Non-invasive brain stimulation in modulation of mental rotation ability: A systematic review and meta-analysis

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Abstract
Mental rotation, the ability to manipulate mental images, is an important function in human cognition. This systematic review and meta-analysis investigates the potential of non-invasive brain stimulation in modulation of this component of visuo-spatial perception. The PubMed database was reviewed prior to 31 September 2020 on randomized controlled trials investigating the effects of repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS) on the mental rotation ability in healthy persons. A total of 17 studies (including 485 subjects) matched our inclusion criteria. Within their scope, overall, 46 sham-controlled experiments were performed. Methodology and results of each experiment are presented in a meta-analysis. The data show a large variety of methods and effects. The influence of (1) stimulation-technique (tDCS, tACS, and rTMS), (2) stimulation protocol (anodal, cathodal, bilateral tDCS, tACS, high-frequency rTMS, low-frequency rTMS, paired pulse rTMS, and theta burst stimulation), (3) stimulation timing (preconditioning and simultaneous), (4) stimulation location (left, right hemisphere, frontal, and parietal area), and (5) stimulus type (bodily and non-bodily) is discussed. The data indicate a beneficial effect of anodal tDCS and of tACS and no effect of cathodal tDCS on the mental rotation ability. Bilateral tDCS protocols both improved and worsened the parameters.

ABBREVIATIONS: aMT, active motor threshold; BOLD, blood-oxygen-level-dependent; CI, confidence interval; cm, centimetre; cTBS, continuous theta burst stimulation; Cz, vertex; DLPC, dorsolateral prefrontal cortex; DMPC, dorsomedial prefrontal cortex; dPMC, dorsal premotor cortex; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; Fz, mesial frontal cortex; h, hour; Hz, hertz; I2, inconsistency test; IAF, individual alpha frequency; IPS, intraparietal sulcus; iTBS, intermittent theta burst stimulation; LOTC, lateral occipitotemporal cortex; LPS, lobus parietalis superior; M1, primary motor cortex; mA, milliampere; min, minute; MRI, magnetic resonance imaging; ms, millisecond; MSO, maximal stimulator output; OF, offline; ON, online; Oz, occipital point; PET, positron emission tomography; PPC, posterior parietal cortex; pprTMS, paired-pulse repetitive transcranial magnetic stimulation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; pTPJ, posterior temporoparietal junction; rMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; s, second; SG, supramarginal gyrus; SMA, supplementary motor area; SSC, somatosensory cortex; T, test; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; TPJ, temporoparietal junction.
assessed. The small effect sizes obtained in mostly rTMS experiments require cautious interpretation.

**KEYWORDS**

mental rotation, non-invasive brain stimulation

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1 | INTRODUCTION

1.1 | Mental rotation

Mental rotation is psychological operation in which a mental image is rotated around some axis in three-dimensional space (Zacks, 2008). Since first presented by Shepard and Metzler (1971), numerous concepts were developed to assess this component of visuo-spatial perception (Figure 1). Current data repeatedly demonstrates correlations between superior mental rotation abilities and “success” in daily life. For example, optimal neurodevelopment during the first few months of life is associated, among others, with good mental rotation ability at age 6–10 years (Serdarevic et al., 2016). A higher mental rotation performance is significantly correlated to better mathematical achievement in boys between 7 and 9 years old and thus has implications for school practice (van Tetering, van der Donk, de Groot, & Jolles, 2019). Athletes and artists may present above average mental rotation performance (Sluming, Brooks, Howard, Downes, & Roberts, 2007; Voyer & Jansen, 2017). For example, professional musicians are 25% faster at mental rotation tasks than academically educated peers (Sluming, Brooks, Howard, Downes, & Roberts, 2007). Amateur gymnasts and orienteers demonstrate 50% better performance in mental rotation of cubes than contemporaries who take no regular sports (Voyer & Jansen, 2017).

On the other hand, relationships were also found between the reduction of mental rotation performance and ageing- or illness-related decline. Elderly (63–80 years) show significantly poorer mental rotation ability than young adults (17–29 years) (Techentin, Voyer, & Voyer, 2014). People who suffered from a major depressive disorder have a worse mental rotation performance than healthy peers (Chen et al., 2014), and the severity of depression symptoms correlates with the reduction of mental rotation ability (Oshiyama et al., 2018). Stroke victims show significantly poorer mental rotation performance than healthy controls (Braun et al., 2017; Daprati, Nico, Duval, & Lacquaniti, 2010), and the amount of sensitivity (Braun et al., 2017) and motor (Daprati, Nico, Duval, & Lacquaniti, 2010) deficits correlates with the disruption of mental rotation performance. Pain-related diseases are also associated with impaired mental rotation performance (Baarbé, Holmes, Murphy, Haavik, & Murphy, 2016; Kohler et al., 2019).

1.2 | Neural background of mental rotation

Several fMRI, PET, and EEG studies investigated the neural background of mental rotation in the last few decades (Hawes, Sokolowski, Ononye, & Ansari, 2019; Searle & Hamm, 2017; Tomasino & Gremsen, 2016; Zacks, 2008). Taken together, the data demonstrate that mental rotation is associated with extensive activation within several cortical areas in both hemispheres (e.g., inferior and superior parietal lobule, inferior frontal gyrus, middle frontal gyrus, supplementary motor area, inferior and middle occipital gyrus, and so forth) and the cerebellum (Hawes, Sokolowski, Ononye, & Ansari, 2019; Searle & Hamm, 2017; Tomasino & Gremsen, 2016; Zacks, 2008). Although bilateral activation was found for most areas (Hawes, Sokolowski, Ononye, & Ansari, 2019; Searle & Hamm, 2017; Tomasino & Gremsen, 2016; Zacks, 2008), some data also detected between-hemispheric asymmetries (Tomasino & Gremsen, 2016; Zacks, 2008). A previous review demonstrates more consistent parietal cortex activity in the right hemisphere and more consistent frontal cortex activity in the left hemisphere (Zacks, 2008). A more recent meta-analysis shows stimulus-dependent between hemispheric differences during mental rotation tasks (Tomasino & Gremsen, 2016). Mental rotation of “non-bodily” stimuli (e.g., Shepard-Metzler objects) induce right-lateralized activation, whereas “bodily” stimuli (e.g., hands and feet) leads to the activation of the bilateral sensorimotor network (Tomasino & Gremsen, 2016). An advanced review also refers stimulus-dependent differences of neural processing (Searle & Hamm, 2017). BOLD activation within the ventral stream and the premotor cortex increases linearly with stimulus discrepancies during mirror/normal discriminations only during mental rotation of bodily stimuli. Similarly, slow negativity over centroparietal regions as recorded by EEG increases for greater rotations only during mental rotation of bodily stimuli. Higher difficulty during mental

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rotation of non-bodily objects did not induce a higher neural network activation (Searle & Hamm, 2017).

