Review

Transcranial magnetic stimulation of visual cortex in memory: Cortical state, interference and reactivation of visual content in memory

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HIGHLIGHTS

▶ We review TMS evidence that visual cortex plays a causal role in memory for visual events.
▶ Memory retention and consolidation alter cortical functional state of visual cortex.
▶ TMS can reactivate visual memory content in occipital cortex and hMT+ into awareness.
▶ Visual cortex contains a topographically organized neural representation of sensory information in memory.
▶ The neural mechanism of memory in visual cortex may be similar for different memory systems.

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ABSTRACT

Memory for perceptual events includes the neural representation of the sensory information at short or longer time scales. Recent transcranial magnetic stimulation (TMS) studies of human visual cortex provided evidence that sensory cortex contributes to memory functions. In this review, we provide an exhaustive overview of these studies and ascertain how well the available evidence supports the idea of a causal role of sensory cortex in memory retention and retrieval. We discuss the validity and implications of the studies using a number of methodological and theoretical criteria that are relevant for brain stimulation of visual cortex. While most studies applied TMS to visual cortex to interfere with memory functions, a handful of pioneering studies used TMS to 'reactivate' memories in visual cortex. Interestingly, similar effects of TMS on memory were found in different memory tasks, which suggests that different memory systems share a neural mechanism of memory in visual cortex. At the same time, this neural mechanism likely interacts with higher order brain areas. Based on this overview and evaluation, we provide a first attempt to an integrative framework that describes how sensory processes contribute to memory in visual cortex, and how higher order areas contribute to this mechanism.

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1. Introduction

Traditionally, the brain's neural systems that retain perceptual experiences in memory are considered to be independent and architecturally non-overlapping with those that encode the sensory information [1–3]. Neurophysiological [4,5] and functional neuroimaging studies [6–11] have shown that memory retention and formation is associated with increased activity in mammalian prefrontal and parietal cortex, with little evidence for activity in sensory areas beyond the initial sensory stimulation. However, this classic notion is now met with controversial findings that show that sensory cortex plays a role in memory processing [12–14]. Several neurophysiological studies showed increased brain activity in visual cortex during the short-term retention of visual information, well after stimulus presentation [15–17]. Further, retrieval of episodic memories can activate modality-specific sensory cortex [18], and structural damage to visual cortex may lead to amnesia of visual memories [19], suggesting that visual cortex is involved in long-term memory storage. These and other findings suggest that, rather than being a reflexive encoding mechanism of sensory information, visual cortex is actively involved in memory consolidation and retrieval.

The correlational nature of the majority of these studies prevents a causal inference of sensory cortex activity in memory functions. To address causality in brain–behavior relations requires the experimental manipulation of brain activity and measure memory performance as a consequence. A classic example of such an approach are the studies by Penfield and co-workers [20,21], who intracranially stimulated sensory cortex in patients who were to undergo brain surgery. They found that stimulation of sensory cortex resulted in reactivation of autobiographical memories in the respective sensory modality, to a perceptual degree that closely resembled real-life sensory experiences. Clearly, the invasive nature of the measurement and recruitment of specific patient populations limits the broad application of this procedure. Transcranial magnetic stimulation (TMS) has proved to be a useful alternative to achieve localized brain stimulation in healthy participants [22–24]. In TMS, biphasic current flow through one or more coils of wire generates a magnetic pulse. Positioning the TMS coil over a position on the scalp allows delivery of the magnetic pulse to the cortical tissue underneath the coil, which locally alters electrical current flow in the neural tissue. This method can thus be used to experimentally test the functional role of sensory cortex in particular memory functions, or probe the criteria under which sensory cortex is functionally relevant to memory.

Following the classic memory-perception division, TMS has been applied to sensory cortex to study perception [25,26], and to higher order regions, such as lateral prefrontal and posterior parietal cortex, to study memory functions (e.g., [27–30]). Comparatively little work addresses how sensory cortex contributes to memory. However, the scientific interest in this topic is rapidly increasing. In this review, we discuss how TMS can be used to study this issue. We illustrate how different TMS protocols can be used to probe the functional contribution of visual cortex in memory retention and consolidation, and memory retrieval. An important consideration is that the available studies present a large heterogeneity of memory paradigms to investigate explicit and implicit memories at shorter and longer time scales. This heterogeneity precludes casting the review according to a particular memory model. Instead, we opted for an empirical approach, in which we discuss a more general mechanism of how sensory cortex contributes to memory formation and retrieval. We speculate on how memory mechanisms in sensory cortex are shared between different memory systems, and how they contribute to memory formation at different time scales. We think that our approach appreciates the value of the TMS studies of memory in sensory cortex, and

provides a parsimonious platform to synthesize the findings and derive future hypotheses for testing.

2. Considerations in this review

2.1. Structuring of the review

In this review we adopt an empirical approach to discuss the currently available literature. Table 1 lists the studies that are discussed in this review. Most studies use a 'learning by breaking' approach, in which TMS pulses are administered in order to interrupt neural functioning of the targeted area, thereby interfering with information processing and resulting in worsened cognitive performance. If memory retention requires activity in visual cortex, then a TMS pulse that alters brain activity in visual cortex will interrupt retention, leading to decreased memory performance. This approach has been used to study the contribution of visual cortex to implicit and explicit memory retention and consolidation on shorter and longer time scales.

In addition, TMS has also been used as a way to 'reactivate' visual content in memory into awareness (see Table 1). The handful of pioneering studies conducted so far demonstrate that TMS is especially suited for this approach, in which visual memory content is made available to awareness by inducing artificial sensory experiences, or phosphenes. A useful characteristic of phosphenes is that they reflect functional properties of the stimulated area [31–33]. For example, phosphenes induced with occipital TMS are observed in the visual field contralateral to the side of stimulation, and their visual field position follows the positioning of the coil over the scalp in a retinotopic fashion [33]. Phosphenes induced by TMS over central and lateral occipital sites are typically stationary, and can be of a particular color, shape or brightness. Phosphenes induced with TMS over the human motion complex (hMT+) exhibit localized movement [34,35]. Reactivation studies utilize this property of phosphenes to 'unveil' the current neural representation or 'brain state' of sensory cortex during memory retention or retrieval phases. In turn, these results provide further insight into the neural memory representations in visual cortex.

2.2. Positioning the TMS coil over visual cortex

An important factor in increasing the probability of finding an effect of TMS on behavior is how well TMS targets the cortical locus of interest [36,37]. Here, the strategy of coil positioning over the scalp may be crucial in attaining a strong behavioral effect. The most straightforward approach is to place the coil at the scalp position relative to the inion, an anatomical landmark on the scalp. Many researchers have used this approach to target the cortical representation of central (foveal) vision, or, with a more lateral positioning, to target one of the two hemifields (Fig. 1A). Based only on scalp coordinates, this approach ignores the large inter-individual variability in occipital cortical morphology and functional-anatomical mapping [38]. A more dynamic approach, and unique to TMS of visual cortex, is to induce phosphenes with TMS at different positions over the scalp in order to identify optimal coil position (Fig. 1B). The retinonotopic behavior of occipitally-induced phosphenes can be utilized to position the TMS according to the visual field location of the phosphenes [39–41], while moving phosphenes indicate stimulation of hMT+ or other cortical areas relevant for motion perception [34,35,42]. Importantly, phosphene localization requires subjective reports, and the probability of reliably seeing phosphenes differs across individuals, resulting from individual differences in cortical morphology, functional-anatomical mapping, the distance between scalp and cortex that the magnetic field must bridge and other

Table 1
Studies discussed in the review. Entries are organized according to TMS approach (interference (IF) or reactivation (RE)), memory paradigm (short-term memory (STM) or perceptual learning (PL)) and year of publication.

