causal models of the relationships between specific activated or inhibited neural regions and functional changes in cognition. The main advantages of TMS over neuroimaging techniques are: (1) it has a higher spatial resolution than EEG, Event-Related Potentials (ERP) or MEG; (2) it achieves a higher temporal resolution than functional Magnetic Resonance Imaging (fMRI) or PET; and (3) it is based on interference and not correlation (Walsh and Cowey, 2000).

TMS in cognitive studies is currently entering a new phase of sophistication as increasing knowledge of its physiological effects has allowed the development of new experiments in combination with other techniques (Pitcher et al., 2021) as new protocols emerge. However, there is insufficient knowledge on the differential effects of various TMS protocols and stimulation parameters on numerical cognition.

This systematic review aimed to synthesize the evidence that different TMS protocols provide regarding the neural basis of numerical cognition in healthy adults.

2. Methods

This systematic literature review followed a predefined protocol registered in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019120056). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement's guidelines and recommendations (Page et al., 2021) to reliably structure the gathered information in this review.

2.1. Information Sources and Search

We conducted the literature search using a two-steps process. First, we used standard search databases, PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), and Web -of -Science (http://www.isiknowledge.com) to identify articles investigating human numerical cognition by using TMS in the last 12 years (January 2009 to May 2021). This timeframe considers that prior systematic reviews included data published until 2008. Second, we reviewed the reference sections of book chapters and review articles to identify any other relevant studies. We included documents published in English or Spanish. We excluded works on non-human subjects, unpublished studies, and conference papers.

The systematic searches performed in both databases used a series of TMS and numerical cognition keywords, including the subdomains of number representation, number processing and non-symbolic quantity processing, subitizing, counting, mental arithmetic, and the relation between number processing and time-space representation, among others. Search terms included: "Noninvasive brain stimulation”, “transcranial magnetic stimulation”, "Theta burst stimulation" AND "numerical cognition", "mathematical cognition", "maths abilities", "number processing" "magnitude processing", "arithmetic", "subitizing", "counting", “Spatial Numerical Association of Response Codes (SNARC)", “numerosity”, “calculation”. Appendix A contains the exact search terms and restrictions.

2.2. *Eligibility criteria*

We included studies focused on healthy adults and excluded patients with atypical neurologic development or behavior, patients with any neurologic condition, and children. The intervention of the studies included any transcranial magnetic stimulation such as a single pulse TMS, multiple pulse TMS, repetitive TMS, and theta-burst stimulation.

The primary outcome measures were any change in numerical cognition processes (i.e., number representation, quantity processing, mental arithmetic, subitizing, counting, and the relation between number processing and time-space representation) evidenced by numerical or magnitude tasks measured with any independent variable like reaction times, accuracy, congruency effects, among others.

The secondary outcomes were NIBS’s neural effects, considering any structural and functional data obtained using neuroimaging techniques or other ancillary studies. These techniques, following or related to NIBS administration, included computerized tomography (CT) scan, MRI, fMRI, PET, single-photon emission computed tomography (SPECT), MEG, EEG, ERP, event-related spectral perturbation (ERSP), steady-state visually evoked potential (SSVEP), doppler, and near-infrared spectroscopy (NIRS). We excluded articles focused only on changes in other cognitive domains not related to numerical cognition. Furthermore, we delimited the selection to experimental studies, including randomized clinical trials and quasi-experimental designs, and omitted observational and review studies.

2.3. *Strategy for data extraction*

Five reviewers simultaneously screened titles, abstracts, and keywords to check for the fulfillment of inclusion and exclusion criteria. The authors independently reviewed the resulting articles for eligibility in full text and hand-searched each article’s reference lists to ensure literature saturation. We extracted the data and processed them in Excel spreadsheets. Then, we categorized data according to (1) bibliography details of primary papers: authors, title, year, and journal, (2) demographics: number of participants, age, and gender, (3) TMS protocol: intensity, frequency, and timing of stimulation, (4) study design, (5) control condition, (6) localization methods, and (7) sites and behavioral effects. We contacted the authors to gather additional information or clarify concepts when necessary.

We performed a quality assessment at the study level and between studies, including internal validity, randomization, group allocation, or blinding. We also appraised generalizability and external validity. All reviewers participated in quality assessment and resolved disagreements by consensus.

2.4. *Evidence synthesis and data analysis*

We focused on a qualitative synthesis to describe the studies’ main contributions, outstanding findings, applicability, and limitations, due to the high variability in the subdomains of numerical cognition studied, the tasks used, and the outcomes measured. We structured the synthesis around the stimulation protocol, the predominant cognitive effects, and the procedure details. To understand the outcomes derived from the neural correlations, we analyzed how the studies established a connection between these correlations and their cognitive correspondence, for instance, by directly measuring the outcomes using cognitive tasks and questionnaires or interpreting their results based on existing literature.

3. Results

Fig. 1 shows the initial search results, the screening process, and the final selection after excluding articles not complying with the inclusion criteria. We included 21 studies in the final selection. Table 1 shows the bibliographic and demographic characteristics of the studies and the cognitive function analyzed.

3.1. *TMS protocol*

All the studies included in this review are based on the magnetic simulation disruptive power. Table 2 gives an overview of the TMS procedure and the stimulation effects in each case. The studies reviewed used a variety of TMS paradigms depending on the number and frequency of pulses delivered: four studies used single pulse (spTMS), one study used paired pulses (pTMS), three papers used triple pulses (tTMS), nine papers used standard repetitive TMS (rTMS), and four studies used a subtype of repetitive stimulation called continuous theta-burst stimulation (cTBS). Fig. 2 shows the main differences between these paradigms. None of the studies included in this review used intermittent or intermediate TBS.

3.1.1. *Single-pulse TMS*

Single-pulse TMS consists of discharges of single pulses separated by time intervals of at least 4 s in a way that its individual effects do not sum up over time(Valero-Cabré et al., 2017) as shown in Fig. 2.

TMS applied in single pulses optimizes the high temporal resolution of the technique. When single pulses are applied at variable times during the execution of the task, it is possible to investigate the exact time point in which neural activity at the stimulation site is critical for task performance. Thus, providing chronometry of functional relevance, with a temporal resolution of tens of milliseconds (ms). For example, Rusconi et al. (2013) used spTMS to elucidate the critical time course of the right frontoparietal involvement in mental number space. They applied spTMS over the right posterior parietal cortex (PPC), right frontal eye field (FEF), and right inferior frontal gyrus (IFG) randomly at one of 13 different time points (0, 33, 67, 100, 133, 167, 200, 233, 267, 300, 333, 367, and 400 ms from stimulus onset). The authors used the SNARC effect as a behavioral marker to study TMS’s effects on spatial numerical processing. In Western populations, this effect consists of preferential mapping of small numbers on left responses and large numbers on right responses (Dehaene et al., 1993). Therefore, observed variations in the SNARC effect indicate an altered spatial numerical mapping. Rusconi et al. (2013) observed a reduction in the SNARC effect when delivering TMS over the right FEF (small and large numbers) and the right IFG (small numbers) in the earlier period (~25–60 ms). Additionally, they observed a reduced SNARC effect later (~200 ms) when applying TMS over the right FEF (small numbers).

Conversely, the right PPC - TMS did not interfere with the SNARC. These results probe the causal role of an intact right frontoparietal network in mental number space processing. The right PPC is tied to explicit number magnitude processing, and the right FEF and IFG contribute to interfacing mental visuospatial codes with lateralized

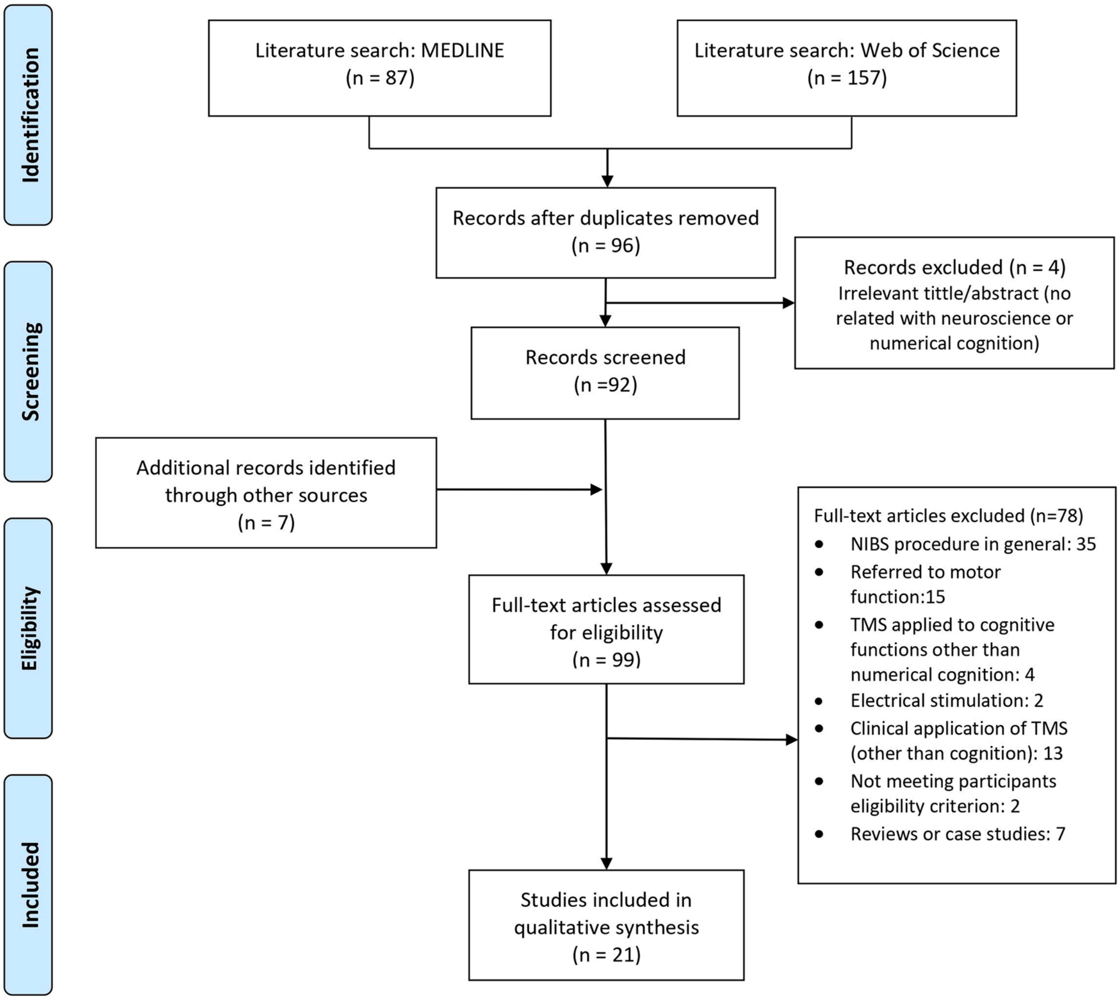

Fig. 1. PRISMA flow diagram illustrating the identification and selection of relevant studies in the systematic review.