Some data explain the neurological background of illness-related disruption of mental rotation (Kohler et al., 2019; Yan et al., 2012). A magnet resonance imaging study revealed that patients who suffer from complex regional pain syndrome have a reduced activation in certain areas including the subthalamic nucleus, nucleus accumbens, and putamen, during mental rotation tasks (Kohler et al., 2019). An electroencephalography study in stroke patients demonstrated a hypoactivity in frontal and central areas of the ipsilesional hemisphere, as well as hypo-activity of the frontal cortex bilateral during a mental rotation task (Yan et al., 2019). Thus, illness-induced reduction of the mental rotation ability seems to be associated with suppressed neural processing. In contrast, a superior mental rotation performance appears to be linked to enhanced neural processes. A fMRI study found that orchestral musicians have a significantly increased activation in Broca’s area during a mental rotation task, in addition to the visuospatial network, which was activated in both musicians and non-musicians (Sluming, Brooks, Howard, Downes, & Roberts, 2007).

1.3 | Non-invasive brain stimulation in modulation of neural and cognitive processing

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current/alternating current stimulation (tDCS/tACS) are innovative methods that can modulate neural processing within the cortex (Giordano et al., 2012).
et al., 2017; Herrmann, Rach, Neuling, & Strüber, 2013; Siebner & Rothwell, 2003) and have therefore the potential to influence the mental rotation ability. TDCS/tACS consists of the application of a low-intensity direct current/alternating current that flows between two electrodes (anode and cathode) (Herrmann, Rach, Neuling, & Strüber, 2013; Nasseri, Nitsche, & Ekhtiari, 2015). One of the electrodes is positioned over the target area (active electrode), the other (reference electrode) over another cranial or extracranial position. TMS is produced by passing short high-current pulses through an insulated coil of wire held over the scalp. The electric pulse induces a rapidly changing magnetic field with lines of flux running perpendicular to the coil (Lang & Siebner, 2007; Siebner & Rothwell, 2003). Acute physiological effects of non-invasive brain stimulation techniques distinguish tDCS/tACS from TMS. TMS produces high intensities of short-lasting electromagnetic currents that lead to a supra-threshold activation of the neurons. In contrast, tDCS/tACS does not generate action potentials in neurons, but bi-directionally modifies their spontaneous firing activity via subthreshold activation (Yavari, Jamil, Mosayebi Samani, Vidor, & Nitsche, 2018). Potentially oversimplifying, the basic idea is (i) anodal tDCS (anode over the target area) and facilitatory rTMS (high-frequency rTMS [≥ 5 Hz], intermittent theta burst stimulation [iTBS], and paired-pulse rTMS [pprTMS] [inter-stimulus interval >5 ms]) increase neuronal excitability and may consequently enhance cognitive performance; (ii) cathodal tDCS (cathode over the target area), inhibitory rTMS (low-frequency rTMS [1 Hz], continuous theta burst stimulation [cTBS], and pp rTMS [inter-stimulus interval ≤ 5 ms]) decreases neuronal excitability and subsequently worsen cognitive performance (Fertonani & Miniussi, 2017; Lang & Siebner, 2007). Indeed, the factors influencing the inter-individual variability of the effect of brain stimulation on neural and cognitive processing are not completely understood. Recent studies show, for example, high interindividual variability regarding the neural responses to “up” and “down” regulating brain stimulation protocols (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013; Wiethoff, Hamada, & Rothwell, 2014). It was also demonstrated that stimulation-timing (preconditioning/preceding versus simultaneously application) plays a critical role on stimulation effects on cognition (Hill, Fitzgerald, & Hoy, 2016; Yeh & Rose, 2019). In the past few years, there has been a rapid increase in the application of non-invasive brain stimulation techniques in modulation of mental rotation in healthy persons. This systematic review aims to investigate if non-invasive brain stimulation is effective in supporting this relevant visuo-spatial ability.

2 | METHODS

2.1 | Study selection

The PubMed database was reviewed up to 31 September 2020 for papers reporting the use of non-invasive brain stimulation in modulation of mental rotation ability in healthy subjects. The screening was performed according to the PRISMA guidelines. Search term (1) “transcranial direct current stimulation” and “mental rotation,” (2) “transcranial alternation current stimulation” and “mental rotation,” and (3) “repetitive transcranial magnetic stimulation” and “mental rotation” were used. Studies matching the following criteria were included: (1) human-studies, (2) prospective studies, (3) healthy subjects, (4) modulation of mental rotation ability by non-invasive brain stimulation, and (5) placebo-controlled study or study with at least two experimental groups/treatments. The screening was performed by two independent reviewers (JV and AE). Disagreements were resolved by consensus.

2.2 | Data extraction and risk of bias

Outcomes reported were (1) participants characteristics (age and gender), (2) methodological approach (number of participants, crossover/parallel groups design, assessments, number and scheduling of evaluations, and stimulation positioning techniques), (3) intervention characteristics (stimulation protocol, stimulation duration, stimulated area, and number of sessions), and (4) outcomes (assessments and between-group differences). The Oxford quality scoring system was applied to evaluate the methodological quality of trials included, such as random allocation, subjects and assessor blinding and description of dropouts and withdrawal (Jadad et al., 1996). Its overall score ranges between 0 and 5. The higher the score, the better the methodological quality of the study. Oxford quality score for studies enrolled in our meta-analysis is presented in Table 1 (tDCS/tACS) and Table 2 (TMS).