Paradigm	Study				TMS			Effect			
	Study	N	Task	Stimulus	Method	Target	Localization	Measure	Area	Topographic	Load
IF (STM)	Beckers and Homberg (1991)	3	DMS	Faces	spTMS	occ	0z	RT			X
	Campana et al. (2002)	7, 5	DET	Motion, color	rTMS	hMT+/occ/PCC	ph	RT	X		
	Cattaneo et al. (2009)	14, 11	STM/MI	Clocks	spTMS	occ/vx	ph	RT	X		
	Catteneo et al. (2011)	10, 8, 7	STM/MI	Gratings	spTMS	occ	ph	ph			
	Slotnick and Thakral (2011)	11	DMS	Motion	spTMS	hMT+	NNf	acc			
	Silvanto and Soto (2012)	8, 10	CD	Gratings	tpTMS	occ	ph	acc			
	Soto et al. (2012)	12	STM/VS	Landolph C,color	tpTMS	occ	inion	acc			
	van de Ven et al. (2012)	12	CD	Abstract shapes	spTMS	occ	ph, NNf	acc		X	X
IF (PL)	Corthout et al. (2000)	4	ID	Letters	spTMS	occ	0z	acc			
	Neary et al. (2005)	4.6	ODT	Gratings	spTMS	occ	inion	acc			
	Brascamp et al. (2010)	9	ILL	Motion	tpTMS	hMT+	NNa	bias			
	De Weerd et al. (2012)	7	ODT	Gratings	rTMS	occ (V1)	NNf	acc		X	
RE	Silvanto et al. (2007)	5, 7	AD	Color	spTMS	occ	inion	ph, acc			
	Jolij and Lamme (2010)	7	ILL	Gratings	spTMS	occ	inion	ph			
	Silvanto and Cattaneo (2010)	9	DMS	Motion	spTMS	hMT+/LOC	ph	ph	X	X	

Abbreviations: acc, accuracy; AD, adaptation task; CD, change detection task; DET, detection task; DMS, delayed match-to-sample; hMT+, human motion complex; ID, identification task; ILL, visual illusion; MI, mental imagery task; NNa(f), anatomical (functional) neuronavigation; LOC, lateral occipital cortex; occ, occipital cortex; ODT, orientation discrimination task; ph, phosphene detection or description; PPC, posterior parietal cortex; RT, reaction time; sp-/tp-/r-, single-pulse, repetitive or triple-pulse TMS; VS, visual search task; vx, vertex.

factors. To overcome some of these factors, the coil can be navigated across the scalp according to neuroanatomical (Fig. 1C) or functionally defined stereotaxic coordinates (Fig. 1D) of individual brains [37,43–45]. In the latter case, functional magnetic resonance imaging (fMRI) can be used to explicitly identify and target primary visual cortex (V1), extrastriate (early visual) cortex (V2/V3), or functionally specialized cortical sites, such as the Lateral Occipital Complex (LOC) or hMT+, as well as eccentricity coordinates. Consequentially, positioning the coil using fMRI-based neuronavigation can improve effect sizes of the TMS manipulation [37]. So far, only few studies have used this approach to investigate memory in visual cortex (see Table 1), but its use will grow with the increasing interest in investigating memory in visual cortex.

3. Memory interference

3.1. Short-term memory

The majority of TMS studies of memory in visual cortex investigated short-term memory performance. Theoretical models for short-term memory are discussed in great detail elsewhere [13,46,47]. Briefly, short-term memory is a capacity-limited memory system that retains information in mind for a short period
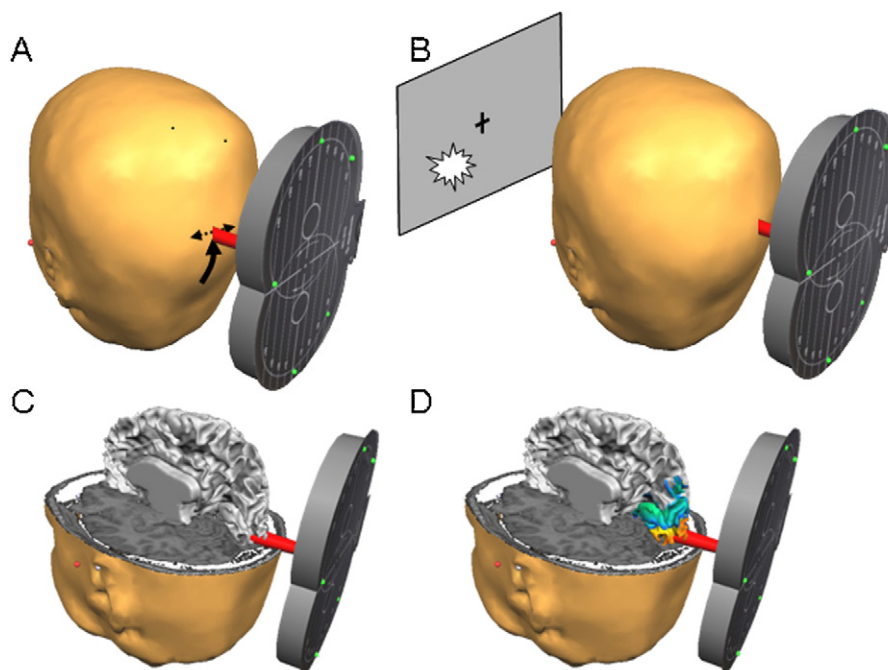
Fig. 1. TMS coil positioning strategies over visual cortex. The illustrations depict different positioning strategies of the TMS coil to target early visual cortex in the occipital lobe. An often used method is to position the coil at or near the inion, the most prominent projection of the occipital bone (A). Positioning can be optimized using phosphene localization, which typically follows the retinotopic organization of early visual cortex (B). Arguably most effective is to 'neuronavigate' the coil over the scalp according to individual brain anatomy (C) or functional mapping of retinotopic position on the cortex (D).

of time. Short-term memory storage is considered to be part of working memory [13,47], which is a cognitive system that exerts cognitive control over items in memory, protects them against interference from irrelevant sources of information, associates them with information in long-term memory, and allocates computational resources to the tasks at hand. The TMS studies that investigated the role of visual cortex in short-term memory used different memory tasks. For better comparison between the studies, we standardize the nomenclature according to the following definitions. In a typical short-term memory trial, *sample items* were briefly shown on the computer screen, and participants had to encode the visual information and keep it in memory during a *retention interval* of varying duration, lasting hundreds of milliseconds up to multiple seconds. Afterwards, a *probe item* was shown and participants judged if it was the same as the sample or not (change detection task), or if it matched to a subset of the sample items (delayed match-to-sample task, DMS). In many cases, participants were aware that their memory of the sample items were tested at a later time point, that is, the short-term memory tasks attempted to tap into explicit memory functions. In addition, memory performance can be measured as a function of increasing memory load (i.e., number of sample items). Retention is more easily interfered with if the number of information elements approaches the capacity limit of visual short-term memory, which is considered to be about four items [48,49]. At higher memory loads, information may not enter the short-term store, while at the same time the increased demand of processing resources may render the information in memory increasingly vulnerable to interfering events.

An immediate test of the hypothesis that visual cortex contributes to memory is to measure memory performance as a consequence of visual cortex stimulation during short-term retention. In the first TMS study of memory in visual cortex [50], three participants completed a DMS task with different memory loads, in which they retained up to four visual items in memory for about half a second. Single-pulse TMS was administered over the occipital pole either during retention or after probe onset. TMS during the retention interval did not affect memory performance. On the other hand, TMS administered after probe onset increased the reaction time as a function of memory load (i.e., item scanning time), which suggested an interference of the memory matching process of single items in memory.

More recent studies, however, have provided accumulating evidence that visual cortex supports memory retention. Silvanto and Soto [51] administered TMS over occipital cortex during a change detection task of oriented gratings. Halfway at the retention interval of 2 s, participants were either briefly shown a distracting stimulus congruent (CON) or incongruent (INC) to the sample item, or no distracter at all (NO). This event was then followed by the presentation of a non-grating mask stimulus. A 10 Hz triple-pulse TMS train was presented at distracter onset (or, during NO trials, when the distracter would have been shown). After the retention interval, participants saw the memory probe and had to report if it matched the sample stimulus. In a non-TMS behavioral experiment participants reported seeing the distracter in less than 20% of the trials. Of these trials, INC distracters decreased memory accuracy, compared to CON and NO distracters. When TMS was administered, memory accuracy decreased for trials in which no distracters were shown, compared to trials with a distracter and to a sham TMS condition, which suggests that TMS affected a memory representation in visual cortex. At the same time, TMS improved performance on trials with INC distracters. Here, TMS may have interrupted the processing of the distracter, thereby inhibiting its otherwise interfering effect on memory performance. Similar effects have been reported in studies of visual perception, in which TMS disrupts the effect of visual masks presented shortly after target presentation [25,52].

