



Review

The chronometry of visual perception: Review of occipital TMS masking studies



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ABSTRACT

Transcranial magnetic stimulation (TMS) continues to deliver on its promise as a research tool. In this review article we focus on the application of TMS to early visual cortex (V1, V2, V3) in studies of visual perception and visual awareness. Depending on the asynchrony between visual stimulus onset and TMS pulse (SOA), TMS can suppress visual perception, allowing one to track the time course of functional relevance (chronometry) of early visual cortex for vision. This procedure has revealed multiple masking effects ('dips'), some consistently ($\sim+100$ ms SOA) but others less so (~-50 ms, ~-20 ms, $\sim+30$ ms, $\sim+200$ ms SOA). We review the state of TMS masking research, focusing on the evidence for these multiple dips, the relevance of several experimental parameters to the obtained 'masking curve', and the use of multiple measures of visual processing (subjective measures of awareness, objective discrimination tasks, priming effects). Lastly, we consider possible future directions for this field. We conclude that while TMS masking has yielded many fundamental insights into the chronometry of visual perception already, much remains unknown. Not only are there several temporal windows when TMS pulses can induce visual suppression, even the well-established 'classical' masking effect ($\sim+100$ ms) may reflect more than one functional visual process.

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1. Introduction

Amassian and colleagues effectively started a new scientific field when they used magnetic pulses to disrupt human vision in 1989 (Amassian et al., 1989). Transcranial magnetic stimulation (TMS) pulses are brief and rapidly changing magnetic fields, elicited by a coil attached to a strong capacitor, which penetrate the skull and induce an electric field in underlying brain tissue. The strength and focality of the induced field depend on coil characteristics. Round coils consist of a single wired loop and induce a large field around their rim. Today, “figure-of-eight” (also called “butterfly”) coils are used more often, since their two adjacent circular windings result in a relatively focal peak magnetic field. Aside from single TMS pulses, short bursts of 2, 3 or even more pulses can be applied to briefly disrupt neuronal processing (for basic TMS methodology see Wassermann et al., 2008). But the more pulses are administered per trial, the less temporally specific the experimental paradigm becomes. And indeed, the potential for temporal specificity is one of the key values of TMS as a research tool. The electromagnetic process underlying a single TMS pulse takes less than a millisecond, but its effects on neurons can last for seconds (Moliadze et al., 2003). Nevertheless, when applied to more robust neuronal populations, i.e. brain regions, TMS is considered a useful tool to probe chronometrically the functional relevance of targeted areas in the intact human brain (Pascual-Leone et al., 2000). In the work that we review here, that targeted area is the human early visual cortex (EVC). As a reference tool, we provide Table S1 (Supplementary material online), which summarizes the stimulation parameters and main results of the chronometric TMS masking studies on EVC discussed in this review.

1.1. TMS masking

TMS was first applied to human motor cortex to successfully elicit muscle contractions (Barker et al., 1985). The work by Amassian et al. (1989) four years later constituted a significant advance for at least three reasons. First, TMS was applied to probe a brain region other than motor cortex, namely occipital cortex, with very clear behavioral/perceptual effects. Second, their study was a clear demonstration of the chronometric potential of TMS as a research tool: they used the brief disruptive effects of magnetic pulses to track the role of occipital cortex in visual perception as a function of time. Third, due to this, something fundamental was added to our knowledge about human vision, since no other method could show if a brain region was necessary (as opposed to merely involved) at a particular point in time and for a particular task.

In this seminal experiment, TMS was applied to posterior occipital cortex where visual information first reaches the human neocortex (Amassian et al., 1989). Visual information consisted of three letters, presented to the participants on a monitor. The task was to report as many of the letters as possible. Occipital TMS pulses were applied at various stimulus onset asynchronies (SOAs) in relation to the visual stimulus onset. This original TMS masking paradigm was thus suited to answer two questions: (1) is early visual cortex functionally relevant for visual task performance? and (2) at which precise points in time is this the case?

Results showed that no letters at all were correctly identified when pulses were applied at 80 or 100 ms SOA. Nearly all letters were correctly identified when pulses were applied before 60 ms, or after 140 ms. Performance was intermediate at SOAs of 60 and 120 ms. Thus, a clear “TMS masking curve” was demonstrated. Besides this important main finding, Amassian et al. (1989) foreshadowed current interests, addressing in their short research report a number of additional questions that are intensively investigated today.