2.3 | Data synthesis and statistical analysis

Effect size and 95% confidence interval were calculated for each study and each assessment. On this basis, means were calculated for each stimulation technique (tDCS/ tACS and rTMS), stimulated hemisphere (left, right, bilateral, and central), stimulated area (frontal, parietal, frontal + parietal, and cerebellum), stimulation timing
| Reference/Oxford quality scoring scale | Number of participants/gender/age | Study design/blinding/positioning techniques | Stimulation protocol | Number of sessions/evaluations | Results (group*time effect/performed tests) |
|---------------------------------------|-----------------------------------|---------------------------------------------|----------------------|-------------------------------|------------------------------------------|
| Moghadas Tabrizi et al., 2019/2       | 60/30 males, 30 females/24 ± 0 years | Parallel groups (15 + 15 + 15 + 15)/subjects blinded/10–20 EEG system | (1) Anodal 1.5-mA tDCS (15 min) over right DLPF (F4), cathode over left supraorbital area | 5 sessions, evaluations: T1 before treatment, T2 post treatment | Anodal 1.5 mA tDCS over right F4 and right P4 significantly better than sham tDCS: Hands (reaction time and accuracy) |
|                                      |                                   |                                             | (2) Anodal 1.5 mA tDCS (15 min) over right PPC (P4), cathode over left supraorbital area |                                             |                                          |
|                                      |                                   |                                             | (3) Sham 1.5-mA tDCS (15 min, current turned off after 30 s) over right DLPF (F4), cathode over left supraorbital area |                                             |                                          |
|                                      |                                   |                                             | (4) Sham 1.5 mA tDCS (15 min, current turned off after 30 s) over right PPC (P4), cathode over left supraorbital area |                                             |                                          |
| Kasten et al., 2018/2                 | 20/12 males, 8 females/26 ± 3 years | Parallel groups (10–10)/subjects blinded/10–10 EEG system | (1) IAF tACS (20 min), at individual intensity (0.715 mA at mean), and frequency (10.5 Hz at mean), over Oz, cathode over Cz | 1 session, evaluations: T1 before treatment, T2 post treatment | IAF tACS at individual intensity, and frequency significantly better: Shepard-Metzler objects (accuracy) |
|                                      |                                   |                                             | (2) sham tACS (20 min, current turned off after 30 s), anode over Oz, cathode over Cz |                                             | No significant differences: Shepard-Metzler objects (reaction time) |
| Oldrati et al., 2018/2                | 27/9 males, 18 females/27 ± 6 years | Parallel groups (10–9–8)/subjects blinded/10–20 EEG system | (1) Anodal 1.5-mA tDCS (20 min) over left DLPC (F3), cathode over right deltoid muscle coupled with visuospatial skill training | 1 session, evaluations: T1 24 h before treatment, T2 24 h after treatment | Anodal 1.5 mA tDCS over left DLPC coupled with visuospatial skill training significantly better than sham tDCS, and anodal 1.5 mA tDCS over left DLPC followed by visuospatial skill training: Paper folding and cutting task (accuracy) |
|                                      |                                   |                                             | (2) Anodal 1.5-mA tDCS (20 min) over left DLPC (F3), cathode over right deltoid muscle followed by visuospatial skill training |                                             | No significant differences: Shepard-Metzler objects (accuracy) |
|                                      |                                   |                                             | (3) Sham tDCS (20 min, current turned off after 5 s), anode over left DLPC-F3, cathode over right deltoid muscle coupled with/ followed by visuospatial skill training |                                             |                                          |
| Kikuchi et al., 2017/3                | 40/40 males, 0 females/20–43 years | Parallel groups (20–10–10)/subjects blinded/10–10 EEG system | (1) Simultaneously 2.0-mA tDCS unilateral (20 min), anode over right LOTC (PO8), cathode over right DLCPC (F4) | 1 session, evaluations: T1 during treatment | Simultaneously 2.0 mA tDCS with anode over right LOTC, and cathode over right DLCPC significantly better than simultaneously 2.0 mA tDCS, with anode over right DLCPC, and |

(Continues)
| Reference/Oxford quality scoring scale | Number of participants/gender/age | Study design/blinding/positioning techniques | Stimulation protocol | Number of sessions/evaluations | Results (group*time effect/ performed tests) |
|---------------------------------------|-----------------------------------|---------------------------------------------|---------------------|-------------------------------|---------------------------------------------|
| van Elk et al., 2017/1                | 45/45 males, 0 females/21 ± 3 years | Parallel groups (16–15–14)/subjects blinded/10–20 EEG system | right DLPC (F4), cathode over right LOTC (PO8) (3) Sham tDCS (20 min, current turned off after 5 s), the same electrodes-positions as during active tDCS | 1 session, evaluation: T1 during treatment | cathode over right LOTC: Hands (accuracy) |
|                                       |                                   |                                             | Simultaneously 1-mA tDCS bilateral (20 min) with anode over right SG (CP6), and cathode over left SSC (C3) (2) Simultaneously 1-mA tDCS bilateral (20 min) with anode over left SSC (C3), and cathode over right SG (CP6) |                       | Bilateral 1 mA tDCS with anode over right SG, and cathode over left SSC significantly poorer than sham, and bilateral 1 mA tDCS, with anode over left SSC, and cathode over right SG: Avatar (reaction time for stimuli with high angular disparity ([180°] and for stimuli rotated along x and y axes) No significant differences: Avatar (reaction time for stimuli with low angular disparity ([0°, 60°, 120°] and for stimuli rotated along z axis) |
| Date et al., 2015/1                   | 28/14 males, 4 females/24 ± 4 (20–37 years) | Crossover (28–28)/subjects blinded/ TMS | (1) Anodal 1-mA tDCS (10 min) over left M1, cathode over right supraorbital area | 1 session, evaluations: T1 before treatment, T2 post treatment | Anodal 1 Hz tDCS significantly better: Hands (reaction time) No significant differences: Hands (accuracy) |
| Foroughi et al., 2015/2               | 45/11 males, 34 females/20 ± 2 years | Parallel groups (15–15–15)/subjects blinded/10–5 EEG system | (1) Anodal 2-mA tDCS (30 min) over right PPC, cathode over left upper arm (2) Cathodal 2-mA tDCS (30 min) over right PPC, anode over left upper arm (3) Sham tDCS (30 min, current turned off after 5 s) over right PPC, reference over left upper arm | 1 session, evaluations: T1 before treatment, T2 during treatment | Anodal 2 mA tDCS over right PPC significantly improved between T1 and T2: Shepard-Metzler objects (accuracy) Cathodal 2 mA tDCS over right PPC significantly deteriorated between T1 and T2: Shepard-Metzler objects (accuracy) No significant differences: Sham tDCS over right PPC |

Note: Cz, vertex; DMPC, dorsomedial prefrontal cortex; DLPC, dorsolateral prefrontal cortex; EEG, electroencephalography; h, hour; Hz, Hertz; IAF, individual alpha frequency; LOTC, lateral occipitotemporal cortex; mA, milliamperere; min, minute; M1, primary motor cortex; Oz, occipital point; PPC, posterior parietal cortex; s, second; SG, supramarginal gyrus; SSC, somatosensory cortex; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; T, test; TPJ, temporoparietal junction.
| Reference/Oxford quality scoring scale | Number of participants/gender/age | Study design/blinding/positioning techniques | Stimulation protocol | Number of sessions/evaluations | Results (group * time effect/performed tests) |
|---------------------------------------|-----------------------------------|---------------------------------------------|----------------------|-------------------------------|---------------------------------------------|
| Zeugin et al., 2020/0                  | 30/15 males, 15 females/25 ± 5 years | Crossover (30–30), subjects blinded/10–20 EEG system | (1) 1-Hz rTMS (1200 pulses, 90% rMT) over right TPJ  
(2) Sham rTMS (1-Hz rTMS, 1200 pulses, 90% rMT, coil at the same position) over Cz | 1 session, evaluations: T1 immediately after rTMS | 1 Hz rTMS over right TPJ significantly better than sham rTMS: faces (reaction time) |
| Cona et al., 2017/0                    | 15/5 males, 10 females/25 (21–31) years | Crossover (15–15–15), subjects blinded/neuronavigation, MRI scan | (1) 10-Hz rTMS (112 × 5 pulses, 100% rMT) over right dPMC  
(2) 10-Hz rTMS (112 × 5 pulses, 100% rMT) over left dPMC  
(3) Sham rTMS (10 Hz rTMS, 112 × 5 pulses, 100% rMT, coil at 45°) over Cz | 1 session, evaluations: T1 during rTMS (350 ms after each stimulus onset 5 rTMS pulses applied) | 10 Hz rTMS over right dPMC significantly poorer than sham rTMS: Shepard-Metzler objects (accuracy for the same stimuli), hands (reaction time for the same stimuli)  
10 Hz rTMS over right dPMC significantly poorer than sham rTMS and 10 Hz rTMS over left dPMC: Shepard-Metzler objects (reaction time for the same stimuli), hands (reaction time for the same stimuli)  
10 Hz rTMS over left dPMC significantly poorer than sham rTMS: Shepard-Metzler objects (accuracy for the same stimuli)  
No significant differences: Shepard-Metzler objects (accuracy and reaction time for the mirror stimuli), hands (accuracy for the same and the mirror stimuli, reaction time for the mirror stimuli) |
| Cona et al., 2016/1                    | 16/5 males, 11 females/24 (21–30) years | Crossover (15–15–15), subjects blinded/ 
M1 determined by TMS, SMA determined in relation to vertex (3 cm anterior, 0.5 cm left) | (1) 10-Hz rTMS (112 × 5 pulses, 110% rMT) over left SMA  
(2) 10-Hz rTMS (112 × 5 pulses, 110% rMT) over left M1 | 1 session, evaluations: T1 during rTMS (350 ms after each stimulus onset 5 rTMS pulses applied) | 10 Hz rTMS over left SMA significantly better than sham rTMS and 10 Hz rTMS over left M1: Shepard-Metzler objects (reaction time for the same stimuli, accuracy for the same stimuli with high angular disparity [100°, 150°]), hands (reaction time for the same stimuli, accuracy for the same stimuli with high angular disparity [100°, 150°]) |