Further evidence for a memory representation in early visual cortex comes from a study by our group [39]. Participants completed a change detection task using small abstract shapes, in which the memory load varied between one and three simultaneously presented items across trials. A memory trial could be presented in one of the two hemifields. The TMS coil was positioned such that it affected processing of one hemifield, leaving the other as within-subject performance control. Single pulses were administered at 100, 200 or 400 ms into the retention interval. Results showed that TMS impaired memory performance when high load memory trials were presented in the visual field affected by TMS at 200 ms into the retention interval (Fig. 2A). Similar results were obtained in a non-TMS behavioral version in which a distracter stimulus replaced the TMS pulses. Interestingly, this is the first study to show an effect of memory load in TMS interference of memory, which fits the notion of a capacity-limited short-term memory system [48,53]. Memory retention is more vulnerable to interference if the memory load approaches the capacity limit. Human fMRI studies showed a neural correlate for the capacity limitation of VSTM in frontal and parietal cortex [6,8], in which brain activity increased monotonically with higher memory loads until the capacity limit was reached. Higher memory loads may then require more neural resources for memory retention, leaving fewer resources available to protect against interfering signals. Thus, these findings show that visual memory in early visual cortex is topographically organized and capacity-limited.

Further, the findings suggest that short-term consolidation occurs early during retention, which coincides with psychophysical assessments of an early short-term consolidation window lasting up to 500 ms [53–55]. Another study by Silvanto and co-workers provided further support for an early short-term consolidation window in visual cortex [56]. Single TMS pulses were delivered over occipital cortex at the onset or end of the retention of visual clock hands in memory. Results showed that TMS at retention onset delayed response times, compared to TMS at the end of retention. (The authors also compared the effect of TMS on memory performance with the effect on visual imagery performance, see below.) Thus, short-term consolidation at least requires a temporal window of ongoing activity in visual cortex. Interruption of this activity may impede on the consolidation process. After this window, information may be represented in visual cortex in a more stable form that is less vulnerable to interference. Of note, memory consolidation likely requires the interaction of activity visual cortex activity with activity in higher order areas (see Section 5). TMS may be well-suited to address these interactions (e.g., [27,57,58]), but this topic falls outside of the scope of this review.

The retention of relevant visual information may further rely on activity in those visual areas that are best suited to process the information, that is, memory in visual cortex may by functionally specific. For example, memory for visual motion may depend on activity of the human motion complex (hMT+). Slotnick and Thakral [44] used a 'list learning' version of the short-term memory task, in which participants saw a sample list of abstract colored shapes sequentially presented in either the left or right visual field. Shapes moved across a virtual arc within the hemifield, or remained stationary. After the sample list was completed, a retention period followed, after which a list of probe items was shown. For each item of the probe list, participants judged if they had seen this item in the sample list, and if so, if they saw the stimulus in the left or right visual field, and if the stimulus had moved or remained stationary. One hertz repetitive TMS was administered over either left or right hMT+ between the presentation of the sample and probe lists. Results showed that TMS over hMT+ decreased memory accuracy for previously moving items, irrespective of TMS location relative to location of the sample items, compared to no-TMS baseline and TMS over stationary stimuli.
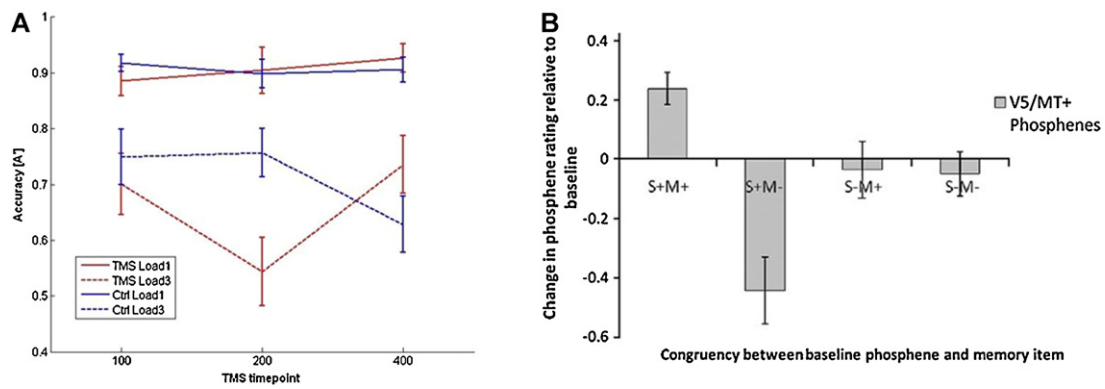
Fig. 2. Effects of TMS over visual cortex on memory. One criterion for a memory representation in visual cortex is that it is topographically organized. (A) Interference of memory retention using TMS shows a topographically organized memory impairment that is sensitive to the short-term capacity limit (van de Ven et al. [39]). Reproduced with permission. (B) TMS can also be used to induce phosphenes that contain features of the visual contents of short-term memory (Silvanto and Cattaneo [102]). Memory for visual motion alters the intrinsic motion direction of TMS-induced phosphenes toward the direction in memory only when phosphenes overlap with the visual location of the memory. S+(−), phosphene overlaps (does not overlap) with the memory location; M+(−), motion direction of the memory item is congruent (incongruent) with the intrinsic phosphene motion direction. Reproduced with permission.

Area hMT+ may also be involved in repetition priming of visual motion, a form of short-term implicit memory [42,59]. Repetition priming is a short-lasting form of memory that does not require explicit processing or cognitive effort. Consequentially, information processing is considered to be restricted to lower, sensory levels of processing. In one study [42], participants saw four panels of coherently moving dots (one panel per visual quadrant), of which dot movement in three panels was the same and one was different (odd-one-out). The priming effect was ascertained using a one-back presentation task, in which trial $N − 1$ contained an odd-panel in the same location as trial N. Thus, priming occurred if response to an odd-panel was faster when the odd-panel location was the same as in the previous trial. A short train of 10 Hz rTMS during a 500 ms period was presented 500 ms after stimulus onset. Control conditions included a no-TMS condition, TMS over occipital cortex and TMS over right posterior parietal cortex. Results showed that only TMS over hMT+ abolished the priming effect. Furthermore, TMS over hMT+ and other areas did not affect priming in a color detection task. Thus, information of visual movement is retained in visual areas that are functionally specialized to encode this information.

Together, these studies provide compelling evidence that visual cortex contains a neural representation or memory trace of the visual information. As a consequence, a neural memory representation should lead to altered cortical excitability of the neural networks in visual cortex that support the representation. If so, the memory representation could impede on the processing of other items that share neural resources. Using a sophisticated memory design, Soto et al. [60] investigated this possibility by applying TMS pulses over visual cortex during a visual search task, during which information could be held in short-term memory or not. At trial onset, participants were presented with a memory cue (a colored circle) twice, with varying stimulus-onset-asynchrony (SOA). Then, a search display was briefly shown, containing two Landolph Cs of different orientation (C-opening at different angles) and color, of which participants identified the C with a horizontally oriented opening. The color of the search items was irrelevant. Importantly, in half of the trials, participants passively viewed the memory cues without further instruction to remember, and the trial ended after the search response (*priming* trials). In the other half, participants were required to remember the memory cue, and after the search response the trial continued with the presentation of a probe of which the participants judged if it matched the memory cue (*working memory* trials). In addition, the color of the search target (horizontally oriented C) could be the same as the memory cue (valid) or not (invalid). In all trials, a 10 Hz pulse triplet was administered at onset of the search display. Results showed no effects of TMS or trial validity on short-term memory accuracy. However, TMS did increase search times for working memory trials, compared to the priming trials (and sham TMS). Further, in memory trials the TMS pulses interacted with trial validity in a different way than in priming trials. In memory trials, TMS pulses decreased search accuracy for invalid trials, compared to valid trials. In priming trials, TMS pulses decreased search accuracy for valid trials, compared to invalid trials. Thus, keeping an item in memory for later comparison altered the TMS effect on visual search performance, which indicates that memory retention alters the state of cortical excitability of visual cortex.

In all, these pioneering studies showed that the contribution of occipital cortex to short-term retention is temporally specific, content-related and, in early visual cortex, topographically organized, and capacity-limited. These results were obtained in explicit as well as implicit short-term memory paradigms, which suggests that the putatively independent memory systems share the same mechanism of contribution of visual cortex to memory retention. A further important methodological aspect is that several of these studies used behavioral or functional-anatomical criteria to guide positioning of the TMS coil over early visual cortex [39,51] and hMT+ [44], which increases the likelihood that these effects are obtained from manipulating brain activity in functionally specialized visual cortex. Further corroborating evidence from different memory paradigms is discussed below.