First, they asked whether or not the masking effect is neural in origin. The magnetic stimulation also elicits muscle contractions in the neck, and makes a loud ‘clicking’ sound. These factors may affect attention, which in turn may affect performance in visual tasks (e.g. Duecker et al., 2013). Moreover, a startle response to either of these factors could elicit eyeblinks, which can affect visual performance. Amassian et al. (1989) immediately showed that such non-neural TMS effects could not fully explain the effects, since moving the magnetic coil sideways or upward affected the specific letters that were recognized/reported in exactly the fashion that we should expect based on known retinotopic organization of visual cortex. While this demonstrated a neural disruption, it did not prove that non-neural effects have no influence on the masking curve: each new TMS masking experiment must continue to control for possible non-neural TMS effects.

The original article also addressed the questions: (1) which precise brain regions/processes are affected by the TMS pulses? (2) which stage of visual processing is affected by TMS? (3) can and do the pulses affect conscious and/or unconscious vision selectively? In addition and relation to these questions, more recent TMS masking studies have focused on issue (4) is the ‘classical’ TMS masking effect around 100 ms SOA the only temporal stage at which early visual cortex is functionally relevant for vision?

These questions were prescient, and largely form the foundations of the TMS masking field today. Here, we aim to provide an overview of what has been added to this pioneering work in the last 20 years. We will focus exclusively on TMS masking studies targeting early visual cortex and work related to this. The last specific TMS masking reviews that we know of were published years ago by Kammer (2007, 2008). After that, interesting new work has appeared, clarifying some issues but raising new ones as well. Looking ahead, we will discuss how TMS at quite a few separate SOAs has been shown to induce visual suppression, how such findings depend on behavioral measures of visual processing, and ultimately how even the well-established classical masking effect first reported by Amassian et al. (1989) may not constitute a straightforward stage of processing. In short, the TMS masking field has become enriched, and rather complex in the process. Hopefully this review will provide some handholds in gaining an overview.

2. The multiple regions stimulated in TMS masking

Before diving into the temporal aspects of TMS masking research, it is worth reviewing the spatial domain. After all, while early studies often aimed to target primary visual cortex (i.e. V1 or striate cortex), today there are a number of approaches to target the appropriate region, and there is a growing body of evidence concerning which regions are actually stimulated in these

approaches. The early studies often used an *anatomical landmark* approach, for example by placing the TMS coil 1–3 cm above the inion (e.g. Amassian et al., 1989; Corthout et al., 2002, 2003; Corthout et al., 2000; Corthout et al., 1999a) or over occipital electrode sites according to the international 10/20-system (e.g. Beckers and Homberg, 1991). Another procedure is the *hunting* method. Here the location of the coil is systematically moved (for instance along a predefined grid) starting for example from 2 cm above the inion, until a location where TMS pulses produce visual suppression is found. A large-field visual stimulus can be used to localize the scotoma (as in Kamitani and Shimojo, 1999). A simpler variant of the hunting method is the *phosphene localization* method (e.g. de Graaf et al., 2012; Silvanto et al., 2005a). It makes use of phosphenes, i.e. percepts akin to flashes of light, which TMS applied over visual cortex elicits in many (though not all) participants. Phosphenes from EVC TMS were reported very early on (for instance already by Barker et al. (1985) in an abstract in *J Physiol*, 369), and are established not only as an interesting phenomenon in their own right but also used as a measure of cortical excitability in pathological conditions such as migraine (e.g. Brigo et al., 2013) or dementia with lewy bodies (Taylor et al., 2011). In the context of TMS masking, the phosphene localization method involves systematically moving the coil over posterior occipital cortex (starting e.g. 2 cm above the inion) until a coil position is found where phosphenes are elicited in a specific retinotopic location. This method is based on the assumption that the neural populations that produce phosphenes in a given location of the visual field are also crucially involved in processing visual stimuli that are presented in the same location (an assumption supported by findings that TMS-induced phosphenes and scotomas correspond topographically; Kammer, 1999; Kammer et al., 2005a; Kastner et al., 1998).