(Continues)
| Reference/Oxford quality scoring scale | Number of participants/gender/age | Study design/blinding/positioning techniques | Stimulation protocol | Number of sessions/evaluations | Results (group * time effect/ performed tests) |
|--------------------------------------|-----------------------------------|---------------------------------------------|----------------------|-----------------------------|---------------------------------------------|
| Wang et al., 2016/0                   | 15/6 males, 9 females/2 (21–37 years) | Crossover (15–15)/subjects blinded/neuronavigation, MRI scan | (3) Sham rTMS (10 Hz rTMS, 112 × 5 pulses, 110% rMT, coil at 45°) over Cz | 1 session, evaluations: T1 during ppTMS (1st pulse at 300 s and 2nd pulse at 400 s after stimulus onset) | No significant differences: Shepard-Metzler objects (accuracy and reaction time for the mirror stimuli and for the same stimuli with low angular disparity [0°, 50°]), hands (accuracy and reaction time for the mirror stimuli and for the same stimuli with low angular disparity [0°, 50°]) |
| Picazio et al., 2013/1                | 42/18 males, 24 females/28 ± 4 (19–35 years) | Two experiments with parallel groups (7–7–7, 7–7–7)/subjects blinded/position determined in relation to inion (1 cm inferior, 3 cm left) | (1) 0.2-Hz ppTMS (80 × 2 pulses, separated by 100 ms, 110% rMT) over right pTPJ | 1 session, evaluations: T1 following cTBS | 50-Hz cTBS over left lateral cerebellum significantly poorer than sham TBS, and 50 Hz TBS over right lateral cerebellum: Embodied mental rotation task (reaction time), abstract mental rotation task (reaction time) |
| Pelgrims et al., 2009/0              | 20/20 males, 0 females/26 years | Crossover (20–20–20–20–20)/subjects blinded/MRI scan | (1) 10-Hz rTMS (60 × 5 pulses, 65% MSO) over right LPS | 1 session, evaluations: T1 during rTMS (100 ms after each stimulus onset 5 rTMS pulses applied) | 10-Hz rTMS over right SG significantly poorer than sham rTMS: Hands (reaction time) |

(Continues)
| Reference/Oxford quality scoring scale | Number of participants/gender/ age | Study design/blinding/positioning techniques | Stimulation protocol | Number of sessions/evaluations | Results (group * time effect/ performed tests) |
|---------------------------------------|-----------------------------------|---------------------------------------------|--------------------|-----------------------------|-----------------------------------------------|
| Feredoes & Sachdev, 2006/0             | 20/10 males, 10 females/25 years | Crossover (20–20–20–20)/subjects blinded/10–20 EEG system | (4) 10-Hz rTMS (60 × 5 pulses, 65% MSO) over left SG | 1 session, evaluations: T1 during rTMS (400 ms after each stimulus onset 4 rTMS pulses applied) | 10-Hz rTMS over right LPS significantly poorer than sham rTMS: Letters (reaction time) |
|                                       |                                   |                                             | (5) Sham rTMS (no stimulation, coil at the same position) |                | 10-Hz rTMS over left LPS significantly poorer than sham rTMS: Letters (reaction time) |
|                                       |                                   |                                             | (1) 20-Hz rTMS (38 × 4 pulses, 60% MSO) over right PPC |                | 20-Hz rTMS over right PPC significantly poorer than sham rTMS: Shepard-Metzler objects (accuracy for stimuli with angular disparity 120°) |
|                                       |                                   |                                             | (2) 20-Hz rTMS (38 × 4 pulses, 60% MSO) over left PPC |                | 20-Hz rTMS over left PPC significantly poorer than sham rTMS: Shepard-Metzler objects (accuracy for stimuli with angular disparity of 180°) |
|                                       |                                   |                                             | (3) Sham rTMS (20-Hz rTMS, 38 × 4 pulses, 60% MSO, handle perpendicular) over right PPC |                | No significant differences: Shepard-Metzler objects (accuracy for stimuli with angular disparity of 0° and 60°) |
|                                       |                                   |                                             | (4) Sham rTMS (20 Hz rTMS, 38 × 4 pulses, 60% MSO, handle perpendicular) over left PPC |                | 20-Hz rTMS over right LPS applied 400–600 ms after stimulus onset significantly poorer than sham: Alphanumeric characters (reaction time) |
| Harris & Miniussi, 2003/0              | 33/16 males, 17 females/31 (20–51) years | Four crossover experiments (9–9, 9–9, 9–9, 6–6)/subjects blinded/navigator software | (1) 20-Hz rTMS (32 or 64 × 4 pulses, 110% rMT) over right LPS | 1 session, evaluations: T1 during rTMS (a) 200–400 ms, (b) 400–600 ms, (c) 600–800 ms after each stimulus onset 4 rTMS pulses applied) | No significant differences between (a) sham rTMS and 20 Hz rTMS over left LPS applied 200–400 ms and 600–800 ms after stimulus onset, and (b) sham rTMS and 20 Hz rTMS over left LPS applied 200–400 ms, 400–600 ms, and 600–800 ms after stimulus onset: Alphanumeric characters (reaction time) |
|                                       |                                   |                                             | (2) 20-Hz rTMS (32 or 64 × 4 pulses, 110% rMT) over left LPS |                | |