3.2. Memory retention and mental imagery

An alternative explanation of the effects of TMS on memory is that TMS interfered with visual mental imagery, rather than with memory retention. Mental imagery is the process in which a perceptual image is generated and kept in mind. Mental imagery shares many cognitive functions with sensory processing and memory [61–64], and may also facilitate perception and memory [61,62]. In parallel, the neural correlates of mental imagery overlap to a large degree with those of perception and memory [63–66]. Perception as well as imagery of visual motion is associated with hMT+ activation [67], while imagery of faces and houses activates inferior temporal cortex that is functionally specialized for the perception of the respective items [68,69]. Further, mental imagery may include activity in early visual cortices, including V1 [70,71], if the mental image contains visual details of a high pictorial resolution [72]. This was effectively demonstrated in a TMS study of visual imagery [73], in which participants memorized four

gratings of different orientation, spatial frequency and line length at different locations in the visual field. After memorization, 1 Hz repetitive TMS was administered for 10 min to anatomically neuronavigated early visual cortex, after which participants performed a number of imagery trials in which they were asked to mentally imagine one of the four figures and provide a judgment about one of its stimulus features. Compared to sham TMS, rTMS increased reaction times (but did not alter accuracy) in mental imagery trials. Control trials that included sensory stimulation of the four stimuli (thus, not requiring memory or imagery to perform the task) showed a similar prolongation in reaction times, showing that the imagery effect was indeed related to a TMS-induced impairment of sensory processing. Thus, TMS effects on memory could reflect impaired mental imagery performance if participants consistently used mental imagery to keep visual information available to awareness during the retention period.

However, this imagery explanation of memory retention is not easily supported. In many studies of visual imagery, participants were required to memorize visual information prior to performing the imagery trials, which makes it difficult to parse the cognitive and neural mechanisms of imagery from those of memory retention and retrieval. Interestingly, TMS may be able to separate the temporal mechanisms of memory retention from mental imagery [56]. Participants completed visual short-term memory and imagery trials, in which they judged if a dot presented at the end of the trial fell within an area spanned by two clock hands that were indicated at the onset of the trial. In the imagery task, participants were visually shown a digital clock time and had to imagine the clock hands. In the memory task, participants were shown the clock hands and had to retain the image in memory. A single TMS pulse was delivered over occipital cortex or vertex at the start of retention (i.e., immediately after sample offset) or at probe onset (i.e., at end of the 2 s retention interval). Pulses presented at the start of retention increased reaction times for the memory trials, but not for the imagery trials, which indicates that the processes of memory and imagery differ at the start of retention. Possibly, in memory retention the brain activity associated with sensory encoding continued after stimulus offset, whereas in imagery the visual cortex was not yet involved in image generation. Pulses delivered at the probe onset resulted in faster responses for both imagery and memory, which could indicate that memory and imagery share neural resources at later stages of processing. However, TMS presented at probe onset could have served as an attentional cue to the matching procedure, thereby resulting in TMS facilitating performance.

The argument of overlapping resources can be extended even further, where it can be argued that keeping a mental image in awareness is a specific form of memory retention or rehearsal [63,74], in which the neural representation is activated to such a level that it enters awareness [75]. Indeed, visual working memory performance is associated with visual imagery performance [74], and may even be predicted by the strength of mental imagery [76]. A recent TMS study provided further support for this notion [77]. Participants kept a visual image in mind for 2 s of a previously presented gratings at the center of fixation. Gratings were presented at one of three visual contrasts (10, 50 and 90%). A single TMS pulse was given at the end of retention at or slightly below phosphene threshold (PT) and participants had to indicate if they saw a phosphene. Overall, phosphene detection increased with the visual contrast of the grating (and, by inference, of the image of the grating), most notably so for phosphenes induced at a sub-PT intensity. More specifically, phosphene detection at sub-PT increased with increasing stimulus contrast. These findings thus indicate that stimulus contrast, and putatively contrast information of the mental image, affect cortical excitability of early visual cortex far beyond the temporal window of sensory stimulation.

Thus, visual imagery and visual memory share functional resources from early visual cortices in similar ways, thereby demonstrating that the functional overlap between memory and perception are relevant for information processing. Whether the two cognitive functions exist on a continuum of mental representations or reflect distinct processes remains to be elucidated.

3.3. Perceptual learning

The hypothesis of memory formation in visual cortex has also been investigated in a different type of memory paradigm, in which participants are trained to improve on a visual skill without explicit instructions to memorize the visual information. In visual skill learning, or perceptual learning, a memory representation implicitly forms over time during repeated stimulus exposures [78–80]. Skill learning typically follows a multi-phase pattern, in which rapid initial performance improvement is followed at a later moment by slow, asymptotic improvement [80–83]. The sensory memory that is required to become a skilled expert may include changes in synaptic plasticity in sensory cortex that, in the adult brain, occurs only at the asymptotic phases of learning [78–80]. Importantly, the synaptic plasticity in skill learning critically depends on long-term exposure to repeated sensory presentations of the stimuli, and is therefore considered to be independent of short-term memory formation, in which neural representations are more transient and reversible in order to accommodate the retention of new information in a capacity-limited system. However, recent fMRI studies showed altered activity in early visual cortex during and after the first training session [84–86]. These findings are unlikely to represent changes in synaptic plasticity so early in training, before reaching the asymptotic phase. Instead, they could point to functional dynamics that set the stage for more structural and longer-lasting changes in plasticity in case of continued exposure to the stimuli. At these early stages of learning, the memory representation is likely to be reversible and very vulnerable to interference from competing memory representations. In other words, perceptual learning may share these neural dynamics with short-term memory retention, which thus warrants the inclusion of TMS studies of perceptual learning in the discussion of memory formation in visual cortex.

Two TMS studies showed how visual skill learning affected cortical excitability of visual cortex over the course of acquiring the skill. In an early study [87], single TMS pulses were administered over the occipital pole at different timepoints in order to assess the time course of the contribution of visual cortex to the perceptual identification of letters. TMS decreased identification performance associated with three time periods shortly after stimulus onset, which included windows around 10, 60 and 120 ms after onset. Performance decrement remained stable over the course of three weeks when TMS pulses were administered at the earliest window. Interestingly, the performance decrement at the middle and late TMS windows disappeared during these three weeks. Performance decreased again for these stimulation windows after the visual contrast of the letters was diminished. These results showed that repeated exposure to the letters created a memory representation in early visual cortex that weakened the interfering effects of TMS. After decreasing stimulus contrast, the memory representation did not sufficiently facilitate performance, which rendered processing again vulnerable to TMS interference.

Corroborating evidence came from Neary et al. [88], who trained participants on an orientation discrimination task (ODT), during which single-pulse TMS was applied several centimeters above the inion. Three timepoints of stimulation were individually defined using a tilt-discrimination task that was presented prior to the learning paradigm, which included early (80% discrimination accuracy, between 84 and 112 ms after stimulus onset),

peak (~50% accuracy, 98–126 ms) and late windows (80% accuracy, 112–154 ms). Training then commenced across 12 daily sessions, with TMS applied every other session. The authors found that, compared to no-TMS sessions, the initial performance decrements resulting from early and peak TMS timepoints decreased with progression of learning. A control experiment verified that this effect was not caused by adaptation to TMS, leading the authors to conclude that perceptual learning progressively weakened the interfering effects of TMS.

Next to improving task performance, visual skill learning can also counteract intrinsic biases in the perception of ambiguous, bistable stimuli. For example, a typically experienced directional preference in an induced bistable motion illusion decreases over time with repeated exposure to the stimulus. This finding indicates that a memory representation of the stimulus that consolidates over time counteracts or inhibits the intrinsic bias (i.e., a release-from-bias due to memory) [89]. Brascamp et al. [90] applied triple-pulse TMS (25 Hz within each triplet) during perception of this bistable motion stimulus over hMT+, vertex, or not at all (no-TMS baseline condition). Attentive perception was controlled using a one-back experimental design. Within each TMS condition, trials were presented in blocks of 1 min in which the inter-trial-interval (ITI) was kept constant, but ITIs varied between blocks. In TMS conditions, pulses were applied at the midpoint of every third ITI. This task contained two time intervals for analysis: a short (repeated) interval to assess priming between consecutive exposures (short-term implicit memory), and a long interval to assess the release-from-bias effect (long-term implicit memory). The one-back design further contained a variable ITI to assess variability of priming as a function of time between exposures. TMS did not affect performance on the priming trials. However, TMS did affect the longer time interval of perceptual learning: The release-from-bias was prevented from occurring in the hMT+ condition, but not in the vertex condition. The authors interpreted their results as indicating that TMS over hMT+ prevented long-term memory formation of the ambiguous motion.