response codes.

3.1.2. *Multiple pulse TMS*

TMS can also be applied in multiple pulses. Paired pulse TMS consists of two pulses delivered consecutively within a short inter-stimulus interval (see Fig. 2). For instance, Grotheer et al. (2016) applied two pulses separated by 100 ms, whereas Cattaneo et al. (2009) used a triple pulse protocol in which three pulses were delivered with an inter-stimulus interval of 75 ms to study the role of the AG in the modulation of visuospatial attention along the mental number line (MNL).

The selection of the timing of the pulses depends on multiple factors. If the study seeks to establish a causal relationship between the region and the specific cognitive function, the timing should be chosen based on a significant disruption effect. It appears that the most effective timing to apply a disruptive TMS occurs before the peak of the ERP component related to the cognitive function (Cohen Kadosh et al., 2007; Walsh and Cowey, 2000). Based on previous ERP studies that found a modulation of the ERP components during numerical processing, (Cohen Kadosh et al., 2012) defined a TMS protocol applying triple pulses stimulation at 220, 320, and 420 ms after the stimulus onset over the right and left IPS during a numerical Stroop task. This experiment demonstrated the crucial role of the right IPS in automatic and intentional number processing (see TMS effects of this experiment in Table 2).

3.1.3. *Repetitive TMS*

Repetitive TMS is a combination of pulses delivered repeatedly with a short time interval during a long period at a fixed frequency (Valero-Cabré et al., 2017). In this case, the repeated application of pulses at high or low frequencies expands the stimulation time window compared to a single pulse. Consequently, rTMS is frequent in causal cognitive studies due to the presumably temporal summation of the stimulation's disruptive effects (Fresnoza et al., 2020; Klichowski and Kroliczak, 2020; Walsh and Pascual-Leone, 2003). Dormal et al. (2012) used an rTMS protocol to study the bilateral IPS involvement in length and numerosity processing. At 10 Hz, repeated pulses were applied over the left and right IPS during 400 ms, while participants performed a non-symbolic number comparison task and a length comparison task. In the former task, participants had to categorize linear arrays of dots as containing "few" or "many" dots, whereas in the latter, they had to categorize continuously filled rectangles as "short" or "long". The authors found that TMS over the right IPS had effects on the accuracy of both tasks. Therefore, the right IPS' integrity is necessary for discriminating numerosities and performing accurate judgments of lengths.

3.1.4. *Theta-burst stimulation*

Another established form of rTMS is patterned stimulation protocols (see Fig. 3), previously reported in the modulation of neural activity (Sandrini et al., 2011; Thut and Pascual-Leone, 2010). A decade ago, patterned Theta Burst Stimulation (TBS) protocols, intermittent TBS (iTBS), and continuous TBS (cTBS), mimicking the protocols inducing LTP and LTD in animal models, were first implemented for non-invasive neuromodulation. Since then, they have become trendy due to their longer-lasting effects following short stimulation periods compared to most commonly employed classical rTMS paradigms (Huang et al., 2005; Suppa et al., 2016).

Huang et al. (2005) developed an rTMS protocol applying bursts of three 50 Hz pulses in trains repeated at 200-ms intervals (i.e., frequency of 5 Hz) in the range of theta-band. This patterned stimulation is called continuous Theta-Burst Stimulation because 5 Hz frequency belongs to the theta-band range. They demonstrated that this protocol has long-term inhibitory effects. For instance, 20 s of cTBS reduces the motor cortex's excitability up to 20 min (Huang et al., 2005). Another protocol is intermittent TBS (iTBS) repeating burst trains for 2 s every 10 s over 110 s. Conversely, the effects became facilitatory (a second experiment in Huang's study).

Four papers included in this review studied numerical cognition using cTBS. Hayashi et al. (2013) followed the exact stimulation parameters as the primary cTBS protocol (50 Hz bursts, repeated at 5 Hz during 40 s) in an experiment addressing the neural correlates of the interaction between numerosity and time processing. cTBS was applied over the right intraparietal cortex (IPC) and the right IFG to explore the interactions occurring at the perception and decision-making level. Subjects performed two time-numerosity interaction tasks before and after cTBS. A *duration discrimination task*, consisting of discrimination of two dots, was presented for a longer time, and a *duration reproduction task* in which subjects were asked to reproduce the duration of a previous stimulus by holding down the space bar. The authors carried out an additional experiment, applying stimulation only for the IPC, during a non-symbolic comparison task, to establish the IPC's functional role in numerical processing. Overall, results show that cTBS over the right IFG impairs categorical duration discrimination, whereas cTBS over the right IPC modulates the degree of influence of numerosity on time perception and impairs precise time estimation. These results suggest a two-stage model of time-numerosity interactions whereby the parietal region underlying interaction is at the perceptual level, and the prefrontal cortex underlying interaction is at the categorical decision.

Riemer et al. (2016) used a different cTBS protocol to investigate the parietal representation of space, time, and number by analyzing the effects of prolonged cortical inhibition on response codes association and congruency effects. The cTBS protocol used consists of a burst of three biphasic pulses (repeated at 30 Hz) applied during 44 s at 6 Hz (in the range of theta-band), delivered over the PPC. Thus, one train of cTBS consisted of 267 bursts (801 single pulses). Their results show that congruency effects, but not response code association, were affected by cTBS, indicating that congruency between purely perceptual dimensions is processed in PPC areas along with the IPS. In contrast, congruency between percepts and behavioral responses is independent of this region (Riemer et al., 2016). These results are consistent with the idea of a two-stage model proposed by Hayashi et al. (2013). Fig. 3 shows the differences between the two cTBS protocols described above.

Table 1
Bibliographic and demographic characteristics of the studies included in the review and cognitive domain studied.

Study	Sample Total (N)	Mean Age	SD or (Range)	Sex	Cognitive Domain
Cappelletti, 2009	6	22,2	(21–23)	3 M; 3 F	Quantity processing
Salillas, 2009	12	22,3	NS	3 M; 9 F	Number and space
	8	24,1	NS	2 M; 6 F	
Cattaneo, 2009	9	26,25	NS	7 M; 2 F	Number and space
Cohen Kadosh, 2010	7	22,71	2,3	1 M;6 F	Number representation
	6	24,33	2,35	0 M;6 F	
Andres, 2011	10	21	2	10 M;0 F	Arithmetic
Renzi, 2011	18	23,4	2,9	9 M;9 F	Number and space
Rusconi, 2011	10	30,1	NS	5 M;5 F	Number and space
Dormal, 2012	10	24	0,5	10 M;0 F	Numerosity and length processing
Cohen Kadosh, 2012	5	28,6	4,5	4 M;1 F	Number processing
Salillas, 2012	12	23	(21–26)	3 M;9 F	Arithmetic
	10	24	(23–27)	3 M;7 F	
Cheng, 2013	11	24,2	5,2	2 M;9 F	Order and quantity processing
	11	24	5,39	3 M,8 F	
	11	22,6	5,2	2 M;9 F	
Sasanguie, 2013	17	22	4,2	10 M;7 F	Number representation
Rusconi, 2013	21	26	(20–37)	11 M;10 F	Number and space
Hayashi, 2013	26		(19–30)	12 M;14 F	Number and time
	10		(20–30)	3 M;7 F	
	14		(19–36)	6 M;8 F	
	16		(20–30)	7 M;9 F	
Lecce, 2015	14	26,7	(19–40)	5 M;9 F	Number and quantity processing
Riemer, 2016	22		(21–35)	7 M;15 F	Number and space
Maurer, 2016	20	25	(22–29.5)	9 M;11 F	Arithmetic
Grotheer, 2016	13	25	3	1 M;12 F	Number representation
Montefinese, 2017	10	25.27	4.79	3 M;7 F	Arithmetic
	10	28.11	5.19	3 M;7 F	
Fresnoza, 2020	16	26.25	7.07	7 M, 9 F	Arithmetic
Klichowski, 2020	20	20.9	1.6	20–27	Arithmetic

3.2. *On-line versus off-line stimulation*

Based on the high durability of the inhibitory power of repetitive stimulation, in off-line protocols, the tasks are solved after applying the stimulation, given that one train of TBS has an inhibitory behavioral effect that lasts up to 30 min (Nyffeler et al., 2006b). All the studies included in this review that use TBS apply stimulation off-line prior to the task (see Table 2). Additionally, with the repeated application of TBS trains, it is possible to prolong the inhibitory behavioral effects (Nyffeler et al., 2006a). The protocol applied by Riemer (2016) is based on this fact, in which two trains are applied separated by 10 min.