(Continues)
| Reference/Oxford quality scoring scale | Number of participants/gender/age | Study design/blinding/positioning techniques | Stimulation protocol | Number of sessions/evaluations | Results (group * time effect/ performed tests) |
|--------------------------------------|----------------------------------|-----------------------------------------------|---------------------|-------------------------------|-----------------------------------------------|
| Klimesch et al., 2003/2 | 15/6 males, 9 females /25 (18–30) years | Crossover (15–15–15–15–15–15–15–15) /subjects blinded/ 10–20 EEG system | (3) Sham rTMS (20 Hz rTMS, 32 or 64 × 4 pulses, 110% rMT, coil at 45° and reverse) over posterior midline location | 1 session, evaluations: T1 immediately after rTMS | IAF ± 1 Hz rTMS over right IPS significantly better than sham rTMS; Cubes (accuracy) |
|                                 |                                  |                                               | (1) IAF + 1-Hz rTMS (24 pulses, 110% rMT) over right IPS (P6) |                              | IAF ± 1 Hz rTMS over Pz significantly better than sham rTMS; Cubes (accuracy) |
|                                 |                                  |                                               | (2) IAF - 3-Hz rTMS (24 pulses, 110% rMT) over right IPS (P6) |                              | No significant differences between sham rTMS and (a) IAF - 3-Hz rTMS over right IPS, (b) IAF - 3-Hz rTMS over Pz, (c) 20-Hz rTMS over right IPS, and (d) 20-Hz rTMS over Pz; Cubes (accuracy) |
|                                 |                                  |                                               | (3) 20-Hz rTMS (24 pulses, 110% rMT) over right IPS (P6) |                              |                                               |
|                                 |                                  |                                               | (4) IAF + 1-Hz rTMS (24 pulses, 110% rMT) over Pz | 1 session, evaluations: T1 immediately after rTMS |                                               |
|                                 |                                  |                                               | (5) IAF - 3-Hz rTMS (24 pulses, 110% rMT) over Pz |                              |                                               |
|                                 |                                  |                                               | (6) 20-Hz rTMS (24 pulses, 110% rMT) over Pz |                              |                                               |
|                                 |                                  |                                               | (7) Sham rTMS (IAF + 1-Hz rTMS, 24 pulses, 110% rMT, coil at 90°) over left IPS (P6) |                              |                                               |
|                                 |                                  |                                               | (8) Sham rTMS (IAF - 3-Hz rTMS, 24 pulses, 110% rMT, coil at 90°) over left IPS (P6) |                              |                                               |
|                                 |                                  |                                               | (9) Sham rTMS (20 Hz rTMS, 24 pulses, 110% rMT, coil at 90°) over left IPS (P6) |                              |                                               |
| Bestmann et al., 2002/1 | 14/11 males, 3 females/27 ± 6 years | Crossover (14–14–14) /subjects blinded/10–20 EEG system | (1) 20-Hz rTMS (100 × 4 pulses, 120% rMT) over right PPC (P4) | 1 session, evaluations: T1 during rTMS (100 ms after each stimulus onset 4 rTMS pulses applied) | 20-Hz rTMS over right PPC significantly poorer than sham: Centre-out pointing task (reaction time for large angles of rotation [105° and 140°]) |
|                                 |                                  |                                               | (2) 20-Hz rTMS (100 × 4 pulses, 120% rMT) over left PPC (P3) |                              |                                               |
preconditioning = offline, simultaneous = online), and stimuli (bodily and non-bodily). The effects on mental rotation ability were classified using Cohen's effect size definition ($d < 0.2$ “no effect,” $d = 0.2–0.49$ “small effect,” $d = 0.5–0.79$ “medium effect,” and $d \geq 0.8$ “large effect”) (Campbell, Machin, & Walters, 2007). The homogeneity of effects across studies was evaluated using the inconsistency test ($I^2$), where values above 50% were considered indicative of high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003).

3 | RESULTS

In total, 56 articles were identified for the above search procedure. Thirty-nine of them were excluded because of inappropriate article type, outcome, intervention, and/or population. The remaining 17 manuscripts corresponded with our inclusion criteria and were selected for this systematic review and meta-analysis. The detailed summary of the literature search is depicted in Figure 2. Overall, 485 subjects were enrolled. There are no reports of serious adverse events. The trials show a high variability regarding stimulation parameters, participant's characteristics, methodological approach, and effects of non-invasive brain stimulation on mental rotation performance (Figure 3). Table 3 demonstrates relationships between stimulation-induced effects on mental rotation ability and stimulation technique used, stimulation location and timing and stimuli used. Greater effects of mental rotation ability are associated with (1) tDCS and tACS, (2) stimulation of right hemisphere, (3) combined stimulation of frontal and parietal areas, and (4) using bodily stimuli. For more clarity, we split our presentation into studies investigating tDCS/tACS and studies investigating rTMS below.

3.1 | Transcranial direct current/alternating current stimulation

Seven studies evaluated the effect of tDCS/tACS on mental rotation performance. Within their scope, overall, 12 sham-controlled experiments were performed (Table 1).

3.1.1 | Methods

Overall 265 persons (161 males, 104 females), aged between 18 and 43 years, were enrolled. One study applied five tDCS sessions over 15 min (Moghadas Tabrizi, Yavari, Shahrbanian, & Gharayagh, 2019). The
remaining trials performed a single session of tDCS/tACS over 10–30 minutes. Anodal tDCS, (Date, Kurumadani, Watanabe, & Sunagawa, 2015; Foroughi, Blumberg, & Parasuraman, 2015; Moghadas Tabrizi, Yavari, Shahrbanian, & Gharayagh, 2019; Oldrati, Colombo, & Antonietti, 2018), cathodal tDCS (Foroughi, Blumberg, & Parasuraman, 2015), simultaneous tDCS bilateral (anodal tDCS over one hemisphere coupled with cathodal tDCS over the other hemisphere) (van Elk, Duizer, Sligte, & van Schie, 2017), simultaneous tDCS unilateral (anodal tDCS over one area coupled with cathodal tDCS over another area of the same hemisphere) (Kikuchi et al., 2017), and individual alpha frequency tACS (IAF tACS) (Kasten, Maess, & Herrmann, 2018) were evaluated. Exact stimulation parameters and stimulation location are presented in Table 1 and Figure 3. Four trials evaluated the mental rotation ability before and after tDCS application (offline) (Date, Kurumadani, Watanabe, & Sunagawa, 2015; Kasten, Maess, & Herrmann, 2018; Moghadas Tabrizi, Yavari, Shahrbanian, & Gharayagh, 2019; Oldrati, Colombo, & Antonietti, 2018). Two studies applied only evaluation during tDCS (online) (Kikuchi et al., 2017; van Elk, Duizer, Sligte, & van Schie, 2017). One trial tested before and during tDCS stimulation (online) (Foroughi, Blumberg, & Parasuraman, 2015). All studies included sham control. Five studies also compared two different stimulation protocols (Foroughi, Blumberg, & Parasuraman, 2015; Kikuchi et al., 2017; Moghadas Tabrizi, Yavari, Shahrbanian, & Gharayagh, 2019; Oldrati, Colombo, & Antonietti, 2018; van Elk, Duizer, Sligte, & van Schie, 2017). All studies except one (van Elk, Duizer, Sligte, & van Schie, 2017) were randomized trials. Only one study was double-blind (Kikuchi et al., 2017).