Thus, TMS applied during active training may interrupt with the formation of a memory representation in visual cortex. However, an important part of memory consolidation in skill learning occurs during offline periods that are well beyond the time periods of active training [82,91]. Recently, a study from our group investigated if early visual cortex contributes to offline periods of memory consolidation [43]. Here, we used a repetitive TMS (rTMS) protocol that has been shown to generate long-lasting suppression effects of cortical activity [92]. Participants trained on an ODT in two diagonally opposite visual quadrants, of which one was stimulated by rTMS after training, leaving the other as within-subject control. Further, the study used fMRI-based neuronavigation to explicitly target V1. The order of training of the two visual quadrants was counterbalanced across participants. TMS was applied after training in the two quadrants on the first and second day, targeting the same quadrant, with the third day being the behavioral assessment of learning after the last rTMS session. Results showed that rTMS interfered with learning in the TMS-affected quadrant (but not in the control quadrant) at the start of learning. Furthermore, interference only occurred after a training regime in which training in the affected quadrant was followed by training in the control quadrant. In other words, interference of memory formation occurred only if training in the TMS quadrant was separated by an alternative task in another spatial location. These findings suggest that a TMS-interference effect per se on memory formation in visual cortex may be too simplistic an interpretation of skill acquisition in the brain. Rather, we interpreted these findings as evidence of vulnerability of memory formation in early visual cortex as a function of current functional brain state that includes other (higher-order) areas. Although a controversial finding, it appears to coincide with

reports of changes in functional coupling between visual cortex and non-sensory brain areas distributed across the brain [93–96].

In summary, these studies have shown that TMS over occipital cortex may interfere with sensory memory formation that normally occurs at a time scale of multiple days. Particularly, De Weerd et al. [43] showed that rTMS delivered at a time period well after active training ended interrupted memory consolidation. This finding fits with neurophysiological results of ongoing metabolic, synaptic and molecular changes that contribute to the consolidation of memory [96,97]. Crucially, the offline TMS effect rules out the possibility that the learning impairment resulted from interrupted cognitive control or mental imagery performance. Instead, the results provide strong support for a neural representation of memory in early visual cortex. Conversely, it is possible that such a neural representation of memory contributes to the retention of sensory information in visual short-term memory. Application of TMS pulses could interfere with the ongoing activity or functional coupling with higher order areas, thereby interfering with the maintenance of information in visual cortex.

4. Memory reactivation

TMS can also be used to reactivate memory representations in sensory cortex. Penfield and Perot [21] had shown that it is in principle possible to use brain stimulation to reactivate episodic memories into awareness, with a degree of perceptual quality that resembled true sensory experiences. Further, it has been shown that retrieval of autobiographical events from memory reactivates sensory brain areas that were also involved in the initial encoding of the sensory experiences [18]. Neurophysiological studies in rats and non-human primates have also shown that memory consolidation during sleep involves reactivation of 'scripts' of sensory cortical activity [93,96]. In light of these findings, it is plausible that local brain stimulation using TMS could result in reactivation of memory representations into awareness.

Currently, three TMS studies have pursued this intriguing approach. In all studies, TMS pulses were administered over visual cortex in order to induce perceptual experiences that are reminiscent of the actual sensory perceptions. Key to these studies is the induction of phosphenes with TMS. Phosphenes induced by occipital cortex stimulation likely include activity in early visual cortex [32,33]. Further, the cortical excitability of early visual cortex, as a result of sensory [98] or cognitive context [99], affects phosphene perception. These characteristics could thus make phosphenes a useful TMS tool to investigate memory in early visual cortex. Silvanto et al. [100] had participants visually adapt to an iso-luminant colored surface. After adaptation, participants saw an after-image in the opposite color when looking at a black screen. However, TMS-induced phosphenes were of the adapted-to color, rather than the color of the after image. Thus, TMS reactivated the weaker color representation in occipital cortex. Further experiments showed that phosphene-induced 'reactivation' of the adapted color facilitated detection of the adapted color, which normally is harder to detect. The authors suggested that neural cells tuned to the adapted color decrease their excitability, and that this state of decreased excitability made them more sensitive to stimulation with TMS.

TMS-induced phosphenes may also carry relevant stimulus features that are kept in explicit, short-term memory. Jolij and Lamme [101] induced phosphenes during a tilt-illusion experiment. Here, participants saw a large background grating at a left or right-tilted angle, and a small aperture in which an independently titled grating (left, upright or right tilt) was briefly shown. In half of the trials, the background then flipped across the vertical orientation. A TMS pulse was then administered several centimeters above the inion at 300 ms after presentation of the aperture grating. Crucially, in

half of the trials, a second aperture grating was briefly shown just prior to the TMS pulse. Tilt illusion was assessed as the proportion of left-tilt responses of the center (aperture) grating as a function of background tilt, and typically shows that background tilt biases perceived tilt of the aperture grating. Participants reported seeing visual echoes of the aperture stimulus in 33% of the TMS trials on average, that is, TMS-induced phosphenes were perceptually very similar to and were affected by the same contextual influences as the aperture stimuli.

In a similar vein, Silvanto and Cattaneo [102] applied TMS over hMT+ to induce moving phosphenes. The authors placed two coils simultaneously on participants' heads in order to switch quickly between stimulation of lateral hMT+. First, the authors assessed the intrinsic or default directional preference of TMS-induced moving phosphenes in the absence of other stimuli or tasks. Then, participants memorized gratings that moved in a direction congruent or incongruent to the individual's phosphene directional preference. During retention, moving phosphenes were induced. Results showed that phosphenes induced after presentation of bias-congruent memory stimuli increased the reporting of the phosphene directional bias, only when TMS was applied over hMT+ contralateral to the visual field of memory item presentation (Fig. 2B). Thus, memory of movement direction affected TMS-induced phosphene directional movement. This effect was not found after occipital TMS (during which no moving phosphenes were observed).

This handful of empirical reports thus demonstrates that TMS may increase cortical excitability of neural pools that support the representational content in visual cortex up to such a level that the phenomenological content reaches awareness. Reactivation can be elicited with implicitly as well as explicitly memorized information, which again points to a shared memory mechanism in visual cortex between the different memory systems. Further, reactivated information can affect current cognitive information processing [100], which suggests that the reactivated information into awareness could be used to facilitate their memory performance. Following, it may be possible that such reactivations could serve as experimentally controlled rehearsals of the sensory information, which in turn could refresh and strengthen the visual memory representation. This effect is then likely secondary to the TMS-induced reactivation, in which the information that has entered awareness is reprocessed through the visual processing hierarchy, thereby improving memory consolidation. Future studies need to investigate the plausibility of this scenario.

Thus, memory reactivation using TMS-induced phosphenes is a promising TMS paradigm that warrants further investigation. It remains to be seen if TMS can be used to reactivate episodic memories from long-term memories, in the spirit of the experiments by Penfield and Perot [21]. Currently, the magnetic pulse of TMS lacks sufficient spatial resolution to target the small and distributed neurons networks that subserve these memories. However, this could be overcome if the excitability of relevant neural pools is in a cortical state that allows them to be activated by a TMS pulse beyond other non-relevant neural pools. In this regard, the results of the previously studies and others are promising in showing that TMS effects depend on cortical states in visual cortex.

5. Discussion

We reviewed a number of human brain stimulation studies using TMS that addressed the functional contribution of sensory cortex to memory retention and retrieval. In all, the TMS findings suggest that memory of visual information requires activity in visual cortex beyond the periods of sensory perception. The memory-related activity follows the computational principles of the relevant neural networks. Specifically, memory for contrast and abstract shapes requires activity in early visual cortex while memory for motion requires activity in hMT+. In early visual cortex, memory of visual content is topographically organized. Importantly, these contributions of visual cortex to the memory retention and retrieval were found for implicitly as well as explicitly memorized information, and were relevant for memory formation at short as well as longer time scales. Finally, TMS can be used to make the memorized information in visual cortex available to awareness.

We suggest that these TMS findings indicate that sensory cortex contributes to different memory types in a similar manner, in keeping with previous suggestions that the brain's substrate for memory formation and retention is similar for different memory time scales [14]. Neural pools that are relevant for the initial sensory encoding of visual information may show ongoing, reverberating activity during short-term memory retention. These neural dynamics are reversible memory representations that do not last long or can be easily overwritten by new or competing information. But, when repeatedly strengthened, these functional changes gradually turn into more long-lasting and structural plasticity changes for more enduring memories [103].