All the conventional rTMS studies included in this review apply the on-line model (stimulation applied simultaneously to the task), except Fresnoza (2020), in which the tasks are performed before, during, and after stimulation. The study shows a more significant effect of stimulation (off-line); the tasks were performed 60 min after stimulation than on-line (tasks performed simultaneously as the stimulation).

In summary, the selection of the TMS protocol depends on the purpose of the study. Single-pulse exploits the high temporal resolution of

Table 2

Summary of reviewed TMS studies, including stimulation parameters and results. Acrostic used for target regions: IPS: Intraparietal Sulcus, IPC: Intraparietal Cortex, VIPS: Ventral Intraparietal Sulcus, HIPS: Horizontal segment of Intra Parietal Sulcus, PSPL: Posterior Superior Parietal Lobe, PPC: Posterior Parietal Cortex, AG: Angular Gyrus, SMG: Supramarginal Gyrus, IFG: Inferior Frontal Gyrus, NFA: Number Form Area (in the inferior temporal cortex), LO: Lateral Occipital Complex, FEF: Frontal Eye Field, LH: Left hemisphere, RH: Right hemisphere. Acrostic used for TMS protocols: spTMS: single-pulse Transcranial Magnetic Stimulation, pTMS: paired-pulse Transcranial Magnetic Stimulation, tTMS: triple pulse Transcranial Magnetic Stimulation, rTMS: repetitive Transcranial Magnetic Stimulation, cTBS: continuous Theta Band Stimulation (a type of repetitive Transcranial Magnetic Stimulation in the range of theta band). Other acrostics: RT: Reaction Time, SOA: Stimulus Onset Asynchronies, SNARC: Spatial-Numerical Association of Response Codes, STARC: Spatial-Time Association of Response Codes, aMT: active Motor Threshold, rMT: resting Motor Threshold, PT: Phosphene Threshold, MSO: Maximum Stimulator Output.

Study	TMS Protocol (Frequency)	Timing	Intensity	Stimulation sites	Localization method	N	Study design	Control conditions	TMS effects
Cappelletti, 2009	rTMS On-line (10 Hz)	Duration: 500 ms At the stimulus onset	Fixed 60% MSO	Left IPS Right IPS	TMS Neuronavigation based on group Talairach coordinates (previous fMRI study, same tasks, different subjects)	6	Pseudo-randomized controlled trial Within subjects	Sham stimulation same sites (coil sideways) and No-stimulation condition	Quantity judgments with numerical and non-numerical stimuli were significantly impaired (longer RTs) following TMS to either left or right IPS and number conceptual tasks not requiring number comparisons. No impairment was detected for perceptual or conceptual decisions on numbers that did not involve quantity or number stimuli.
Salillas, 2009	spTMS On-line	Exp 1 Pulses 100, 150, 200 ms after the stimulus onset	110% Individual PT	Right VIPS Left VIPS	TMS Neuronavigation (in the absence of radiological images) based on group Talairach coordinates	12	Randomized controlled trial Within subjects	Vertex stimulation	TMS over VIPS results in impaired motion perception and number comparison efficiency, suggesting that these processes share a common neural substrate.
		Exp 2 Pulse 200 ms after the stimulus onset	110% Individual PT	Right VIPS Left VIPS	Individual MRI-guided TMS Neuronavigation	8		None	TMS over the VIPS contralateral to the visual field in which the number was presented resulted in impaired performance compared to ipsilateral VIPS stimulation.
Cattaneo, 2009	tTMS On-line	Pulses at 0, 75, 150 ms in the delay between prime and target stimulus	Fixed 65% MSO	Left AG Right AG	Individual MRI-guided TMS Neuronavigation	9	Pseudo-randomized controlled trial Within subjects	Task control and No-stimulation condition	In the Small Number Prime condition: TMS applied over the right AG abolished the effect of number priming in a line bisection task. TMS over the left AG had no significant effect. In the Large Number Prime condition (attention shifted to the right side of visual space): both left and right TMS over the AG modulated the effect of number priming.
Cohen Kadosh, 2010	TMSA[1] On-line	Biphasic pulses at 180, 280, and 380 ms after the stimulus onset	Fixed 60% MSO	Left IPS Right IPS	TMS Neuronavigation based on group Talairach coordinates (previous meta-analysis)	7, 6	Pseudo-randomized controlled trial Within subjects	Vertex stimulation and baseline task (without stimulation)	Right parietal lobe stimulation showed a dissociation between digits and verbal numbers. The left parietal lobe showed a double dissociation between the

(*continued on next page*)

Table 2 (*continued*)

Study	TMS Protocol (Frequency)	Timing	Intensity	Stimulation sites	Localization method	N	Study design	Control conditions	TMS effects
									different numerical formats. These results suggest that left and right IPS are equipped with notation-dependent numerical representation.
Andres, 2011	rTMS On-line (10 Hz)	Four pulses Duration: 300 ms 100 ms after the stimulus onset	Fixed 65% MSO	Left HIPS Right HIPS Left PSPL Right PSPL	Individual fMRI guided TMS Neuronavigation	10	Randomized controlled trial Within subjects	Vertex stimulation	Left or right HIPS stimulation caused longer RTs in subtraction and multiplication. TMS over the HIPS increased the error rate in the multiplication task. The PSPL is not crucial for basic arithmetic problems: neither operations are solved by calculation procedures (subtraction) nor memory retrieval (multiplication).
Renzi, 2011	TMSA On-line	Single pulse at the stimulus onset	Fixed 65% MSO	Right PPC Left PPC	Based on the 10–20 EEG System	18,11	Randomized controlled trial Within subjects	Vertex stimulation and No-stimulation condition	TMS over left PPC and right PPC caused a reduction of the adaptation effect (difference between RT in the congruent and incongruent trials) in a motion direction adaptation paradigm). These results suggest a functional overlap in neuronal representations of motion direction and numerical magnitude information.
Rusconi, 2011	rTMS On-line (5 Hz)	3 pulses Duration: 400 ms At the stimulus onset	110% Individual aMT	Right IFG Left IFG Right FEF Left FEF	Individual MRI-guided TMS Neuronavigation	10	Pseudo-randomized controlled trial Within subjects	Vertex stimulation	SNARC effect was unaffected by stimulation site in parity judgment. It was eliminated during magnitude judgments for small and large numbers with TMS over right IFG and for small numbers only with TMS over FEF.
Dormal, 2012	rTMS On-line (10 Hz)	5 pulses Duration: 400 ms At the stimulus onset	Fixed 65% MSO	Right IPS Left IPS	Individual fMRI guided TMS Neuronavigation	10	Pseudo-randomized controlled trial Within subjects	Vertex stimulation	TMS over the right IPS increased the error rate in two tasks: a numerosity categorization of linear arrays of dots and a length categorization of continuous filled rectangles. These results imply that the integrity of the right IPS is necessary for discriminating numerosities and performing accurate

(*continued on next page*)

Table 2 (*continued*)

Study	TMS Protocol (Frequency)	Timing	Intensity	Stimulation sites	Localization method	N	Study design	Control conditions	TMS effects
									judgments of lengths.
Cohen Kadosh, 2012	tTMS On-line	Pulses at 220, 320, and 420 ms after stimulus onset	Fixed 60% MSO	Right IPS Left IPS	Individual fMRI guided TMS Neuronavigation	5	Randomized controlled trial Within subjects	Sham stimulation (opposite hemisphere) Baseline task (no TMS)	TMS over the right IPS decreased automatic numerical processing as indicated by a significantly reduced size congruity effect (larger RTs for incongruent trials). TMS over right IPS decreased intentional numerical processing, as indicated by a significantly reduced numerical distance effect.
Salillas, 2012	spTMS On-line	Single-pulse randomly at one of the four SOAs: 150, 200, 250, or 300 ms after the stimulus onset	110% Individual PT	Right HIPS Left HIPS Right VIPS Left VIPS	TMS Neuronavigation (in the absence of radiological images) based on group Talairach coordinates	12	Randomized controlled trial Within subjects	Vertex stimulation	Performance on addition is affected by TMS over HIPS of both hemispheres (increased RTs) but unaffected by VIPS-TMS. Performance on multiplication is affected by VIPS-TMS of both hemispheres and left HIPS-TMS (increased RTs). Efficiency was unaffected by disruption to the right HIPS. There were no significant interaction effects involving SOA.
				Right HIPS Left HIPS Right VIPS Left VIPS	Individual MRI-guided TMS Neuronavigation	10		Contralateral stimulation	TMS over IPS in either hemisphere compared to control sites or contrasting ipsilateral vs. contralateral visual presentation resulted in a loss of efficiency in the form of increased RTs (both in addition and multiplication). Both left and right IPS were implicated in the efficiency of exact calculation.
Cheng, 2013	cTBS Off-line (Burst: 50 Hz, Tain: 5 Hz)[2]	Duration: 20 s	Fixed 40% MSO	Left HIPS Right HIPS	TMS Neuronavigation based on group Talairach coordinates (previous studies)	21	Randomized controlled trial	Vertex stimulation Baseline task (before TBS)	TBS over Left IPS impaired quantity processing (slower RTs) and facilitated order processing (speeded RTs). Right IPS-TBS had no specific effect on either order or quantity processing.
Sasanguie, 2013	rTMS On-line (10 Hz)	Duration: 500 ms At the prime onset	110% Individual aMT	Right IPS Left IPS	TMS Neuronavigation based on group Talairach coordinates (previous study)	17	Pseudo-randomized controlled trial Within subjects	Vertex stimulation	tTMS over left but not right IPS abolished Priming Distance Effect when prime and target are symbolic and non-symbolic