These three methods for positioning the coil successfully elicit masking effects. Yet which is the exact cortical area that is stimulated as a consequence of these localization procedures? This question was addressed early on, using pre-existing anatomical knowledge in combination with behavioral findings (e.g. Kamitani and Shimojo, 1999; Kammer et al., 2005a; Kastner et al., 1998) or co-registration with MRI data (e.g. Potts et al., 1998). Recent studies used fMRI-based mapping of visual cortex in individual participants in combination with modeling of the TMS-induced electric field in the brain to examine this question (Salminen-Vaparanta et al., 2012b; Thielscher et al., 2010). Salminen-Vaparanta et al. (2012b) studied the stimulation site in the anatomical landmark method by making use of fMRI-based retinotopic maps of V1 and V2 subareas and modeling of the TMS-induced electric field in the retinotopic subareas of V1 and V2. They found that when the TMS coil was positioned 2 cm above the inion, both V1 and V2 were stimulated, but there was a great deal of variation between participants. On average, the dorsal V2 was the most affected functional area and the lower visual field areas received the strongest stimulation. For the hunting and phosphene localization procedures, Thielscher et al. (2010) found that V2d was the area most likely responsible for visual suppression of the stimuli in the lower right visual field. In addition, they observed that isolated V3 stimulation produced visual suppression. The modeling of the TMS-induced electric field for two of the participants in Koivisto et al. (2011b) also showed clearly that the stimulation location defined by the hunting method for a stimulus in the left or right lower visual field (2 cm above and 2 cm lateral from inion) resulted in stronger electric field in the corresponding retinotopic area in V2/V3 border than in V1.

Even when explicitly aiming to selectively stimulate V1, using neuronavigation to directly target individual functionally-defined V1, modeling of the electric field showed that the TMS-induced electric field was stronger in V2 than in V1 for about half of the participants in Salminen-Vaparanta et al. (2012b). While it thus

appears to be difficult to selectively disrupt the functioning of V1, selective stimulation of V2 has been confirmed to induce visual suppression (Salminen-Vaparanta et al., 2012a). Thus, although some have argued on functional/behavioral grounds that V1 is the stimulated region in at least some experiments (e.g. Juan and Walsh, 2003), these modeling results converge in suggesting that the traditional anatomical landmark method or hunting methods lead to equally strong or even stronger stimulation of V2 (perhaps also V3) than V1. Whether V1 is directly affected as well may depend on coil positioning and associated eccentricity of the induced scotoma (Kastner et al., 1998).

2.1. Conclusion

The results of recent modeling studies, which addressed the cortical sites of TMS masking effects by simulating the electric fields induced by TMS pulses in classical TMS coil positioning approaches, thus far converge on the following conclusion: it could be a mistake to attribute the visual suppression effects to disruption of V1 only. This is important information, since V1 has often been assumed or reported as the target(ed) region. Of course, especially with closely neighboring and connected functional regions, it is impossible to say precisely how the induced electric field translates to neural activity in those regions. For example, stimulation of V2/V3 might still affect V1 through anatomical connections (Kammer et al., 2005a). Moreover, this line of research should continue, as more precise and meaningful results will be inevitable with further development of both the quality/detail of anatomical brain scans and technology/sophistication of the computational models. For the moment it seems safe to conclude that multiple early visual regions are functionally relevant for visual perception. In the remainder of this review we refer to 'early visual cortex' (EVC) as the TMS-disrupted site in masking studies.

3. The multiple dips in the masking curve

Amassian et al. (1989) found one large dip in the TMS masking curve. By 'dip' we mean a disruption of visual task performance (in graphs generally visualized as a downward deflection from baseline of task performance or visibility report - hence 'dip'). The dip found by Amassian et al. (1989) we have referred to as the 'classical dip' (de Graaf et al., 2011a,b, 2012), because this masking effect around 100 ms SOA has been replicated in every TMS masking study that we know of. Clearly, something fundamental happens in early visual cortex around +100 ms, and it is very susceptible to TMS pulses. But the exact timing of the dip around +100 ms varies between experiments. Moreover, one should question whether this is the only temporal stage in which early visual cortex is functionally relevant for conscious vision.