The discussed TMS findings coincide with psychophysical studies of 'memory masking', in which a distracter stimulus that is shown during retention impairs subsequent recognition [12,104,105]. Memory masking has also revealed an early consolidation window in short-term memory retention, in which the magnitude of impairment diminishes with longer delays between sample and memory mask [53]. Further, memory masking impairments can be obtained with complex stimuli, such as letters [106], as well as with luminance gratings that require activity of neural pools in early visual cortex for encoding [107]. We found that TMS impaired memory performance of abstract shapes in a similar, but stronger, way as memory masking [39]. Thus, the neurophysiological effects of TMS could be comparable to a memory masking or substitution effect, in which the induced brain activity overwrites the neural memory representation. However, there are important differences that limit the generalization between the two approaches. For example, in memory masking the overlap of features of the mask with the relevant features of the memory item modulates the memory impairment [104], which provides information about how visual content is represented in memory. Also, the artificial delivery of TMS pulses may affect visual processing in different ways than visual distracters that traverse the retino-thalamo-cortical pathways (see [26]). It remains to be demonstrated if TMS can be used to achieve similar effects.

The similarity of TMS effect in the different memory paradigms supports the notion that the different memory systems share neural mechanisms in sensory cortex [14,108]. Perhaps most apparent is the topographic organization that is found for short-term memories and in the formation of long-term memories for visual skills. Topographic specificity may be a central feature of the asymptotic phase of visual skill learning [81,91,109], and has been suggested to indicate the presence of local cortical changes in synaptic plasticity that consolidate the perceptual memory into a long-lasting neural representation [78,80]. The supporting evidence for this specificity in short-term memory formation may indicate that, at smaller time scales, non-enduring representations of sensory events are retained in neural pools that initially encoded the information. The short-term retention, however, relies on reverberating neural activity, rather than on the creation of new synaptic connections, which allows the neural cells implicated in the memory to be re-used in forming new short-lasting memories.

Thus, memory for perceptual information could require ongoing activity in functionally relevant visual cortex. The time period of uninterrupted ongoing activity may then dictate the endurance of

the memory. This notion can be further extended to include visual cortex activity during visual perception, i.e., before memory formation is considered to begin. A long tradition of psychophysical studies has shown that visual distracters presented around 80–120 ms after target presentation lead to impaired visual perception of the target [26]. TMS studies have provided causal evidence for the role of visual cortex activity in this time window [41,50,110,111], with several studies reporting the existence of even earlier critical windows [112,113]. One way in which these notions can be combined is the theoretical framework of forward and reversed hierarchies, in which visual perception relies on brain activity progressing up the visual processing hierarchy to higher order areas (feedforward sweep), as well as feedback loops to visual cortex (feedback sweep) [34,114–116]. Visual awareness requires at least one feedforward and feedback sweep occurring within the critical time window of the first 100 ms [114]. By extension, this framework could explain memory formation as the result of multiple cycles of feedforward and feedback sweeps, in which each cycle further strengthens the sensory representation in the neural network and thereby creating a memory engram. This framework also highlights the role of higher order brain areas in maintaining the ongoing activity in visual cortex and protecting it against interference from competing sources. It has been demonstrated that prefrontal and parietal cortex can influence and modulate processing in visual cortex during task performance and short-term memory functions [4,27,58]. These functional couplings may extend well beyond active cognitive performance and thereby contribute to memory consolidation on longer time scales in visual cortex [43,93,95,96]. The functional couplings may change over time, as the memory becomes more consolidated in visual cortex and thus requires less resources from higher order areas [117]. Thus, these frameworks provide well-formalized spatial (i.e., brain areas) and temporal (i.e., critical windows) hypotheses about how sensory cortex contributes to memory formation in the brain. The rich and flexible application of TMS appears very suitable to test these hypotheses.

Finally, the presence of a memory engram in sensory cortex could be relevant in understanding a number of perceptual symptoms in clinical disorders, such as auditory verbal hallucinations (AVH) in schizophrenia [64,118,119] and flashbulb memories in post-traumatic stress disorder (PTSD) [64,108,120]. These symptoms share a phenomenological commonality of a randomly occurring experience of very high perceptual quality or vividness. AVH are typically experienced to be of a perceptual detail that is indistinguishable from true sensory events. This confusion of reality could occur if the neural correlates of AVH strongly overlap with those of true sensory perception of auditory material similar to those of AVH. Indeed, functional neuroimaging studies showed increased activity during episodes of AVH in auditory cortex [119], in some patients including primary auditory cortex. In PTSD, patients experience spontaneous relivings of traumatic events with a high degree of perceptual detail, often occurring in the visual domain [120]. Similar to AVH, these experiences could result from overactivity in visual cortex [121,122]. These and other clinical symptoms suggest pathological mechanisms lead to spontaneous overactivity of sensory memory representations to a degree that the memories enter awareness [64,123]. Understanding the neurobiological mechanism of how sensory cortex consolidates memories could thus provide insights how these aberrant perceptions occur, and could possibly lead to ways to control or even alleviate them.

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References

[1] Linden DEJ. The working memory networks of the human brain. The Neuroscientist 2007;13:257–67.
[2] Goldman-Rakic PS. Cellular basis of working memory. Neuron 1995;14:477–85.
[3] Curtis C, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends in Cognitive Sciences 2003;7:415–23.
[4] Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. The Journal of Neuroscience 1996;16:5154–67.
[5] Rainer G, Asaad WF, Miller EK. Memory fields of neurons in the primate prefrontal cortex. Proceedings of the National Academy of Sciences of the United States of America 1998;95:15008–13.
[6] Linden DEJ, Bittner R, Muckli L, Waltz J, Kriegeskorte N, Goebel R, et al. Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network. NeuroImage 2003;20: 1518–30.
[7] Munk MHJM, Linden DEJ, Muckli L, Lanfermann H, Zanella FE, Singer W, et al. Distributed cortical systems in visual short-term memory revealed by event-related functional magnetic resonance imaging. Cerebral Cortex 2002;12:866–76.
[8] Todd JJ, Marois R. Capacity limit of visual short-term memory in human posterior parietal cortex. Nature 2004;428:751–4.
[9] Jiang Y, Haxby JV, Martin A, Ungerleider LG, Parasuraman R. Complementary neural mechanisms for tracking items in human working memory. Science 2000;287:643–6.
[10] Courtney SM, Ungerleider LG, Keil K, Haxby JV. Transient and sustained activity in a distributed neural system for human working memory. Nature 1997;386:608–11.
[11] Bledowski C, Cohen Kadosh K, Wibral M, Rahm B, Bittner RA, Hoechstetter K, et al. Mental chronometry of working memory retrieval: a combined functional magnetic resonance imaging and event-related potentials approach. The Journal of Neuroscience 2006;26:821–9.
[12] Pasternak T, Greenlee MW. Working memory in primate sensory systems. Nature Reviews Neuroscience 2005;6:97–107.
[13] Jonides J, Lewis RL, Nee DE, Lustig CA, Berman MG, Sledge Moore K. The mind and brain of short-term memory. Annual Review of Psychology 2008;59:193–224.
[14] Fuster J. Memory in the cerebral cortex: an empirical approach to neural networks in the human and nonhuman primate. Cambridge (USA): MIT Press; 1999.
[15] Supèr H, Spekreijse H, Lamme VAF. A neural correlate of working memory in the monkey primary visual cortex. Science 2001;293:120–4.
[16] Fuster J, Jervey J. Neuronal firing in the inferotemporal cortex of the monkey in a visual memory task. The Journal of Neuroscience 1982;2: 361–75.
[17] Miyashita Y, Chang H. Neuronal correlate of pictorial short-term memory in the primate temporal cortex. Nature 1988;331:68–70.
[18] Wheeler ME, Petersen SE, Buckner RL. Memory's echo: vivid remembering reactivates sensory-specific cortex. Proceedings of the National Academy of Sciences of the United States of America 2000;97:11125–9.
[19] Rubin DC, Greenberg DL. Visual memory-deficit amnesia: a distinct amnesic presentation and etiology. Proceedings of the National Academy of Sciences of the United States of America 1998;95:5413–6.
[20] Penfield W. Memory mechanisms. Archives of Neurology and Psychiatry 1952;67:178–91.
[21] Penfield W, Perot P. The brain's record of auditory and visual experience. Brain 1963;86:595–696.
[22] Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000;406:147–50.
[23] Pascual-Leone A, Walsh V, Rothwell JC. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. Current Opinion in Neurobiology 2000;10:232–7.
[24] Sack AT. Transcranial magnetic stimulation, causal structure–function mapping and networks of functional relevance. Current Opinion in Neurobiology 2006;16:593–9.
[25] Kammer T. Masking visual stimuli by transcranial magnetic stimulation. Psychological Research 2007;71:659–66.
[26] Breitmeyer BG, Ro T, Ogmen H. A comparison of masking by visual and transcranial magnetic stimulation: implications for the study of conscious and unconscious visual processing. Consciousness and Cognition 2004;13:829–43.
[27] Zanto TP, Rubens MT, Thangavel A, Gazzaley A. Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. Nature Neuroscience 2011;14:656–61.
[28] Mottaghy FM, Gangitano M, Sparing R, Krause BJ, Pascual-Leone A. Segregation of areas related to visual working memory in the prefrontal cortex revealed by rTMS. Cerebral Cortex 2002;12:369–75.
[29] Hong KS, Lee SK, Kim JY, Kim KK, Nam H. Visual working memory revealed by repetitive transcranial magnetic stimulation. Journal of the Neurological Sciences 2000;181:50–5.
[30] Mottaghy FM, Gangitano M, Krause BJ, Pascual-Leone A. Chronometry of parietal and prefrontal activations in verbal working memory revealed by transcranial magnetic stimulation. NeuroImage 2003;18: 565–75.