(*continued on next page*)

Table 2 (*continued*)

Study	TMS Protocol (Frequency)	Timing	Intensity	Stimulation sites	Localization method	N	Study design	Control conditions	TMS effects
									numerosities. There is no significant effect of right TMS over left or right IPS when symbolic stimuli are used. The results suggest a crucial role of the left hemisphere for the mapping between small symbolic and non-symbolic numerosities.
Rusconi, 2013	spTMS On-line	SOAs 0–400 ms (sampling interval = 33 ms) Starting at the stimulus onset	120% Individual rMT	Right FEF Right IFG Right PPC	Individual MRI-guided TMS Neuronavigation	21	Pseudo-randomized controlled trial Within subjects	Sham stimulation (coil perpendicular) and no stimulation (baseline)	TMS over right FEF reduced SNARC effect in the earlier period (~25–60 ms) with small and large numbers. TMS over right IFG also reduced the SNARC effect with small numbers. Reduced SNARC effect was seen later (~200 ms) with TMS over right FEF (small numbers). Right PPC - TMS did not interfere with the SNARC. These results suggest the causal role of an intact right frontoparietal network in processing mental number space. Right PPC is tied to explicit number magnitude processing, and right FEF and right IFG contribute to interfacing mental visuospatial codes with lateralized response codes.
Hayashi, 2013	cTBS Off-line (Burst: 50 Hz Train: 5 Hz)	Duration: 40 s	Fixed 40% MSO	Right IPC Right IFG	TMS Neuronavigation based on group Talairach coordinates (obtained in the first experiment of the study)	10, 14,16	Controlled trial Within subjects	Vertex stimulation Baseline task (before TBS)	TMS over the right IFG impairs categorical duration discrimination. TMS over the right IPC modulates the degree of influence of numerosity on time perception and impairs precise time estimation. These results suggest a two-stage model of time-numerosity interactions whereby parietal region underlying interaction at the perceptual level, and prefrontal cortex underlying interaction at categorical decisions.
Lecce, 2015	cTBS Off-line		Fixed 40% MSO	Right IPS Left IPS	TMS Neuronavigation	14	Randomized controlled		Left IPS-TBS caused increased Weber

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Table 2 (*continued*)

Study	TMS Protocol (Frequency)	Timing	Intensity	Stimulation sites	Localization method	N	Study design	Control conditions	TMS effects
	(Burst: 50 Hz Train: 5 Hz)	Duration: 20 s 5 min before starting tasks			based on group Talairach coordinates (previous studies)		trial Within subjects	Vertex stimulation Control task	Fraction in incongruent but not congruent trials. Continuous quantity processing remained unchanged. Right IPS stimulation caused increased WF in congruent but not incongruent trials.
Riemer, 2016	cTBS Off-line (Burst: 30 Hz Train: 6 Hz)[3]	Duration: 44 s Two trains applied with an interval of 10 min prior to the tasks	100% Individual rMT	Right PPC	Individual MRI-guided TMS Neuronavigation	22	Controlled trial Within subjects	Sham stimulation (coil turned upside down)	TBS over the right IPS affected congruency effects between space, time, and numbers, but it does not affect response code associations. These results suggest that PPC is involved in the congruency between purely perceptual dimensions but not between percepts and behavioral responses.
Maurer, 2016	rTMS On-line (5 Hz)	10 pulses Duration: 1.8 s At stimulus onset	100% Individual rMT	52 cortical sites	rTMS Mapping Individual MRI-guided TMS Neuronavigation	20	Randomized controlled trial Within subjects		The highest error rate (80%) for all subjects' errors was observed in the right ventral precentral gyrus. A 45% error rate was achieved in the left middle frontal gyrus concerning division tasks. The subtraction task had the highest error rate (40%) in the right AG. In the addition task, a 35% error rate was observed in the left anterior superior temporal gyrus. The multiplication task induced a maximum error rate of 30% in the left AG.[4]
Grotheer, 2016	pTMS On-line	Concurrently with, and 100 ms after the onset of the stimulus	Fixed 50% MSO	Left LO Right NFA	Individual fMRI guided TMS Neuronavigation	13	Pseudo-randomized controlled trial Within subjects	Vertex stimulation	TMS over the right NFA significantly impaired the detection of briefly presented and masked Arabic numbers compared to vertex stimulation. Stimulation over the NFA also impaired the detection of Roman letters. Stimulation of the lateral occipital complex (LO) did not affect the detection of numbers or letters.
Montefinese, 2017	rTMS On-line (10 Hz)	Four pulses Duration: 100 ms At the stimulus onset	Fixed 65% MSO	Experiment 1: Right HIPS Left HIPS	TMS Neuronavigation based on group Talairach	10	Pseudo-randomized controlled trial	Vertex stimulation	Experiment 1: TMS caused a significantly greater involvement of the right HIPS than left

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Table 2 (*continued*)

Study	TMS Protocol (Frequency)	Timing	Intensity	Stimulation sites	Localization method	N	Study design	Control conditions	TMS effects
				Right VIPS Left VIPS	coordinates (previous studies)		Within subjects		HIPS and bilateral VIPS in solving complex operations.
				Experiment 2: Right AG Left AG Right SMG Left SMG		10		Vertex stimulation	Experiment 2: The asymmetry (i.e., right greater than left) of the rTMS interference was stronger over the SMG than the AG.
Fresnoza, 2020	rTMS On-line Off-line (1 Hz)	Duration: 15 min Tasks were performed before, during, and after stimulation	110% Individual aMT	Left HIPS Left AG	Individual fMRI guided TMS Neuronavigation	16	Single-blinded randomized controlled trial Within subjects	Vertex stimulation	Left AG stimulation produced impairment in the retrieval and on-line calculation of multiplication problems and impairment in the retrieval (but not on-line calculation) of subtraction problems. Left HIPS did not affect both operations regardless of strategy.
Klichowski, 2020	rTMS On-line (10 Hz)	4 pulses Duration: 100 ms At the stimulus onset	Fixed 65% MSO	Right SMG Left SMG	TMS Neuronavigation based on group Talairach coordinates (previous studies)	20	Controlled trial Within subjects	No stimulation	Neither the accuracy for adding prices nor calculating discounts were affected by rTMS applied to the left or right SMG. Further analyses of RTs for correctly performed calculations showed that complex shopping calculations involve SMG asymmetrically while simpler calculations do not.

[1] TMS Adaptation paradigm (Silvanto et al., 2008) is based on the state-dependency of TMS. Because the initial neural activation state determines the effects of TMS, TMSA enables improved functional resolution by differential stimulation of distinct but spatially overlapping neural populations within a stimulated region. Thus, by using adaptation to manipulate neural activation states before TMS application, one can control which neural populations are preferentially activated by TMS.

[2] Following the protocol designed by Huang, Edwards, Rounis, Bhatia, and Rothwell (2005), where bursts of 3 stimuli at 50 Hz (i.e., 20 ms between each stimulus) were repeated at intervals of 200 ms (i.e., 5 Hz, in the range of theta band)

[3] Bursts containing three biphasic pulses (repeated at 30 Hz) were applied during 44 s at 6 Hz (in the range of theta band). Thus, one train of cTBS consisted of 267 bursts (801 single pulses).

[4] Authors defined Error Rate as a function of three "error types": No-response errors (no answer at all during stimulation); Hesitations (delayed answer during stimulation); Calculation errors.

the technique, thus allowing a functional chronometric map. On the other hand, repetitive and patterned TMS protocols have been used to establish causal information based on disruptive power protocols. In numerical cognition, rTMS has provided a more accurate spatial map of the regions causally involved in the different functions. (We summarize the main results in Section 3.7).

3.3. State-dependent TMS

The magnitude and direction of TMS-driven modulatory effects depend on the initial state of the stimulated brain tissue. According to these state-dependent stimulation effects, Silvanto et al. (2008a) developed a new TMS adaptation (TMSA) that increases the technique's functional resolution. They used adaptation to influence the initial state of a subset of cells that encode particular stimulus attributes (Silvanto et al., 2008a). In the pioneer study, subjects adapted to color/orientation combinations for 30 s and subsequently reported the color of test stimuli. TMS was delivered during the test stimulus presentation, resulting in TMS improving the processing of adapted attributes while decreasing the performance of non-adapted attributes (Silvanto et al., 2007). Therefore, this method allows to selectively excite and suppress an anatomically overlapping population of neurons based on the state-dependency effects of TMS.