### 3.1.2 | Effects

Table 1 presents the effects of tDCS/tACS on mental rotation ability as detected in the enrolled studies. The data indicate supporting effects of anodal tDCS and of tACS (Date, Kurumadani, Watanabe, & Sunagawa, 2015; Foroughi, Blumberg, & Parasuraman, 2015; Kasten, Maess, & Herrmann, 2018; Moghadas Tabrizi, Yavari, Shahrbanian, & Gharayagh, 2019; Oldrati, Colombo, & Antonietti, 2018) and a worsening effect of cathodal tDCS (Foroughi, Blumberg, & Parasuraman, 2015) on the mental rotation ability. Opposite effects were demonstrated for reverse electrode positioning during simultaneous
stimulation (Kikuchi et al., 2017; van Elk, Duizer, Sligte, & van Schie, 2017). Anodal tDCS over the right parietal cortex coupled with cathodal tDCS over the right frontal cortex induces an increase, reverse electrode placement a decrease of mental rotation ability (Kikuchi et al., 2017). Anodal tDCS over the left parietal cortex coupled with cathodal tDCS over the right parietal cortex induces a significant worsening in comparison to a reverse protocol (van Elk, Duizer, Sligte, & van Schie, 2017). The effect size calculation (Figure 3) detected statistically relevant effects in a most experiments that reported significant intervention-induced changes within their cohorts (Table 1).

3.2 | Repetitive transcranial magnetic stimulation

Ten studies tested rTMS on influencing the mental rotation ability. In total, 34 placebo-controlled experiments were applied (Table 2).

3.2.1 | Methods

Overall 220 subjects (112 males, 108 females), aged 19–51 years, were included. All studies tested single rTMS session. Between 24 and 1200 rTMS pulses were applied per intervention; 10-Hz rTMS (Cona, Marino, & Semenza, 2016; Cona, Panozzo, & Semenza, 2017; Pelgrims, Andres, & Olivier, 2009), 20-Hz rTMS (Bestmann, Thilo, Sauner, Siebner, & Rothwell, 2002; Feredoes & Sachdev, 2006; Harris & Miniussi, 2003; Klimesch, Sauseng, & Gerloff, 2003), 1 Hz rTMS (Zeugin, Notter, Knebel, & Ionta, 2020), individual alpha frequency-based rTMS (Klimesch, Sauseng, & Gerloff, 2003), ppTMS (Wang, Callaghan, Gooding-Wiliams, McAllister, & Kessler, 2016), and cTBS (Picazio, Oliveri, Koch, Caltagirone, & Petrosini, 2013) were applied. Exact stimulation parameters and stimulation locations are presented in Table 2 and Figure 3. Most trials evaluated the mental rotation ability during rTMS application (online). Two to five TMS pulses were applied 100–800 ms after each stimulus presentation in these experiments.
Only three trials performed evaluation after rTMS completion (offline) (Klimesch, Sauseng, & Gerloff, 2003; Picazio, Oliveri, Koch, Caltagirone, & Petrosini, 2013; Zeugin, Notter, Knebel, & Ionta, 2020). A sham control was performed in all studies. Furthermore, all studies except for two (Wang, Callaghan, Gooding-Williams, McAllister, & Kessler, 2016; Zeugin, Notter, Knebel, & Ionta, 2020) compared the effects of two or more different stimulation protocols. Only some trials mentioned a randomized allocation (Bestmann, Thilo, Sauner, Siebner, & Rothwell, 2002; Cona, Marino, & Semenza, 2016; Klimesch, Sauseng, & Gerloff, 2003; Picazio, Oliveri, Koch, Caltagirone, & Petrosini, 2013). No study was double-blind.

### 3.2.2 Effects

Table 2 presents the effects of rTMS on mental rotation ability as detected in the included trials. Online 10-Hz rTMS over frontal lobes led to (i) improving (left SMA stimulation) and (ii) deterioration (right and left dPMC stimulation) or no significant changes (M1 stimulation) (Cona, Marino, & Semenza, 2016) of mental rotation ability. Online 20-Hz rTMS over both the right and the left posterior lobes induced deterioration of the observed parameters (Pelgrims, Andres, & Olivier, 2009). Online 20-Hz rTMS over both the left (PPC stimulation) and the right (PPC and LPS stimulation) parietal lobe deteriorated mental rotation ability (Bestmann, Thilo, Sauner, Siebner, & Rothwell, 2002; Feredoes & Sachdev, 2006; Harris & Miniussi, 2003). However, online 20-Hz RTMS over left parietal cortex (LPS stimulation) did not induce significant changes (Harris & Miniussi, 2003). Online ppTMS over the right posterior cortex showed no effect (Wang, Callaghan, Gooding-Williams, McAllister, & Kessler, 2016). Offline 1-Hz rTMS over this area improved the mental rotation ability (Zeugin, Notter, Knebel, & Ionta, 2020). Offline rTMS in the individual alpha frequency + 1 Hz (IAF + 1-Hz rTMS) applied over both central frontal cortex and the right parietal cortex increased mental rotation performance (Klimesch,
Sauseng, & Gerloff, 2003). Offline rTMS in individual alpha frequency 3 Hz (IAF 3-Hz rTMS) and 20-Hz rTMS over the same areas induced no effects (Klimesch, Sauseng, & Gerloff, 2003). Offline cTBS deteriorated mental rotation when applied over the left cerebellum but induced no changes by application over the right cerebel- lum (Picazio, Oliveri, Koch, Caltagirone, & Petrosini, 2013). Despite the intervention-induced changes reported in individual trials (Table 2), the effect size calculation (Figure 3, Table 3) detected statistically relevant effects only in a small part of the experiments.

4 | DISCUSSION

The aim of this systematic review and meta-analysis was to investigate whether non-invasive brain stimulation can support the mental rotation ability in healthy subjects. The available data demonstrate great inhomogeneity of effects across the experiments and indicate that non-invasive brain stimulation can both support and deteriorate this important visuo-spatial ability. In fact, the effect size calculation detected a relevant intervention-induced improvement of mental rotation in nine protocols. In contrast, eight protocols evoked a relevant worsening of this ability. The remaining 23 protocols did not have a clear effect (Figure 3, Table 3). The reasons for these inconsistencies may be the high heterogeneity of experiments regarding stimulation techniques (tDSC/tACS and rTMS), stimulation parameters (different protocols, durations, and intensities), stimulation location (different brain areas and hemi- spheres), stimulation timing (online and offline), and mental rotation objects (bodily and non-bodily). We will discuss how these factors may influence the effects of non-invasive brain stimulation on the mental rotation ability.