3.1. The feedforward-feedback hypothesis

Visual information passes early visual cortex on its way to the rest of the brain along several pathways (e.g. DeYoe et al., 1994; Felleman et al., 1997). This first pass-through can be referred to as a 'feedforward sweep' (Lamme and Roelfsema, 2000). But according to various psychological and neurobiological models (Bullier, 2001; Lamme, 2001; Lamme et al., 2000; Pollen, 2003), a feedback signal to early visual cortex might be functionally relevant for vision as well. This recurrent signal could be important to 'check' processing results with the input (Bullier, 2001; Di Lollo et al., 2000), to fill in the finer details of the visual image (Hochstein and Ahissar, 2002), or be responsible for visual awareness of the stimulus (Lamme, 2001; Lamme et al., 2000). Whichever particular theory on the role of recurrent processing is correct, a 'feedforward-feedback hypothesis' might be considered to predict not one, but at least two dips in

the TMS masking curve. In what follows directly below, we consider studies using static visual stimuli.

3.2. The ~30 ms dip

Corthout et al. (1999a,b, 2002, 2003) reported that TMS pulses around 20–40 ms have an effect on visual task performance. This seems an interesting yet odd dip. For example based on visual evoked potential (VEP) studies it has often been assumed that visual inputs do not arrive at EVC until around 50–60 ms post-stimulus (Baseler and Sutter, 1997; Vanni et al., 2004; Di Russo et al., 2002). However, although a strong response to visual input in human EVC seems to arise around that time, invasive recordings in monkeys (Celebrini et al., 1993; Cowey, 1964; Knierim and van Essen, 1992) and humans (Wilson et al., 1983) indicate that the earliest activity in V1 can start before this. And independent evidence suggests that around 100 ms SOA, recurrent activation of V1 can already take place (see below). Lamme and Roelfsema (2000) and Lamme et al. (1998) moreover provided evidence that two distinct periods of activity in V1 may occur, of which the first could start as early as 40 ms. So, hypothetically, a first masking dip at around 20–40 ms could reflect a feedforward stage of visual processing, while the classical 100 ms masking dip could reflect feedback processing.

On the other hand, there do not seem to be many replications of this early dip. That seems strange if 20–40 ms TMS pulses disturb an automatic feedforward process: *all* information is *always* fed forward, so disruption of feedforward activity should be an effect that is found relatively easily and without much dependence on the visual stimuli or other experimental parameters. Kammer (2008) reviewed the evidence for the ‘early’ dip around 20–40 ms and found it inconclusive. He speculated that perhaps inter-individual differences in (functional) anatomy could explain why only sometimes the early dip is found. Perhaps stimulation of precisely V1 (rather than V2/V3) might be necessary for the early dip and so the early dip could only be found in participants whose primary visual cortex lies relatively close to the surface. But a recent experiment targeting specifically V1 with the aid of fMRI-based mapping of visual cortex also failed to reproduce the 20–40 ms dip (Salminen-Vaparanta et al., 2012b).

Paulus et al. (1999) found a TMS masking effect at 15–45 ms that was separate from a second dip at the classical window around 100 ms. They found this early dip, however, only for achromatic stimuli, and not chromatic stimuli, in the same observers. They interpreted their data in relation to magnocellular and parvocellular pathways, noting that both pathways are involved in achromatic stimuli, but only the parvocellular pathway is involved in chromatic stimuli. Magnocellular signals are known to be transmitted faster through the early visual areas than parvocellular signals (e.g. Nowak et al., 1995). Maybe the early dip could thus be a “magnodip” and the classical dip a “parvo-dip”? Or perhaps the early dip is only found when stimuli are specifically tuned to massively involve the magnocellular pathway. Corthout et al. (1999a,b, 2002, 2003) found behavioral impairment around 20–40 ms several times, but not always as a ‘separate’ dip (i.e. sometimes ‘fused’ with other dips). Paulus et al. (1999) found it, and Kammer et al. (2003) found it in one subject out of three. We have previously tested for it and failed to replicate (de Graaf et al., 2011b; Jacobs et al., 2012b) systematically, although when using simple achromatic orientation stimuli we recently did find some (yet inconclusive) evidence for TMS-induced suppression at +20 ms, in a subset of participants (unpublished results). Overall, null results here are difficult to generalize (de Graaf and Sack, 2011) and positive results must be duly credited.

In (intermediate) conclusion, the 20–40 ms dip seems elusive, possibly dependent on stimuli, and not straightforward to interpret. We will see below (see The ‘negative’ dips) that TMS pulses

applied prior to stimulus presentation also affect visual performance, showing that TMS can affect visual processing also when applied before online processing of the visual stimulus has begun. If that is possible, then our lack of an unambiguous a priori interpretation of a 20–40 ms dip should not refrain us from investigating this potential dip further.