The transcranial magnetic stimulation adaptation paradigm (TMSA) can be applied in cognitive studies using adaptation to manipulate neural activation states before TMS application, thus controlling which neural populations are preferentially activated by TMS (Silvanto and Pascual-Leone, 2008). For instance, Cohen Kadosh et al. (2010) used TMSA to examine the existence of functionally segregated overlapping populations of neurons for different numerical formats within the IPS. They tested two competing hypotheses: whether number-sensitive neurons code numbers in a format-independent fashion or preferably in a format-dependent fashion. In the first experiment, subjects were adapted to digits (i.e., 7), while in the second, they were adapted to

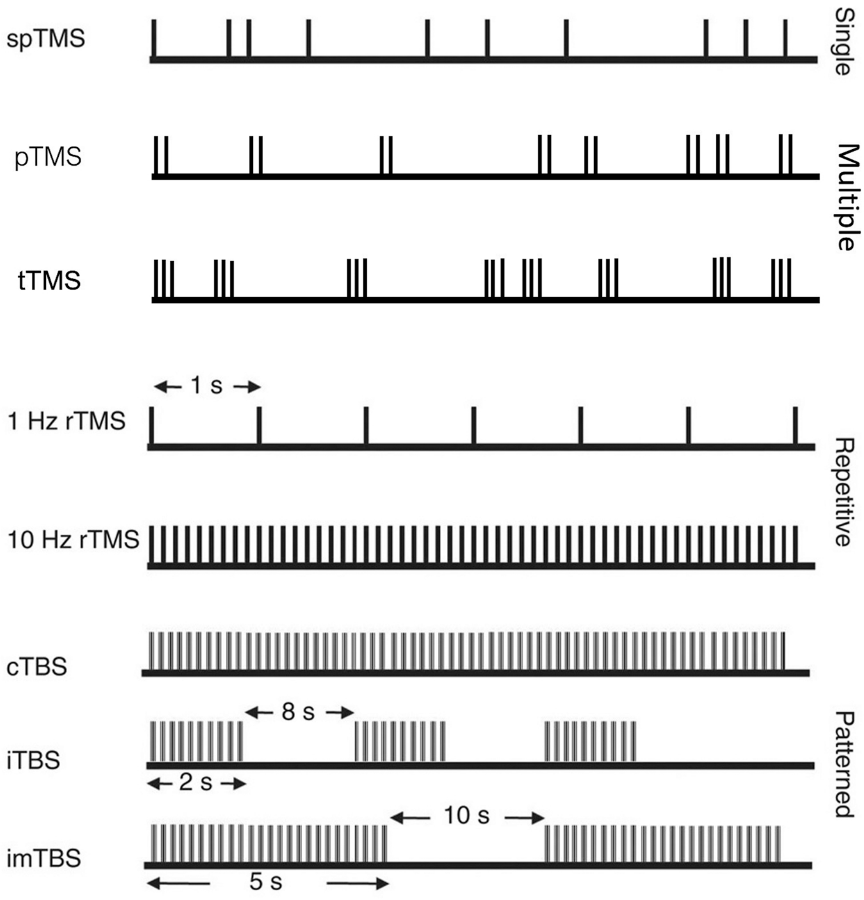

Fig. 2. TMS protocols. TMS protocols differ in the number and frequency of pulses delivered. In single-pulse stimulation (spTMS), individual pulses are delivered separately for at least 4 s. In multiple TMS, several pulses are applied with an inter-stimulus interval of a few milliseconds: either paired pulses TMS (pTMS) or triple pulses TMS (tTMS). In repetitive TMS, trains of pulses are applied with a fixed frequency (low frequency: 1–5 Hz, or high frequency: 5–20 Hz). Theta-burst stimulation consists of applying bursts of several pulses, repeated at a frequency close to 5 Hz (cTBS), or each burst is applied for 2 s and repeated every 10 s for 190 s (intermittent TBS, iTBS). In a third variant, intermediate TBS (imTBS), 5 s burst trains are repeated every 15 s.
Figure adapted with permission from Dayan et al. (2013).

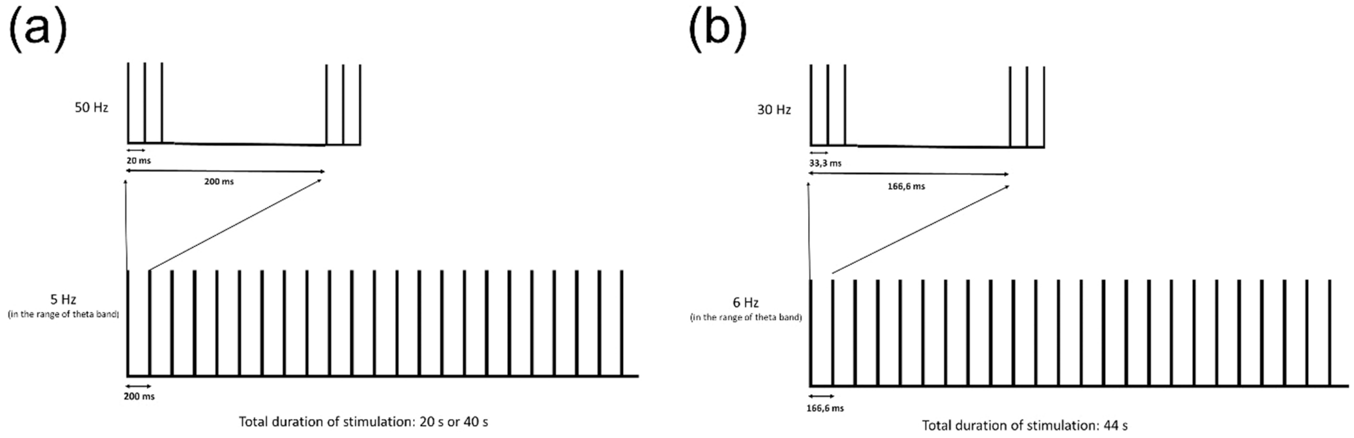

Fig. 3. Different protocols used in theta burst stimulation (TBS). TBS is a repetitive transcranial magnetic stimulation with a series of bursts (3 or 8 pulses) repeated in the theta band range (i.e., near 5 Hz). (a) The original protocol designed by (Huang et al., 2005) consisted of short bursts of 3 pulses at 50 Hz (i.e., interval inter-stimulus of 20 ms), which are repeated every 200 ms (frequency of 5 Hz, in the range of theta band) as a continuous train during 20 s or 40 s (b) Riemer et al. (2016) used a modified protocol with bursts containing three biphasic pulses (applied at 30 Hz) repeated at 6 Hz during 44 s. Note the inter-stimulus intervals represented in the figure.

verbal numbers (i.e., SEVEN). Results show that both parietal lobes are equipped with format-dependent populations of neurons that encode quantity. The TMSA effect modulates the adapted format's quantity processing, thus yielding a positive beta value between adaptation and numerical distance only to the numerical format adapted. Concretely, in experiment 1 (digit adapted) TMSA effect decreases according to the distance of the numbers of the MNL, only for digits but not for verbal numbers, in both left and right IPS. Conversely, in experiment 2 (number words adapted), only left IPS revealed such a TMSA effect for verbal numbers. In conclusion, Cohen Kadosh et al. (2010) found that right parietal lobe stimulation has a dissociation between digits and verbal numbers, whereas the left parietal lobe has a double dissociation between these different numerical formats.

Nevertheless, the use of TMSA in cognitive studies requires special attention to experimental design. It is crucial to ensure that specific neuron populations' initial state has been specifically affected. Renzi et al. (2011) used state-dependent TMS to investigate whether the PPC has selective neurons for motion direction and magnitude. Subjects were adapted to either random-dot displays moving to the left or the right. Motion direction adaptation was followed by trials of numerical magnitude judgments, with a single pulse TMS applied over the left PPC, the right PPC, or vertex at target onset. In this study, participants had to carry out an additional control experiment to ensure that the effect was due to PPC-TMS adaptation of neurons selective for both motion direction and numerical magnitude, rather than reversing spatial attention habituation (see details in Renzi et al., 2011). Data obtained indicate that direction of motion did not habituate spatial attention. Somewhat, PPC-TMS's effect on numerical processing was affected by the congruence of the adapting stimulus's motion direction. These effects demonstrate that motion adaptation modulates the initial state of neuronal representations causally involved in numerical magnitude judgments, providing evidence for a functional overlap in neuronal representations of motion direction and numerical magnitude.

3.4. Intensity

The choice of stimulation intensity in a cognitive experiment is not easy. In cognitive and perceptual studies, there is evidence that the effects of stimulation depend on intensity; for example, Schwarzkopf demonstrated in an on-line protocol that, at low intensity, TMS facilitated a perceptual task while higher TMS produced an impairment (Schwarzkopf et al., 2011). On the other hand, adjusting the intensity to be comparable between some subjects and others is necessary. There are three options: stimulating all subjects at the same absolute intensity, stimulating all subjects at the same intensity relative to the motor threshold, or stimulating all subjects at the same intensity relative to the phosphene threshold (PT).

It is not evident whether an absolute or relative value is better because we do not know precisely what a given stimulation level means in cortical modulation. Moreover, the stimulation threshold seems area-dependent (Stewart et al., 2001).

3.4.1. Relative to the individual motor threshold (MT)

The stimulation intensity is set to a percentage of the individual MT, either the resting motor threshold (rMT) or the active motor threshold (aMT). rMT is the lowest intensity capable of inducing a motor evoked potential (MEP) exceeding a defined amplitude in half of the trials when stimulation is applied to the motor cortex. On the other hand, aMT is the lowest intensity that produces a MEP with an amplitude greater than 5 out of 10 trials while the subject maintains a voluntary contraction. Both measures can also be assessed by visual inspection, i.e., observing a twitch in a tense or relaxed muscle. Studies have demonstrated high concordance between electrophysiological and visual MT estimations (Pridmore et al., 1998).

This method of determining the intensity is the alternative even when applying stimulation over non-motor cortical regions, as in the studies included in this revision. Rusconi et al. (2011); and Sasanguie et al. (2013) used protocols in which intensity was 110% of the individual aMT to stimulate prefrontal and parietal regions related to numerical representation. Rusconi et al. (2013) applied intensities of 120% of the individual rMT to investigate the right frontoparietal network related to mental number space. On the other hand, Maurer et al. (2016); and Riemer et al. (2016) used an intensity of 100% of the individual rMT in patterned TMS protocols over various cortical regions to investigate their involvement in numerical cognition.