[31] Ray PG, Meador KJ, Epstein CM, Loring DW, Day LJ. Magnetic stimulation of visual cortex: factors influencing the perception of phosphenes. Journal of Clinical Neurophysiology 1998;15:351–7.

[32] Kammer T. Phosphenes and transient scotomas induced by magnetic stimulation of the occipital lobe: their topographic relationship. Neuropsychologia 1998;37:191–8.

[33] Kammer T, Puls K, Erb M, Grodd W, Strasburger H. Transcranial magnetic stimulation in the visual system. II. Characterization of induced phosphenes and scotomas. Experimental Brain Research 2005;160:129–40.

[34] Pascual-Leone A, Walsh V. Fast backprojections from the motion to the primary visual area necessary for visual awareness. Science 2001;292:510–2.

[35] Silvanto J, Cowey A, Lavie N, Walsh V. Striate cortex (V1) activity gates awareness of motion. Nature Neuroscience 2005;8:143–4.

[36] Graaf TD, Sack AT. Null results in TMS: from absence of evidence to evidence of absence. Neuroscience & Biobehavioral Review 2011;35:871–7.

[37] Sack AT, Cohen Kadosh R, Schuhmann T, Moerel M, Walsh V, Goebel R, et al. Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. Journal of Cognitive Neuroscience 2009;21:207–21.

[38] Rademacher J, Caviness VS, Steinmetz H, Galaburda AM. Topographical variation of the human primary cortices: implications for neuroimaging, brain mapping, and neurobiology. Cerebral Cortex 1993;3:313–29.

[39] van de Ven V, Jacobs C, Sack AT. Topographic contribution of early visual cortex to short-term memory consolidation: a transcranial magnetic stimulation study. The Journal of Neuroscience 2012;32:4–11.

[40] Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G. Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. Cerebral Cortex 2008;18:2010–8.

[41] Sack AT, van der Mark S, Schuhmann T, Schwarzbach J, Goebel R. Symbolic action priming relies on intact neural transmission along the retino-geniculo-striate pathway. NeuroImage 2009;44:284–93.

[42] Campana G, Cowey A, Walsh V. Priming of motion direction and area V5/MT: a test of perceptual memory. Cerebral Cortex 2002;12:663–9.

[43] De Weerd P, Reithler J, van de Ven V, Been M, Jacobs C, Sack AT. Posttraining transcranial magnetic stimulation of striate cortex disrupts consolidation early in visual skill learning. The Journal of Neuroscience 2012;32:1981–8.

[44] Slotnick SD, Thakral PP. Memory for motion and spatial location is mediated by contralateral and ipsilateral motion processing cortex. NeuroImage 2011;55:794–800.

[45] Sack AT, Kohler A, Linden DEJ, Goebel R, Muckli L. The temporal characteristics of motion processing in hMT/V5+: combining fMRI and neuronavigated TMS. NeuroImage 2006;29:1326–35.

[46] Miyake A, Shah P. Models of working memory: mechanisms of active maintenance and executive control. Cambridge (UK): Cambridge University Press; 1999.

[47] Baddeley A, Hitch G. Working memory. In: Bower GH, editor. The psychology of learning and motivation: advances in research and theory. Academic Press; 1974. p. 47–89.

[48] Cowan N. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. The Behavioral and Brain Sciences 2001;24:87–114 [discussion 114–85].

[49] Luck SJ, Vogel EK. The capacity of visual working memory for features and conjunctions. Nature 1997;390:279–81.

[50] Beckers G, Homberg V. Impairment of visual perception and visual short term memory scanning by transcranial magnetic stimulation of occipital cortex. Experimental Brain Research 1991;87:421–32.

[51] Silvanto J, Soto D. Causal evidence for subliminal percept-to-memory interference in early visual cortex. NeuroImage 2011;59:840–5.

[52] Ro T, Breitmeyer B, Burton P, Singhal NS, Lane D. Feedback contributions to visual awareness in human occipital cortex. Current Biology 2003;13:1038–41.

[53] Vogel EK, Woodman GGF, Luck SJ. The time course of consolidation in visual working memory. Journal of Experimental Psychology: Human Perception and Performance 2006;32:1436–51.

[54] Shapiro K, Raymond J, Arnell K. Attention to visual pattern information produces the attentional blink in rapid serial visual presentation. Journal of Experimental Psychology: Human Perception and Performance 1994;20:357–71.

[55] Chun MM, Potter MC. A two-stage model for multiple target detection in rapid serial visual presentation. Journal of Experimental Psychology: Human Perception and Performance 1995;21:109–27.

[56] Cattaneo Z, Vecchi T, Pascual-Leone A, Silvanto J. Contrasting early visual cortical activation states causally involved in visual imagery and short-term memory. The European Journal of Neuroscience 2009;30:1393–400.

[57] Sack AT, Camprodon J, Pascual-Leone A, Goebel R. The dynamics of interhemispheric compensatory processes in mental imagery. Science 2005;308:702–4.

[58] Feredoes E, Heinen K, Weiskopf N, Ruff C, Driver J. Causal evidence for frontal involvement in memory target maintenance by posterior brain areas during distracter interference of visual working memory. Proceedings of the National Academy of Sciences of the United States of America 2011;108:17510–5.

[59] Campana G, Cowey A, Walsh V. Visual area V5/MT remembers what but not where. Cerebral Cortex 2006;16:1766–70.

[60] Soto D, Llewelyn D, Silvanto J. Distinct causal mechanisms of attentional guidance by working memory and repetition priming in early visual cortex. The Journal of Neuroscience 2012;32:3447–52.

[61] Finke RA, Shepard RN. Visual functions of mental imagery. In: Boff K, Kaufman L, Thomas J, editors. Handbook of perception and human performance. Wiley; 1986.

[62] Kosslyn SM. Image and brain: the resolution of the imagery debate. Cambridge (USA): MIT Press; 1996.

[63] Farah MJ. Current issues in the neuropsychology of image generation. Neuropsychologia 1995;33:1455–71.

[64] van de Ven V, Linden DEJ. The role of mental imagery in aberrant perception: a neurobiological perspective. Journal of Experimental Psychopathology 2012;3:274–96.

[65] Sack AT, Schuhmann T. Hemispheric differences within the fronto-parietal network dynamics underlying spatial imagery. Frontiers in Psychology 2012;3:214.

[66] Kosslyn SM, Ganis G, Thompson WL. Neural foundations of imagery. Nature Reviews Neuroscience 2001;2:635–42.

[67] Goebel R, Khorram-Sefat D, Muckli L, Hacker H, Singer W. The constructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. European Journal of Neuroscience 1998;10:1563–73.

[68] O'Craven KM, Kanwisher N. Mental imagery of faces and places activates corresponding stimulus-specific brain regions. Journal of Cognitive Neuroscience 1999;12:1013–23.

[69] Ishai A, Ungerleider LG, Haxby JV. Distributed neural systems for the generation of visual images. Neuron 2000;28:979–90.

[70] Kosslyn SM, Thompson WL, Kim IJ, Alpert NM. Topographical representations of mental images in primary visual cortex. Nature 1995;378:496–8.

[71] Slotnick SD, Thompson W, Kosslyn SM. Visual mental imagery induces retinotopically organized activation of early visual areas. Cerebral Cortex 2005;15:1570–83.

[72] Kosslyn SM, Thompson WL. When is early visual cortex activated during visual mental imagery? Psychological Bulletin 2003;129:723–46.