3.3. The ~200 ms dip

Consistent with the feedforward–feedback hypothesis are reports of a TMS masking dip *after* the classical masking window around 100 ms: such findings lend themselves to interpretation of the classical dip as a feedforward stage of processing while the later dip could reflect feedback processing.

Recently, a second masking dip at 220 ms SOA, clearly separated from the classical dip, was reported (Camprodon et al., 2010). The participants performed forced-choice discrimination between natural images of birds and large mammals. This essentially constitutes a categorization task, arguably ‘higher-order’ than for example orientation discrimination tasks. Koivisto et al. (2011a) also lent support to the feedforward–feedback hypothesis. Using a task of categorizing visual natural scenes (animals vs. nonanimals), they targeted EVC and lateral-occipital cortex (LO: a higher-order ventral stream region). EVC was functionally relevant (the classical dip) before LO, and still functionally relevant after LO started around 150 ms to become functionally relevant. Although two separate EVC dips were not observed, the pattern of results was not in line with a fully feedforward account, which cannot explain why early visual cortex should be functionally relevant after visual inputs have already reached LO. Evidence that feedback signals to early visual cortex can indeed modulate (conscious) perception in interaction with TMS pulses was provided earlier (Ro et al., 2003). More recently, Wokke et al. (2013) showed that, for an illusory stimulus, EVC was functionally relevant only in a later stage (160–182 ms) than LO was functionally relevant (100 ms).

Previously, Heinen et al. (2005) found two dips, one (just) within the classical window starting at 130 ms, one quite late starting at 250 ms. Their study focused on figure-ground segregation processes, and their rather late ‘classical’ effect from 130 to 160 ms is perhaps not so straightforwardly connected to TMS masking effects using more generic visual stimuli and tasks (see also Wokke et al., 2012). Taken together, these various studies suggest that EVC may be functionally relevant at a late stage when more ‘complex’ or ‘higher-order’ visual processes are required. In support of this conjecture, Juan and Walsh (2003) found that double-pulse TMS over EVC impaired visual search of single features at 80/120 ms, whereas search of feature conjunctions was impaired by TMS applied 200/240 ms after stimulus onset. Testing 100–450 ms SOAs, Dugué et al. (2011) found that attention-demanding serial visual search was impaired when TMS was applied over early visual cortex 300 ms after the onset of the stimulus array, whereas TMS had no effect on more automatic parallel search. Koivisto and Silvanto (2012) extended these findings by suggesting that the late V1/V2 activity period after 200 ms does not necessarily reflect the requirement of serial visual search through a complex display but generalizes also to a situation that is more specific to feature binding.

Attempts to replicate the late ~200 ms masking dip with simple forms or other simple static stimuli have not appeared successful so far (Jacobs et al., 2012a,b; Koivisto et al., 2012; Railo and Koivisto, 2012). For example, a recent study by our group applied single TMS pulses across the identical post-stimulus temporal range measured by Camprodon et al. (2010) and with identical resolution, during visual discrimination of symbolic arrow stimuli (Jacobs et al., 2012a). The classic masking dip was clear, but no TMS effects after 120 ms were observed. Thus, it seems that the late dip can

be produced only with rather complex stimuli and/or tasks that require figure–ground segregation (Camprodon et al., 2010; Heinen et al., 2005) or feature binding/conjunction search (Dugué et al., 2011; Juan and Walsh, 2003; Koivisto and Silvanto, 2012). See also Chambers et al. (2013) and Allen et al. (2014) for more recent demonstrations of late TMS-induced visual suppression effects.

3.4. Conclusion

While the latter postulation does lend support to the feedforward–feedback hypothesis, it also suggests that the feedforward–feedback framework in the current context may need to be refined. It has been suggested that much processing occurs within 100 ms from stimulus onset, involving perhaps multiple loops of feedforward–feedback (e.g. Bullier, 2001; Corthout et al., 2003; Foxe and Simpson, 2002; Juan and Walsh, 2003). Rather than trying to decide whether the classical dip is either feedforward or feedback, and which secondary dips then constitute the alternative, it may be more useful to consider whether there are not multiple stages at which EVC is functionally relevant and to begin probing the conditions under which these stages appear in TMS masking contexts. As a case in point, a recent study showed that when peripheral stimuli had to be compared, even though TMS pulses targeted foveal cortex, the contribution of EVC was necessary for accurate performance as late as 350–400 ms (Chambers et al., 2013). In conclusion, EVC may be crucial in various stages of visual processing over hundreds of milliseconds, depending on stimulus and task parameters.