3.4.2. Relative to individual PT

Since stimulation of the visual cortex can elicit phosphenes (bright spots of light in the visual field), it can serve as a self-reporting method for determining the relative intensity of a stimulation protocol. Like MT, PT is the lowest intensity capable of inducing phosphene perceptions in half of the trials (Elkin-Frankston et al., 2011).

The experiments developed by Salillas et al., (2012, 2009) used individual PT to determine the magnetic stimulation intensity applied over the parietal cortex in the numerical cognition study. They applied the pulses at the same relative intensity of 110% of the individual PT.

3.4.3. Fixed absolute intensity

Nevertheless, it has become common to stimulate all subjects at the same absolute intensity (a percentage of the maximum stimulator output, MSO), especially in numerical cognition studies, in which the most common target sites in the prefrontal and parietal cortices do not produce a readily and objective, quantifiable response. They are also unrelated to the motor or visual regions associated with motor responses or phosphenes.

Most of the studies included in this review used an MSO fixed intensity. The value of the intensity depends on the TMS protocol. Studies using single, multiple, or repetitive TMS applied pulses at an intensity ranging from 60% to 65% of the MSO. In the cTBS protocols, the stimulation duration is more considerable than the previous protocols, and the pulses' intensity is lower, around 40% of the MSO.

The fixed intensity approach reduces experiment duration and moderates the number of magnetic pulses by eliminating the individual threshold phase. The fixed stimulation value is usually defined based on literature, considering the lowest intensity capable of affect behavior when TMS is applied over the target region. Some studies in this review report the correspondence between intensity based on individual threshold and the machine's intensity (see Table 3).

3.5. Localization methods

Accuracy in coil placement is crucial in TMS studies. In the active TMS protocols, the figure-of-eight coil is placed tangentially to the scalp over the target region, since in this way, the smallest angle implies the shortest path for the magnetic field to cross the skull and reach the target cortical region (Valero-Cabré et al., 2017). The studies included in this review used this standard configuration (see appendix B). However, various methods are helpful to place the coil on the exact area of the scalp that covers a particular cortical region. The most frequent is to use neuronavigation stereotaxic systems, which track the coil position in a 3D reconstruction of each participant's MRI head-brain volume in real-time. Nevertheless, it can also be done based on the 10 EEG system. The articles included in this review use five different strategies to accurately position the coil over the target region.

Eight studies used neuronavigation systems based on group coordinates (from previous studies), five used individual MRI-guided neuronavigation, five used fMRI-guided neuronavigation, and one study localized the coil based on the 10–20 EEG system. Finally, two studies developed by Salillas et al., (2012, 2009) used the SoftTaxic Evolution Navigator system that works without radiological images.

3.5.1. Individual fMRI guided TMS Neuronavigation

The most precise system is the individual fMRI-guided TMS Neuronavigation, in which target areas are identified based on individual

Table 3
Correspondence between relative and absolute intensities used in TMS studies.

Study	Target region	Relative Intensity	Absolute intensity (% MSO)		
			Mean	Range	SD.
Riemer, 2016	Right PPC	100% rMT	47.3% MSO	32–60%	
Rusconi, 2013	Right PPC	113% rMT	51% MSO		7.6
	Right FEF		49% MSO		9.3
	Right IFG		48% MSO		8.1
Maurer, 2016	Right hemisphere	100% rMT	35% MSO	32 – 37%	
	Left hemisphere		32% MSO	30 – 34%	

functional activation maps. For instance, Andres et al. (2011) carried out a two-experiment study in which they initially determined the parietal areas involved in subtraction and multiplication utilizing fMRI. Then, they applied rTMS over the regions showing a maximal increase of activity, located in the IPS horizontal segment (HIPS) and the posterior superior parietal lobe (PSPL). TMS was applied 100 ms after the onset of the stimulus to interfere on-line with solving the arithmetic operations: subtraction and multiplication. Table 2 shows the main effects of TMS over target sites. Results point to the left HIPS' essential role in arithmetic and indicate the right HIPS contribution, suggesting that the two homologous areas play complementary roles. In contrast, the PSPL seems to underlie processes that are not crucial to solving basic subtraction and multiplication problems.

3.5.2. *Individual MRI-guided Neuronavigation*

The TMS coil can be navigated with the frameless stereotaxic systems to target specific anatomical areas based on individual subjects׳ structural brain images. This system provides on-line information about the location of the coil.

Cattaneo et al. (2009) used this procedure in a study addressing the AG's role in modulating visuospatial attention by the MNL. In this study, the researchers localized AG in each subject based on sulcal landmarks from individual MRI scans projected to the scalp surface utilizing the co-registration system. Before testing, T1-weighted MRI scans were obtained from each participant. The specific site was defined as the region directly adjacent to the superior temporal sulcus's dorsolateral projection, which bifurcates the AG. The stimulation sites were then localized using the stereotaxic system. In this study, the Talairach coordinates of the projected cortical area were measured for all subjects, resulting in the principal Talairach coordinates in both hemispheres: − 46, − 66, 38 (SD=4.6, 4.1, 6.4) and 46, − 64, and 34 (SD=4.5, 3.3, 3.6).

3.5.3. *TMS Neuronavigation based on group Talairach or MNI coordinates*

Another possibility is the so-called "probabilistic approach," in which the coordinates could be generated from previous studies (Sandrini et al., 2011). For instance, Sasanguie et al. (2013) addressed the bilateral IPS in two cross-notational priming experiments. They used the MNI coordinates of the activation peak from a precedent fMRI study of number priming. This localization method does not consider individual structure-function differences, requiring larger sample sizes.

Another stereotactic neuronavigation technique was utilized by Salillas et al. (2012), with a system that works in the absence of radiological images. Although individual radiological head images (i.e., MRIs) were not available, they automatically estimated Talairach coordinates of cortical sites underlying coil locations for each subject. Then, they determined the stimulation sites by entering the Talairach coordinates of the reference points.

3.5.4. *Based on the 10–20 EEG System*

In contrast, the less precise method of positioning the coil is based on the 10–20-EEG system (Jasper, 1958; Klem et al., 1999). In this case, the experiment time is shorter, and there is no need to take images previously. Using a TMS-adaptation paradigm, Renzi et al. (2011) studied the overlapping representations of numerical magnitude and motion direction in the PPC. They included three TMS conditions in the study: the right PPC, the left PPC, and the vertex. Target sites were localized based on the 10–20 EEG system.

3.6. *Study design and control conditions*

The TMS studies included in this review have an experimental design: pseudo-randomized (n = 12) or randomized controlled trials (n = 9). Sample sizes ranged from 5 to 22 participants. Most of them use a within-subject design (n = 20), in which every participant receives all the different stimulation conditions (see Table 2). One of the studies employed a between-subjects design (Cheng et al., 2013).

Because TMS generates auditory and tactile sensory effects and could impact performance during on-line experiments, it is essential to ensure control. Moreover, TMS may interfere with cerebral networks' activity and even produce artifacts when other measures are recorded. Robertson et al. (2003) point out four possible ways for dealing with these difficulties in the use of TMS for cognitive studies: (1) control condition based on sham or placebo TMS, (2) control condition based on stimulating alternative cortical sites, (3) control condition based on behavioral dissociation, or (4) a double dissociation: behavioral and structural. All the TMS studies included in this review used one or a combination of these control conditions.

3.6.1. *Control condition based on sham or placebo TMS*

Cappelletti et al. (2009); Cohen Kadosh et al. (2010); Riemer et al. (2016); and Rusconi et al. (2013) placed the coil sideways or perpendicular to the skull surface in order to mimic the effects of active stimulation and used this sham stimulation as a control condition. Further, in Cappelletti et al. (2009) study, they used two control conditions: sham stimulation and no stimulation, finding no significant difference between these two conditions across any of the tasks or stimuli used.

3.6.2. *Control condition based on stimulating alternative cortical sites*

Another control method is to stimulate a second area of the brain that meets two conditions: distance from the target area at least 1.5–2 cm (i.e., the spatial resolution of TMS) and not being involved in the cognitive network active during task execution. In this method, TMS is applied to the control area in the same conditions and the same parameters used for the target area. The Control area can be proximal in the same hemisphere but finding a region unrelated to the task is not easy. Also, the contralateral region can be used as a control, as long as the function to be analyzed is clearly lateralized. However, the region most frequently used as a control in numerical cognition TMS studies is the scalp vertex region in the intersection (Cz position according to the 10–20 EEG system).

Andres et al. (2011); Cheng et al. (2013); Dormal et al. (2012); Grotheer et al. (2016); Hayashi et al. (2013); Cohen Kadosh et al. (2010); Lecce et al. (2015); Montefinese et al. (2017); Renzi et al. (2011); Rusconi et al. (2011); Salillas et al., (2012, 2009); and Sasanguie et al. (2013) used vertex as control site in their TMS experiments. This region is selected because vertex stimulation reproduces the auditory and somatosensory activations caused by parietal TMS while not affecting number processing.

3.6.3. *Behavioral dissociation and double dissociation*

Besides the control conditions mentioned above, it is also frequent to use behavioral dissociation. In this case, an alternative behavioral task of equivalent difficulty is performed, with the same stimulation parameters delivered in the same area. The stimulation should not elicit changes over the control task.

By combining behavioral dissociation with site control, Cohen Kadosh et al. (2010), in a TMS-adaptation paradigm, established a double dissociation of format-dependent and number-specific neurons in the parietal cortex.

3.7. *Effects*

All studies used the performance in behavioral tasks related to numerical cognition as an outcome. The independent variables used were: (1) reaction times, (2) accuracy (as % error), and (3) changes in congruency effects or response code association effects. None of the studies reported improvements in the performance of the analyzed tasks. Depending on the region stimulated and the task assessed, the studies showed impairment or no effect (Table 2).