[73] Kosslyn SM, Pascual-Leone A, Felician O, Camposano S, Keenan JP, Thompson WL, et al. The role of area 17 in visual imagery: convergent evidence from PET and rTMS. Science 1999;284:167–70.

[74] Baddeley A, Andrade J. Working memory and the vividness of imagery. Journal of Experimental Psychology: General 2000;129:126–45.

[75] Driver J, Frith C. Shifting baselines in attention research. Nature Reviews Neuroscience 2000;1(2):147–8.

[76] Keogh R, Pearson J. Mental imagery and visual working memory. PLoS ONE 2011;6(12):e29221.

[77] Cattaneo Z, Pisoni A, Papagno C, Silvanto J. Modulation of visual cortical excitability by working memory: effect of luminance contrast of mental imagery. Frontiers in Psychology 2011;2:29.

[78] Seitz A, Watanabe T. A unified model for perceptual learning. Trends in Cognitive Sciences 2005;9:329–34.

[79] Gilbert C. The neural basis of perceptual learning. Neuron 2001;31:681–97.

[80] Tsodyks M, Gilbert C. Neural networks and perceptual learning. Nature 2004;431:775–81.

[81] Karni A, Sagi D. Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. Proceedings of the National Academy of Sciences of the United States of America 1991;88:4966–70.

[82] Karni A, Sagi D. The time course of learning a visual skill. Nature 1993;365:250–2.

[83] Schoups AA, Vogels R, Orban G. Human perceptual learning in identifying the oblique orientation: retinotopy, orientation specificity and monocularity. The Journal of Physiology 1995;483(Pt 3):797–810.

[84] Schwartz S, Maquet P, Frith C. Neural correlates of perceptual learning: a functional MRI study of visual texture discrimination. Proceedings of the National Academy of Sciences of the United States of America 2002;99:17137–42.

[85] Yotsumoto Y, Watanabe T, Sasaki Y. Different dynamics of performance and brain activation in the time course of perceptual learning. Neuron 2008;57:827–33.

[86] Yotsumoto Y, Sasaki Y, Chan P, Vasios CE, Bonmassar G, Ito N, et al. Location-specific cortical activation changes during sleep after training for perceptual learning. Current Biology 2009;19:1278–82.

[87] Corthout E, Uttl B, Walsh V, Hallett M, Cowey A. Plasticity revealed by transcranial magnetic stimulation of early visual cortex. Neuroreport 2000;11:1565–9.

[88] Neary K, Anand S, Hotson JR. Perceptual learning of line orientation modifies the effects of transcranial magnetic stimulation of visual cortex. Experimental Brain Research 2005;162:23–34.

[89] Pearson J, Brascamp J. Sensory memory for ambiguous vision. Trends in Cognitive Sciences 2008;12:334–41.

[90] Brascamp JW, Kanai R, Walsh V, van Ee R. Human middle temporal cortex, perceptual bias, and perceptual memory for ambiguous three-dimensional motion. The Journal of Neuroscience 2010;30:760–6.

[91] Schoups A, Vogels R, Qian N, Orban G. Practising orientation identification improves orientation coding in V1 neurons. Nature 2001;412:549–53.

[92] Iyer MBM, Schleper N, Wassermann EM. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. The Journal of Neuroscience 2003;23:10867–72.

[93] Ji D, Wilson M a. Coordinated memory replay in the visual cortex and hippocampus during sleep. Nature Neuroscience 2007;10:100–7.

[94] Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M. Learning sculpts the spontaneous activity of the resting human brain.

Proceedings of the National Academy of Sciences of the United States of America 2009;106:17558–63.

[95] Tambini A, Ketz N, Davachi L. Enhanced brain correlations during rest are related to memory for recent experiences. Neuron 2010;65:280–90.

[96] Hoffman KL, McNaughton BL. Coordinated reactivation of distributed memory traces in primate neocortex. Science 2002;297:2070–3.

[97] Wilson MA, McNaughton Z BL. Reactivation of hippocampal ensemble memories during sleep. Science 1994;265:676–9.

[98] Boroojerdi B, Bushara KO, Corwell B, Immisch I, Battaglia FP, Muellbacher W, et al. Enhanced excitability of the human visual cortex induced by short-term light deprivation. Cerebral Cortex 2000;10:529–34.

[99] Bestmann S, Ruff CC, Blakemore C, Driver J, Thilo KV. Spatial attention changes excitability of human visual cortex to direct stimulation. Current Biology 2007;17:134–9.

[100] Silvanto J, Muggleton NG, Cowey A, Walsh V. Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. The European Journal of Neuroscience 2007;25:1874–81.

[101] Jolij J, Lamme V. Transcranial magnetic stimulation-induced visual echoes' are generated in early visual cortex. Neuroscience Letters 2010;484(3):178–81.

[102] Silvanto J, Cattaneo Z. Transcranial magnetic stimulation reveals the content of visual short-term memory in the visual cortex. NeuroImage 2010;50:1683–9.

[103] Dudai Y. The neurobiology of consolidations, or, how stable is the engram? Annual Review of Psychology 2004;55:51–86.

[104] Magnussen S, Greenlee MW. The psychophysics of perceptual memory. Psychological Research 1999;62:81–92.

[105] Enns J, Di Lollo V. What's new in visual masking? Trends in Cognitive Sciences 2000;4:345–52.

[106] Jolicoeur P, Dell'Acqua R. The demonstration of short-term consolidation. Cognitive Psychology 1998;36:138–202.

[107] Magnussen S, Greenlee MW, Asplund R, Dyrnes S. Stimulus-specific mechanisms of visual short-term memory. Vision Research 1991;31:1213–9.

[108] Rubin DC. A basic-systems approach to autobiographical memory. Current Directions in Psychological Science 2005;14:79–83.

[109] Dill M, Fahle M. The role of visual field position in pattern—discrimination learning. Proceedings of the Royal Society of London Series B Biological Sciences 1997;264:1031–6.

[110] Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell A, Eberle L. Suppression of visual perception by magnetic coil stimulation of human occipital cortex. Electroencephalography and Clinical Neurophysiology 1989;74:458–62.

[111] Kammer T, Puls K, Strasburger H, Hill NJ, Wichmann FA. Transcranial magnetic stimulation in the visual system. I. The psychophysics of visual suppression. Experimental Brain Research 2005;160:118–28.

[112] Jacobs C, Goebel R, Sack AT. Visual awareness suppression by pre-stimulus brain stimulation; a neural effect. NeuroImage 2012;59:616–24.

[113] Corthout E, Uttl B, Ziemann U, Cowey A, Hallett M. Two periods of processing in the (circum)striate visual cortex as revealed by transcranial magnetic stimulation. Neuropsychologia 1999;37:137–45.

[114] Lamme V, Roelfsema P. The distinct modes of vision offered by feedforward and recurrent processing. Trends in Neurosciences 2000;23:571–9.

[115] Hochstein S, Ahissar M. View from the top: hierarchies and reverse hierarchies in the visual system. Neuron 2002;36:791–804.

[116] Koivisto M, Railo H, Revonsuo A, Vanni S, Salminen-Vaparanta N. Recurrent processing in V1/V2 contributes to categorization of natural scenes. The Journal of Neuroscience 2011;31:2488–92.

[117] Ahissar M, Hochstein S. The reverse hierarchy theory of visual perceptual learning. Trends in Cognitive Sciences 2004;8:457–64.

[118] Seal ML, Aleman A, McGuire PK. Compelling imagery, unanticipated speech and deceptive memory: neurocognitive models of auditory verbal hallucinations in schizophrenia. Cognitive Neuropsychiatry 2004;9:43–72.

[119] Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. American Journal of Psychiatry 2011;168:73–81.

[120] Brewin CR, Gregory JD, Lipton M, Burgess N. Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. Psychological Review 2010;117:210–32.

[121] Lanius RA, Williamson PC, Densmore M, Boksman K, Neufeld RW, Gati JS, et al. The nature of traumatic memories: a 4-T FMRI functional connectivity analysis. The American Journal of Psychiatry 2004;161:36–44.

[122] Osuch EA, Benson B, Geraci M, Podell D, Herscovitch P, McCann UD, et al. Regional cerebral blood flow correlated with flashback intensity in patients with posttraumatic stress disorder. Biological Psychiatry 2001;50:246–53.

[123] Ffytche DH, Blom JD, Catani M. Disorders of visual perception. Journal of Neurology, Neurosurgery, and Psychiatry 2010;81:1280–7.