3.5. The ‘negative’ dips

When occipital TMS pulses are applied *prior* to the visual stimulus onset (i.e. at negative SOAs), effects on visual task performance have also been reported. Corthout et al. (1999a,b) found that TMS pulses prior to visual stimuli could impair performance. The classical masking effect and a pre-stimulus masking effect have been compared to paracontrast and metacontrast visual masking, respectively (Breitmeyer et al., 2004). But in subsequent work, Corthout et al. (2000) postulated two pre-stimulus (i.e. negative) dips, which they dubbed “dip0” and “dipX”. Corthout et al. (2003) reported these dips to be separable. Dip0 was around –50/–40 ms, dipX was around –10 ms.

The conceptual problem with negative dips is twofold. First, if visual inputs will arrive to occipital cortex tens of milliseconds after the TMS pulse, how can the pulse disrupt vision? Second, eye blinks with various degrees of severity can be induced by occipital TMS, for instance as a startle-reflex to muscle contractions or the loud clicking noise. Eye blinks during or around stimulus presentation would obviously confound the data.

The potential contribution of TMS-induced eye blinks to the negative dip has been examined in three ways. First, based on the original logic from Amassian et al. (1989), it is possible to test whether or not the negative dip is retinotopic. For the ~–50 ms negative dip, this did not seem to be the case (Corthout et al., 2003; Jacobs et al., *in press*). Second, one may study when eye blinks interfere with visual processing, and how long it takes for an eye blink to be elicited by a TMS pulse. Stimulation of the facial nerve (resulting in reflex blinking) could affect visual discrimination of letters presented within an SOA corresponding to dip0 (~–50 ms) but not dipX (~–10 ms) (Amassian et al., 1998). Eye-tracking studies with occipital TMS also suggest that blinking could principally explain the –50 ms masking effect (measuring the latency of ‘pupil-covering’ after a pulse) (Corthout et al., 2000, 2011). From this, Corthout et al. (2011) recently concluded “that dip0 is almost certainly caused by pupil covering and that dipX is almost certainly not caused by pupil covering” (p. 248). However, even if eye blinks do

contribute to a masking dip this does not exclude the possibility of a concurrent neural effect. And so as a third approach, eye blinks can be measured and trials with blinks simply eliminated from the data to evaluate whether visual suppression still takes place at negative SOAs. Our lab recently replicated the negative dip at a broad range of SOAs (from –80 to –40 ms) and used electro-oculography (EOG) to measure eye muscle activations during a TMS masking experiment. Removing trials with eye blinks did reduce the average extent of visual suppression by TMS, but negative SOAs still showed significant masking effects (Jacobs et al., 2012b). Only one large negative dip was found, which was variable in latency across the participants, so the postulated dip0 and dipX were not separated. But all this work does suggest that at least some pre-stimulus masking (negative dip) is possible. We recently demonstrated, using TMS over a range of TMS intensities at SOAs of +90 ms and –25 ms, that the pre-stimulus masking effect can be detected using orientation stimuli (de Graaf et al., 2011a). In a new study, we moreover showed that these TMS masking effects at an SOA of –20 ms are retinotopically specific, while TMS masking at an SOA of –50 ms involved non-specific effects (Jacobs et al., *in press*).