All the rTMS studies included in this review are based on the "virtual lesion metaphor," whose initial definition quotes: "in the context of a task, the induced current operates as neural noise; that is, the pulse adds random activity during organized activity in the cortical region. This neural noise serves to delay or disrupt performance, and in this sense, TMS operates as a lesion" (Walsh and Rushworth, 1999, p. 127). This strategy sought to show the involvement of specific brain structures in specific cognitive functions.

Magnetic stimulation was applied to the parietal and frontal regions. The main target regions were the intraparietal sulcus (11 studies), the angular gyrus (3 studies), and other parietal structures (6 studies). In addition, three studies applied stimulation over prefrontal sites, and 1 study applied stimulation to the left lateral occipital complex (LO) and the right Number Form Area (NFA).

The cognitive functions analyzed in the studies included in this review cover a wide range of cognitive functions (see Table 1). Thus, allowing an accurate map of the regions involved in each cognitive function. We will summarize TMS's main effects on parietal structures (IPS and AG) and other structures.

3.7.1. *Intraparietal sulcus*

IPS is at the center of numerical cognition (Butterworth and Walsh, 2011; Cohen Kadosh et al., 2015). Therefore, various processes associated with this structure have been studied using TMS to establish causal relationships between neural substrates and domain-specific cognitive functions associated with numerical and spatial quantities processing.

Regarding the processing of numerosity and lengths, the right IPS proved to be fundamental since when its activity is disrupted, higher error rates are more common, hindering adequate processing of both magnitudes. This phenomenon suggests that they are processed by the same general magnitudes system (Dormal et al., 2012). However, Lecce et al. (2015) concluded that the processing of numerosities and continuous quantities are, to a certain extent, independent in the parietal cortex. A worse performance was obtained in the incongruous tasks when simulating left IPS. For the right IPS, subjects did not perceive the facilitating effect of the quantity's continuous characteristics in congruent tasks.

On the other hand, (Cappelletti et al., 2009) studied whether the bilateral IPS is necessary for quantity judgment, even when no numerical information is implied, such as deciding if a coat is bigger than a coat *bikini*. Likewise, conceptual tasks, including number symbols without quantity comparisons, such as interpreting a group of numbers as a date, can be impaired following TMS over the IPS. However, TMS did not impair perceptual decisions on number stimuli without numerical meaning like color judgment. Hence, the simple presence of numbers is not sufficient for IPS critical involvement, as are conceptual-level operations (Cappelletti et al., 2009).

Likewise, Sasanguie et al. (2013) found in their study that the TMS in bilateral IPS did not affect the "priming distance effect" in the tasks of pure stimuli with different notations (for example, dots vs. tones or digits vs. words- number). The priming distance effect was annulled when the left IPS was inhibited in the mixed tasks (symbolic and non-symbolic numerical information). This effect is relevant in mapping small symbolic and non-symbolic stimuli where both hemispheres would process the non-symbolic information, but the left would be in charge of activating the semantic areas for mapping (Sasanguie et al., 2013).

Previously, the numerical processing was assumed to be format-independent (Cohen Kadosh and Walsh, 2009). However, Cohen Kadosh et al. (2010) contradicted this assumption. They revealed that number-sensitive neurons encode numbers depending on the format in the IPS since there was a dissociation between digits and number words in the right IPS, as well as a double dissociation of the different formats in the left IPS, which could indicate that the numerical information is specific and not abstract.

Additionally, the NFA has proved crucial for fluency in letter and number processing since it is responsible for early visual processing of these stimuli, suggesting that numerical processing could be format-dependent (Grotheer et al., 2016).

Regarding automatic and intentional numerical processing, only when the IPS' right side is stimulated is there a size effect and a distance effect significantly smaller than the sham control and the left IPS. Consequently, these numerical processing types would share the same mechanism in the parietal cortex in charge of numerical cognition (Cohen Kadosh et al., 2012).

HIPS on the left hemisphere is crucial for numerical comparison focused on discrete quantities such as numerosities. HIPS-TMS produces a detriment in ordinal processing - reflected in a higher Weber fraction - and a facilitating effect in processing quantities - shorter reaction times. Therefore, ordinal and quantity processing would be distinct ways of manipulating the number with different parietal lobe manifestations (Cheng et al., 2013). Similarly, the bilateral HIPS is necessary for operations that involve precise calculation such as addition (Salillas et al., 2012) and operations that use memory retrieval processes such as multiplication, especially in the left HIPS (Andres et al., 2011).

The ventral portion of the IPS (VIPS) on the right hemisphere was identified as the center of the efficacy of multiplication because when stimulated, the participants obtain longer reaction times in these tasks in a way comparable to the effect of TMS on the left HIPS, denying the fact that only the hemisphere left of the IPS plays a vital role in multiplication (Salillas et al., 2012).

Likewise, Salillas et al. (2009) found that TMS over this same area reduces performance in visual motion processing and numerical comparison tasks. Therefore, it is likely that the number has a component of movement, and the VIPS would be part of the circuit in charge of integrating them, at the same time that it would have the function of complementing the HIPS in numerical comparison tasks and acting on the MNL.

3.7.2. *Angular Gyrus*

The AG is part of the neural circuit that modulates the role of the MNL in visuospatial representations. As proof of this, Cattaneo et al. (2009) used TMS in a priming paradigm with a line bisection task to evaluate bias in the spatial allocation of visual attention induced by exposure to small (16–24) or large (76–84) ends of the MNL. This task requires marking the midpoint of a line. Under normal conditions, each trial is preceded by a fixation image, while in the priming condition, the presentation of number digits, either small or large, preceded the target line. TMS over the right AG produced a decreased priming in small numbers while, for large numbers, the same effect was obtained in both hemispheres, particularly in the right hemisphere priming reversal effects (Cattaneo et al., 2009).

Montefinese et al. attributed a certain degree of participation to the HIPS, VIPS, AG, and supramarginal gyrus (SMG) areas in the processing of complex calculation: addition and subtraction of two digits so that these arithmetic operations would share brain networks to carry out the tasks successfully (Montefinese et al., 2017). However, despite the bilateral stimulation of all the structures, some presented more asymmetries than others, as in the case of right HIPS, which exhibited a predominant role compared to left HIPS and bilateral VIPS in summation. On the other hand, the bilateral SMG had a more significant effect on subtraction as AG had a greater effect on addition because they intervene in numerical verbal processing and visuospatial attention (Maurer et al., 2016; Montefinese et al., 2017). Finally, the study revealed that the right hemisphere would not be limited to numerical approximations or discriminations and has importance in complex computation, possibly due to visuospatial strategies (Montefinese et al., 2017).

3.7.3. *Other neural structures*

The dorsal frontoparietal circuits play an essential role in producing and maintaining numbers and space mapping (Rusconi et al., 2013). Both the rFEF and the rIFG are involved in the circuits for spatial attention and the SNARC effect, where the rIFG is in charge of orienting attention along the entire number mental line, and the rFEF focuses on small numbers exclusively (contralateral orienting). Similarly, Rusconi et al. (2013) attributed these structures to integrating the number's implicit spatial codes and the lateralized responses.

Additionally, TMS's caused a neuronal overlap of representations in the direction of movement and numerical magnitudes on bilateral PPC when comparing magnitudes tasks with large and small numbers (Renzi et al., 2011).

Regarding the integration of number, space, and time, in terms of the number-time relationship, the rIFG is necessary at the perceptual level, and the right IPC would be the center of integration between number and space that would process these magnitudes at the categorical. This statement coincides with the general theory of magnitudes (Hayashi et al., 2013). On the other hand, Riemer et al. (2016) found a dissociation between congruency effects and response code association, proving that the congruence between purely perceptual dimensions (space, time, and number) is processed by the PPC, while the congruence between those dimensions and behavioral responses is independent of the PPC.

4. Discussion

This review concludes that TMS applied to regions of the parietal cortex and prefrontal cortex has neuromodulatory effects, which translate into measurable behavioral effects affecting cognitive functions related to numerical and magnitude processing and arithmetic. Thus, TMS is a valuable technique for establishing relationships between specific brain structures and certain cognitive functions, at least as far as numerical cognition is concerned. To our knowledge, this is the most extensive systematic review showing the ongoing consolidation of TMS for the study of numerical cognition in recent years.

One of the advantages of NIBS over other techniques used to study the neural basis of cognitive processes is that stimulation can provide more robust interference-based evidence. However, we cannot infer causality without confirming that the stimulation above a specific region effectively modulates its activity. We assume this is the case in most studies, but a more robust inference should show that this regional activity was altered due to NIBS. Even in this case, there is the question of the contribution of other regions.

This systematic review shows the advantage of magnetic stimulation in numerical cognition studies because it allows spatial, temporal, and functional resolution that other techniques cannot achieve. In cognitive studies, NIBS (including both magnetic and electrical stimulation) have a higher functional resolution than neuroimaging techniques such as MRI, PET, or MEG, since they provide interference maps, which indicate the regions whose involvement (direct or by networks) is crucial for the cognitive function of interest. Furthermore, TMS protocols based on the state-dependency allow exploiting the functional resolution of the technique by differential stimulation of distinct but spatially overlapping neural populations within a stimulated region (Silvanto et al., 2008a; b). For instance, Cohen Kadosh controlled the initial activity utilizing neural population adaptation to distinct number formats (digits or verbal numbers). This experiment allowed differentiating functionally segregated overlapping populations of neurons for different numerical formats within the IPS. It evidenced a dissociation between digits and verbal numbers in the right IPS and a double dissociation between the different numerical formats in the left IPS (Cohen Kadosh et al., 2010).