4.1 | Stimulation technique-dependent effects

The effect size calculation demonstrated that tDSC/ tACS induced greater effects on mental rotation ability than rTMS. In fact, only two rTMS protocols but 10 tDSC/tACS protocols induced relevant effects (Figure 3, Table 3). It is not clear whether and to what extent the differences reflect the differential impact of the various techniques on the human brain and cognition, and which role other factors (such as patient characteristics, study design, etc.) play. The included tDSC/ tACS studies differ considerably from rTMS studies regarding the applied methodological approaches. A major part of the rTMS studies performed stimulation during the cognitive task (online). In contrast, tDCS/ tACS studies performed simultaneous and preconditioning stimulation equally frequently (Figure 3). This is an important point because previous reviews and meta-analyses indicate that stimulation-timing may relevantly impact stimulation effects of cognitive performance (Hill, Fitzgerald, & Hoy, 2016; Yeh & Rose, 2019). Moreover, most rTMS studies did not perform a conventional repetitive application of TMS pulses with a constant frequency. Instead, short sequences of two to five pulses (with a given fre- quency) were time locked to the stimulus presentation during the cognitive task. A repetitive application of 38–200 sequences were performed in each subject within a few minutes (Table 1, Figure 3). The question is whether those protocols can be clearly considered as repetitive application of TMS? In contrast, a conventional uninterrupted stimulation was performed in all tDSC/tACS studies. Given these inconsistencies, we will discuss the rTMS and the tDSC/tACS studies separately.

4.2 | TDCS/tACS for modulation of the mental rotation ability

The effect size calculation indicates that tDCS/tACS is effective in the modulation of mental rotation (Figure 3, Table 3). However, the effects are highly inhomogeneous. We will discuss how stimulation-timing, electrodes-polarity, stimulation location and type of stimuli may influence the effectiveness.

4.2.1 | Stimulation-timing dependent effects

Overall 12 placebo-controlled experiments investigated tDCS in the modulation of the mental rotation ability. Only two protocols did not induce any relevant effect on the observed parameters (Foroughi, Blumberg, & Parasuraman, 2015; van Elk, Duizer, Sligte, & van Schie, 2017). Interestingly, both ineffective protocols performed simultaneous stimulation (online). Similarly, an earlier review and meta-analysis demonstrated that only offline (but not online) anodal tDCS significantly supports working memory in healthy populations (Hill, Fitzgerald, & Hoy, 2016). Interestingly, an opposite effect (supportive influence of online, but not offline anodal tDCS) was observed in neuropsychiatric populations (Hill, Fitzgerald, & Hoy, 2016). In any case, the available data indicate that tDCS/tACS timing may significantly influence the stimulation effect on human cognition.
4.2.2 | Electrodes-polarity dependent effects

Our data show polarity-dependent effects in accordance with the oversimplified theory that indicates that anodal tDCS/tACD improves and cathodal tDCS/tACS deteriorates cognitive performance (Fertonani & Miniussi, 2017). Similar results are presented in an earlier systematic review and meta-analysis that investigates the effect of tDCS over the dorsolateral prefrontal cortex on human cognition (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). Only anodal stimulation supported cognitive processing in both healthy and neuropsychiatric samples. Cathodal protocols did not induce significant effects (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). The data also show that a reverse positioning of electrodes during simultaneous unilateral stimulation evokes reverse cognitive changes (Kikuchi et al., 2017). While anodal stimulation over the right parietal cortex and cathodal stimulation over the right frontal cortex improves the mental rotation ability, the reverse electrode placement leads to its deterioration (Kikuchi et al., 2017). This result is supported by a previous systematic review and meta-analysis that detected between-hemispheric asymmetries during mental rotation tasks (Zacks, 2008). Parietal cortex activity is somewhat more consistently observed in the right hemisphere, whereas frontal cortex activity is more consistently observed in the left hemisphere (Zacks, 2008). This explains the supportive effect of anodal (and not of cathodal) tDCS over the right parietal regions.

4.2.3 | Stimulation-location dependent effects

Our data indicate that the positioning of the active electrode over the right hemisphere is more effective than both left hemispheric and simultaneous bilateral stimulation (with the anode over one hemisphere and the cathode over the other) (Figure 3, Table 3). Finally, simultaneous application over the right hemisphere (with electrodes over parietal and frontal cortical areas) induces greater effects than all another protocols (Kikuchi et al., 2017). In accordance, a previous meta-analysis emphasizes the superior role of the right hemisphere during some mental rotation tasks (Tomasino & Gremese, 2016). Whereas mental rotation of bodily stimuli (e.g., hands and feet) leads to the activation of the bilateral sensorimotor network, non-bodily stimuli (e.g., Shepard-Metzler objects) induce right lateralized activation (Tomasino & Gremese, 2016).

4.2.4 | Stimulus-type dependent effects

The effect size calculation indicates that tDCS/tACS is more effective in modulation of the mental rotation of bodily stimuli than in the modulation of non-bodily objects. A previous review refers to stimulus-dependent differences of neural-processing (Searle & Hamm, 2017). BOLD activation within the ventral stream and the premotor cortex increases linearly with stimulus discrepancies during mirror/normal discriminations, but only during mental rotation of bodily stimuli. Similarly, slow negativity over centroparietal regions as recorded by EEG increases for greater rotations only during mental rotation of bodily objects. Higher difficulty during mental rotation of non-bodily stimuli did not induce higher activation of the neural network (Searle & Hamm, 2017). It is conceivable, that stronger activation of the neural network during mental rotation tasks provides more opportunity for modulation with non-invasive brain stimulation and has thus greater effects on cognitive performance.

4.3 | rTMS for modulation of the mental rotation ability

The effect size calculation demonstrates that rTMS has only limited effectiveness in the modulation of the mental rotation ability (Figure 3, Table 3). From a total of 28 experiments, only two protocols induce relevant effects. However, Table 2 shows that any part of mental rotation tasks could be significantly influenced by this method. We will discuss how different factors influence the effectiveness of rTMS.

4.3.1 | Stimulation-timing dependent effects

The effect size calculation demonstrates relevant changes of mental rotation ability in one-half of the experiments that applied preconditioning stimulation and only in one-fifth of experiments that performed a simultaneous stimulation (Figure 3, Table 3). Thus, offline application seems to have more potential to influence the visuospatial ability. Similarly, a meta-analysis detected timing-dependent effects of rTMS for modulation of working memory (Yeh & Rose, 2019). Offline 20-Hz rTMS induces an improvement and online 20-Hz rTMS a deterioration of the observed parameters (Yeh & Rose, 2019). Moreover, in the framework of online stimulation, the timing of rTMS pulses in relation to cognitive tasks significantly impacted their effects. A study demonstrated that 20-Hz rTMS that was applied over the right lobus parietalis
superior 400–600 ms after stimulus onset affected the reaction time during mental rotation of alphanumeric characters (Harris & Miniussi, 2003). The same protocol applied 200–400 ms and 600–800 ms after stimulus onset did not induce any effects (Harris & Miniussi, 2003).