How can we explain these TMS masking effects? At post-stimulus (positive) SOAs, TMS presumably affects the signal-to-noise ratio of online visual information processing (see Reichenbach et al., 2011, and for a general recent review see Miniussi et al., 2013). A recent computational model of TMS-induced suppression of local visual circuit responses could reproduce in large part the classical masking effect but showed no suppression for pre-stimulus (‘negative’) SOAs (Miyawaki et al., 2012). A fundamentally different suppression mechanism must occur for negative SOAs. In de Graaf et al. (2011a), we suggested that while post-stimulus TMS pulses disrupt the signal-to-noise ratio (SNR), pre-stimulus TMS pulses may put occipital cortex in a particular state that is not conducive to future information processing. We speculated that this may involve a modulation of intrinsic brain oscillations in the visual system’s natural frequency band (alpha-band: ~8–12 Hz) (Jacobs et al., 2012a,b) since previous work showed that the power (Thut et al., 2006) and phase (Busch et al., 2009; de Graaf et al., 2013; Mathewson et al., 2009) of ongoing parieto-occipital alpha oscillations determine visual task performance. Other (potentially related/coinciding) neural accounts of the pre-stimulus masking dip that have been suggested are interference with expectation or attentional processing prior to stimulus onset (Laycock et al., 2007) and extension of the TMS effect into lower level (sub)cortical visual areas either via recurrent connections (Stevens et al., 2009) or antrhodromically through feedforward connections (Covey, 2008). These various explanations are not mutually exclusive, but further work is required to probe their contributions.

3.6. The classical dip: ~100 ms

In the TMS masking literature, there is one dip that is clear and uncontested: the classical dip around +100 ms. Amassian et al. (1989) initially supposed that the masking curve delineated the timing of information entering and exiting EVC; an interpretation both elegant and straightforward. Perhaps because of this, the classical masking dip is fairly undifferentiated in the current TMS masking literature. There are a limited number of studies focusing on how various factors (e.g. TMS coil shape, TMS intensity, occipital targeting method, visual stimulus type) affect parameters of the classical dip (e.g. width of the curve, onset of the curve, peak masking latency, recovery of performance). For example, early studies explored the effect of TMS intensity on the width of the masking curve. Beckers and Homberg (1991) reported that increasing TMS intensity leads to an earlier onset of the masking curve (see also Corthout et al., 2000; Kammer et al., 2005b). More recently, we

explored how intensity affects the findings when focusing on certain SOAs of interest and measuring both objective and subjective visual performance: both were similarly affected for both negative and classical SOAs; see de Graaf et al. (2011a) and Jacobs et al. (in press). In an exploratory study with a 'sensitive paradigm' we obtained at least two closely neighboring masking dips within the classical dip, with performance returning to baseline in-between (de Graaf et al., 2011b). Other parameter explorations have included the effect of stimulus or background luminance on masking onset latency (e.g. Kammer et al., 2005b; Masur et al., 1993; Miller et al., 1996; with increasing luminance masking starts at earlier SOAs), and even the effect of perceptual learning on TMS masking (Neary et al., 2005). Recent studies have also indicated that the type of stimulus can have an effect on the latency of the classical dip. de Graaf et al. (2012) in a within-subject design obtained an earlier peak masking latency when presenting gratings as compared to faces. Superimposing these stimuli in a follow-up measurement did not replicate this difference, yet suggested slower recovery of the masking curve when subjects performed a task on the faces information, as compared to focusing on the gratings in the same superimposed images. Koivisto et al. (2011b) found in a between-subjects design a similar slower recovery for 'higher-order information', this time for judgments of symbolic arrow direction as compared to the orientation of bars.

3.7. Conclusion

In sum, there is a growing body of evidence that the details of the classical masking effect can depend on experimental parameters. Moreover, on reflection a window spanning 60 ms to 140 ms SOA is so broad, it seems implausible that one simple and same process is going on in all the TMS masking studies addressing the classical masking effect. New evidence supports a growing intuition that the classical masking effect is not a straightforward one-stage process of early visual cortex passing on visual inputs. Moreover, Abrahamyan et al. (2011) showed that when the intensity of TMS is just below phosphene threshold, visual task performance can actually be improved rather than impaired, whereas masking occurs with higher than phosphene threshold intensities. Thus, weak intensity TMS pulses bring the activation of neurons closer to the detection threshold, whereas strong pulses decrease the detection of sensory events, suggesting nonlinearity in the input response functions of the neurons. Not only the role of EVC around 100 ms, also the effect of a single TMS pulse may be more complex than conventionally considered. In sum, a focus on the classical dip as either the feedforward stage or the feedback stage in the context of the feedforward–feedback hypothesis, and an interpretation of TMS pulses as simply inducing a transient 'virtual lesion', may have been overly simplistic. Increased complexity holds the potential for increased insights into brain and early visual processing, which makes the reviewed findings both intriguing and promising. Before considering the classical masking dip further, another body of relevant literature should be considered.