TMS has made it possible to study the time course of numerical cognition processes regarding temporal resolution. For example, single pulse protocols achieve a temporal resolution of tens of milliseconds, allowing the study of the exact moment at which neuronal activity at the site is critical for performing the task. Rusconi et al. studied the time course of the right frontoparietal network involved in processing mental number space by applying single-pulse TMS over right PPC, right FEF, and right IFG, every 33 ms during 400 ms. The analysis of the different effects of stimulation in the early period (~25–60 ms) and the late period (~200 ms) in the studied areas suggests that right PPC is tied to explicit number magnitude processing and that rFEF and rIFG contribute to interfacing visuospatial mental codes with lateralized response codes (Rusconi et al., 2013). In contrast, this level of temporal resolution is not achievable with other NIBS, such as transcranial direct current stimulation (tDCS), where stimulation times vary between 10 and 30 min, to produce neuromodulatory effects (i.e., tDCS numerical cognition studies: Clemens et al., 2013; Klein et al., 2013, Sarkar et al., 2014; Grabner et al., 2015; Schroeder et al., 2017; Hartmann et al., 2019; Mosbacher et al., 2020). To the best of our knowledge, only one study of numerical cognition in the last 20 years applies tDCS in a reduced time window (1600 ms; Javadi et al., 2014); however, this resolution is far from the tens of milliseconds of the TMS. Due to the temporal resolution of TMS and EEG, there is hardly any other possibility to study the effects of the pre-stimulus state more effectively (Parkin et al., 2015).

In terms of spatial resolution, the behavioral spatial resolution of TMS effects ranges from 0.5 to 1.5 cm depending on the stimulated tissue (e.g., Beckers and Hömberg, 1992; Brasil-Neto et al., 1992; O'Shea and Walsh, 2007), and due to the rapid decline of the magnetic field, it does not reach depths greater than 2–3 cm below the skull (Sandrini et al., 2011). For electrical stimulation, the spatial resolution depends on the size of the electrode (Datta et al., 2009; Kuo et al., 2013), and the effects are not limited to the area immediately below the electrodes but to all areas affected by the electric field generated between electrodes (Cohen Kadosh, 2014), even reaching deep regions (To et al., 2018).

The studies included in this review show an additional advantage of TMS over tDCS, consisting of precision in identifying the anatomical or functional region to be stimulated. When combined with stereotaxic navigation systems associated with individual MRIs, TMS tracks in real-time the coil position in a 3D reconstruction of each participant's MRI head-brain volume, thus allowing a precise localization of the areas, which considers individual differences. On the other hand, numerical cognition studies using tDCS or high-definition transcranial direct current stimulation (HD-tDCS) employ conventional positions of the 10–20 EEG system (García-Sanz et al., 2021). Location is crucial in numerical cognition studies since significant individual differences in IPS anatomy exist (Zilles et al., 2003).

Nevertheless, when using NIBS to establish structure-function relationships, it is essential to consider the factors that influence the effects of stimulation and experimental design that guarantee their reliability and validity. We should also consider that inter- and intra-individual variables potentially explain TMS effects in healthy individuals (Gießing et al., 2020). These variables include anthropometrics factors such as sex (Turco et al., 2021; Pitcher et al., 2003) and age (Müller-Dahlhaus et al., 2008), genetic factors (Cheeran et al., 2008; Li Voti et al., 2011; Mori et al., 2011), and cortical networks organization (Cárdenas-Morales et al., 2014; Nettekoven et al., 2015), among other factors. Moreover, the modulatory effects depend on the TMS parameters: frequency, duration, and intensity (Parkin et al., 2015). TMS intensity is an essential variable in cognitive and perception studies because low intensities facilitate behavior, whereas high intensities cause impairment (Schwarzkopf et al., 2011). The study by Fresnoza et al. (2020) shows the importance of the time variable: the results show different effects of stimulation depending on whether the stimulation is applied online (during tasks) or offline (tasks performed after stimulation). The results show that participants were significantly faster in solving arithmetic problems 60 min after stimulation (off-line) than before and during (on-line) stimulation. They were faster in solving arithmetic problems when the left hIPS was stimulated than the vertex and AG. Moreover, the analysis showed that the participants were slower in solving multiplication than subtraction and slower in retrieving the answer than calculating it, particularly 60 min after stimulation (Fresnoza et al., 2020).

It is vital to consider factors for a proper experimental design selection and a thorough description of the methodology to ensure replicability. The choice between a parallel design (between subjects) or a crossover design (within-subjects) will depend on the expected interindividual variability. However, there is increasing interest in factorial designs that combine various stimulation protocol modalities with different stimulation sites and control tasks.

Using TMS for cognitive neuroscience studies requires considering state-dependency before drawing conclusions. Since it also interacts with brain state and baseline performance level (Silvanto et al., 2018). Investigations developed by (Renzi et al., 2011) and by (Cohen Kadosh et al., 2010) on magnitude processing show dependence on neuronal populations' initial activation state. Currently, the action mechanism of TMS to modulate behavior is a controversial issue, which limits the interpretation of many TMS studies. The three main models are: (a) the classical model that proposes that TMS modulates behavior by suppressing neuronal signals (Harris et al., 2008), (b) the model that postulates that TMS adds or induces neural noise (Walsh & Pascual Leone, 2003; Silvanto and Muggleton, 2008; Ruzzoli et al., 2010), and (c) a more recent one which considers TMS effects as an interaction between ongoing brain activity and TMS intensity (Silvanto and Cattaneo, 2017). This third model considers that low intensities can exert a facilitating or disrupting effect depending on the ongoing brain activity (Schwarzkopf et al., 2011), while a high-intensity TMS causes a synchronized high-frequency burst of discharge in a relatively large population of neurons followed by depression which effectively disrupts perceptual, motor, and cognitive processes in the human brain (Siebner et al., 2009). Therefore, at high intensities, the effect will be disruptive, while at low intensities, the effect depends on the activity of neuronal populations. Therefore, in research seeking to apply TMS to the clinical setting, it is crucial to consider that the effects will vary according to the initial state and the baseline performance level.

Besides, state-dependent changes in TMS-induced effects on functional connectivity between stimulated and distant areas correspond to regional activity in the stimulated cortex, suggesting a more substantial influence of TMS on active corticocortical connections. This phenomenon implies that when the connections are in an activated state, neuronal excitation propagates more efficiently through a neural network that seems to have a more disruptive effect on the functional interaction between the stimulated area and brain regions connected. In summary, state-dependency is crucial when interpreting the TMS effects in cognitive studies in general and, particularly, in numerical cognition.

This systematic review highlights two of the main current limitations in the field of numerical cognition: the lack of standardization in tasks (which would allow a better comparison between studies) and the lack of studies trying to target network activity to show a causal relationship between network activity and numerical cognition (by combining TMS with other techniques such as EEG). The studies included in this review employ different tasks to analyze distinct components of numerical cognition, but in the time range analyzed, no two studies use the same behavioral marker to measure the effects of stimulation. To overcome this, Zanon et al. (2021) developed the numerical stimuli generator, which is a step towards the standardization of non-symbolic numerical experiments. Regarding the approach and the combination with other techniques, all the studies analyzed in this review utilize the classical region-function mapping view. Although some studies considered and analyzed the networks involved (i.e., Hayashi et al., 2013; Montefinese et al., 2017; Rusconi et al., 2011), none directly addressed how TMS can interfere with network activity and related functions, considering neural outcomes measured by any other technique. (i.e., CT, MRI, fMRI, PET, MEG, EEG, NIRS). However, some studies analyze the neural effects of electrical stimulation in other regions (Clemens et al., 2013; Rutsche et al., 2015; Mosbacher et al., 2020).

In conclusion, the use of TMS for the study of the neural bases of numerical cognition allows addressing issues such as localization, timing, lateralization and has allowed establishing site-function dissociations and double site-function dissociations. Moreover, this technique is in a moment of expansion due to the growing knowledge of its physiological effects and the enormous potential of combining TMS with other techniques such as EEG, fMRI, or NIRS to reach a more precise brain mapping and to achieve a network approach.

5. Limitations

We acknowledge some limitations in this systematic review, including selection bias, since our search algorithm included only publications specifically reporting the effect of TMS on numerical cognition. We also acknowledge language bias since we only included articles in English and Spanish; however, they cover most of the current literature. Besides, our review results are only generalizable to analyzing healthy adults' numerical cognition.

Regarding the influence of waveform of magnetic pulses (monophasic or biphasic) in the motor cortex, TMS applied with monophasic or biphasic pulses produces different effects (Arai et al., 2005, 2007; Sommer et al., 2018). Considering that the effects of TMS in some regions and others are not comparable, it would have been interesting to compare the incidence of the waveform (monophasic or biphasic) in the effects on numerical cognition. However, this comparison was not possible due to missing data in the reviewed articles.

International collaborative efforts and exhaustive registries can help consolidate how TMS and other NIBS techniques might influence numerical cognition for cognitive enhancement in healthy subjects and the implications for individuals with different neurological conditions or neurodevelopmental disorders.

CRediT authorship contribution statement

Sara Garcia-Sanz: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper; Kemel A. Ghotme: Contributed data or analysis tools, Performed the analysis, Wrote the paper; Daniel Hedmont: Contributed data or analysis tools, Performed the analysis, Wrote the paper; Maria Yesenia Arévalo-Jaimes: Contributed data or analysis tools, Performed the analysis, Wrote the paper; Roi Cohen Kadosh: Conceived and designed the analysis, Performed the analysis, Wrote the paper; Josep M. Serra-Grabulosa: Performed the analysis, Wrote the paper; Diego Redolar-Ripoll: Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper.

All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jneumeth.2022.109485.

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