4.3.2 | Stimulation-frequency dependent effects

The data did not demonstrate frequency-dependent effects in accordance with the assumed supportive effects of high-frequency (≥5 Hz) and deteriorating effects of low-frequency (1-Hz) rTMS (Siebner & Rothwell, 2003). The studies show both supportive and disruptive effects of high-frequency protocols (Table 2). Ten-hertz rTMS induced worsening (Cona, Panozzo, & Semenza, 2017; Pelgrims, Andres, & Olivier, 2009) as well as improvement of the mental rotation ability (Cona, Marino, & Semenza, 2016). Twenty-hertz rTMS evoked deterioration (Feredoes & Sachdev, 2006; Harris & Miniussi, 2003) or no changes of the assessed parameters (Klimesch, Sauseng, & Gerloff, 2003). Individual alpha frequency + 1-Hz rTMS improved the mental rotation ability (Klimesch, Sauseng, & Gerloff, 2003). Individual alpha frequency–3-Hz rTMS did not affect the visuo-spatial performance (Klimesch, Sauseng, & Gerloff, 2003). Only one study tested a low-frequency stimulation protocol up to now. Its results show supporting effects of 1-Hz rTMS on the mental rotation ability (Zeugin, Notter, Knebel, & Ionta, 2020). One trial applied 50-Hz cTBS and demonstrated worsening of the mental rotation ability (Picazio, Oliveri, Koch, Caltagirone, & Petroolini, 2013). This is in accordance with the simplified concept that indicates supporting effects of iTBS and impeding effects of cTBS on neural and cognitive processing (Siebner & Rothwell, 2003); 0.2-Hz pp rTMS did not modulate the performance during the visuo-spatial task (Wang, Callaghan, Gooding-Williams, McAllister, & Kessler, 2016) and contradicts the positive role of paired-pulse rTMS with inter-stimulus interval >5 ms on neural and cognitive processes (Siebner & Rothwell, 2003). In accordance with our findings, the available systematic reviews and meta-analyses demonstrate that effects of diverse rTMS protocols for modulation of human cognition and behaviour are often contrary to the conventional frequency-dependent view (Siebner & Rothwell, 2003). A recent meta-analysis indicates a disruptive effect of 10-Hz and 20-Hz rTMS and no effect of 1 Hz or 5 Hz on attention, executive, language, memory, motor, and perception (Beynel et al., 2019). Another meta-analysis shows both improving and deteriorating effects of 20-Hz rTMS on working memory depending on the stimulation-timing (Yeh & Rose, 2019). In contrast, only positive effects were found for 1-Hz rTMS (Yeh & Rose, 2019).

4.3.3 | Stimulated hemisphere-dependent effects

The effect size calculation did not detect relevant effects regarding the stimulated hemisphere (right versus left) on rTMS effectiveness (Figure 3, Table 3). However, a closer look at our studies detected some hemisphere-dependent effects (Table 2). On the one hand, 10-Hz rTMS over both the right and the left dorsal premotor cortex impaired accuracy for the same stimuli during mental rotation of Shepard-Metzler objects (Cona, Panozzo, & Semenza, 2017). Only right hemispheric stimulation delayed reaction time for the same stimuli during mental rotation of both Shepard-Metzler objects and hands (Cona, Panozzo, & Semenza, 2017). This result contradicts the findings of an earlier meta-analysis that detected a more consistent parietal cortex activity in the right hemisphere, and frontal cortex activity in the left hemisphere during mental rotation tasks (Zacks, 2008). On the other hand, 20-Hz rTMS applied over the right lobus parietalis superior 400–600 ms after stimulus onset affected reaction time for alphanumeric characters (Harris & Miniussi, 2003). The same stimulation over the homologous area did not evoke any changes (Harris & Miniussi, 2003). This finding confirms the prominent role of right parietal areas (in comparison to the left hemisphere) during neural control of visuo-spatial tasks (Zacks, 2008). Another study indicates the prominent role of the left lateral cerebellum (in comparison to the homologous area) during mental rotation (Picazio, Oliveri, Koch, Caltagirone, & Petroolini, 2013). Fifty-hertz cTBS over left but not over the right hemisphere delayed reaction time during embodied and abstract mental rotation tasks (Picazio, Oliveri, Koch, Caltagirone, & Petroolini, 2013). One study demonstrates a differential involvement of both hemispheres depending on the stimuli angular disparity (Feredoes & Sachdev, 2006). Twenty-hertz rTMS over both the right and the left posterior parietal cortex impaired mental rotation of Shepard-Metzler objects (Feredoes & Sachdev, 2006). While the right hemispheric stimulation influenced stimuli with angular disparity of 120°, the left hemispheric stimulation affected stimuli with angular disparity of 180°. Stimuli with angular disparity of 0° and 60° were not affected (Feredoes & Sachdev, 2006). The differential involvement of the hemispheres depending on the stimuli angular disparity is a new finding, which has not been described in previous reviews and meta-analyses (Beynel et al., 2019; Yeh & Rose, 2019).
4.3.4 | Stimulated area-dependent effects

The effect size calculation shows no relevant impact of the stimulated region (frontal versus parietal) on rTMS effects (Figure 3, Table 3). However, some studies found significant stimulated area-dependent effects (Table 2). The data indicate that a simple subdivision of brain network in either “frontal” or “parietal” is too coarse to detect the effective involvement of specific brain regions during mental rotation tasks (Cona, Marino, & Semenza, 2016; Pelgrims, Andres, & Olivier, 2009). Ten-hertz rTMS over both the right and the left lobus parietalis superior delayed the reaction time during mental rotation of letters but not hands (Pelgrims, Andres, & Olivier, 2009). The same protocol applied over both the right and the left supramarginal gyrus slowed reaction time during mental rotation of hands but not letters (Pelgrims, Andres, & Olivier, 2009). Similarly, 10-Hz rTMS over the left primary motor cortex did not induce any changes (Cona, Marino, & Semenza, 2016).

4.3.5 | Stimulus-type dependent effects

The effect size calculation shows relevant effects in one third of the experiments that used bodied stimuli and only in one fifth of experiments that used non-bodied stimuli (Figure 3, Table 3). Similar effects were also detected for tDCS/tACS studies. The reason for this phenomenon may be stimulus-dependent differences of neural processing as described on a previous review (Searle & Hamm, 2017). Increased difficulty during mental rotation of bodily stimuli induces an increased activation of the neural network. Higher difficulty during mental rotation of non-bodily stimuli did not induce any effects (Searle & Hamm, 2017).

5 | CONCLUSIONS

The systematic review and meta-analysis presented here shows that non-invasive brain stimulation is effective in modulating the mental rotation ability. The available data indicates a supportive effect of anodal tDCS and of tACS and no effect of cathodal tDCS. Bilateral tDCS/tACS both supported and deteriorated the visuospatial performance. Only small effects were obtained in most rTMS experiments. Stimulation timing, stimulation location and stimulus type are factors that impact the effects of both tDCS/tACS and rTMS. Future research may apply these methods in cohorts with impaired mental rotation ability, such as major depressive disorder, stroke, and pain-related diseases.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS
JV and PJ concepted and designed the study. JV and AE performed the data acquisition. JV analysed and interpreted the data and wrote the first version of the manuscript. PJ and AG contributed to data interpretation and reviewed the manuscript.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15490.

DATA AVAILABILITY STATEMENT
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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