3.8. Two dips in motion masking studies

We have been liberal with our use of the 'feedforward–feedback hypothesis', referring to a collection of theories that have one thing in common: EVC is functionally relevant not only when information first reaches it, but also afterwards, when information feeds back to it from higher-order areas. The most straightforward type of evidence for this scenario would come from a pattern of TMS results in a specific task where 1) early visual cortex is shown to be relevant, 2) a higher-order visual region is shown to be relevant after this, 3) early visual cortex is again shown to be functionally relevant after the functionally relevant window of the higher-order region. To test

this particular framework, two visual areas need to be stimulated in the same subjects: early visual cortex and a higher-order visual region that can be targeted by TMS.

One candidate higher-order region for demonstrating the feedforward–feedback cycle between EVC and extrastriate cortex is the human motion area V5, or hMT. Pascual-Leone and Walsh (2001) used two TMS coils, one targeting hMT and one targeting EVC. TMS over hMT induced moving phosphenes. EVC was then stimulated at various SOAs around the hMT stimulation pulse. Interestingly, a TMS pulse to EVC (below phosphene threshold), when applied some 30–40 ms after the pulse to hMT, abolished the apparent movement of the phosphenes or abolished the moving phosphenes altogether. This indicated that some form of recurrent signals from hMT to early visual cortex were actually necessary for the visual awareness of moving phosphenes to arise. Silvanto et al. (2005a) also stimulated hMT, but with a subthreshold pulse (which in isolation did not lead to any, moving or otherwise, phosphenes) and early visual cortex with a suprathreshold pulse. Suprathreshold pulses to early visual cortex in isolation led to stationary phosphenes, but when they were preceded (by some 10–50 ms) by subthreshold hMT stimulation the phosphenes took on hMT characteristics: they became bigger and were moving (Silvanto et al., 2005a). Thus, the backprojections could determine the content of the conscious visual experiences.

These studies showed that feedback per se is necessary for moving phosphenes perception, and that feedback per se can code-terminate the contents of conscious perception. But these results do not yet validate the feedforward–feedback hypothesis for regular visual perception. Silvanto et al. (2005b) asked subjects to report awareness of motion dot displays, while applying TMS to EVC or hMT across a range of SOAs. EVC was functionally relevant first, then hMT was functionally relevant but EVC was not, and subsequently, EVC was again functionally relevant in a second, distinct masking dip. In both time windows when EVC was functionally relevant, hMT was not. In this scenario, the first EVC masking dip could represent a feedforward stage, and the second EVC masking dip must represent a feedback stage. hMT does its functionally relevant processing in-between.

It would be valuable to directly relate such motion masking findings to the multiple masking dips reported in stationary masking experiments. Unfortunately, studies with two separate dips in motion perception (Koivisto et al., 2010; Silvanto et al., 2005b) have often triggered the TMS pulses in relation to stimulus offset. And since the stimulus durations were determined separately for each individual participant, TMS latencies cannot be straightforwardly translated to SOAs. If we do calculate the SOAs for stimuli with an average duration (67 ms) in Koivisto et al. (2010), the SOA for the early EVC dip was 87 ms and for the late EVC dip it was 127 ms. The early dip, hypothetically corresponding to the feedforward stage, thus falls clearly into the time window of the "classical dip", while the later dip, hypothetically corresponding to recurrent feedback, seems to parallel the end part of the classical dip. This might suggest that the classical dip cannot be said to reflect one of these stages, but in itself contains several stages. More on this conjecture below.

3.9. Conclusion

Whereas TMS masking began with a single masking effect around +100 ms SOA, the field today is focusing on a range of temporal stages. More research is required to understand precisely under which experimental conditions the early 20–40 ms dip can be found, and in which paradigms the late ~+200 ms obtains. The former remains elusive, yet the latter appears to reflect a relatively advanced functional stage of processing; perhaps early visual cortex receiving task-relevant recurrent projections from higher-order regions such as parietal cortex. After early reports

by Corthout et al. (see references above) interest in negative dips has recently renewed, since TMS-induced eye blinks cannot explain all negative (TMS pulses applied prior to visual stimulus) masking effects. Finally, ongoing research aims to delineate how experimental parameters affect the classical masking effect. There are increasing indications that there is more to this temporal stage than was initially supposed. We return to that theme below.

4. Multiple measures of vision: conscious and unconscious processing

Amassian et al. (1989) already noted that sometimes participants were correct in their identification of the presented letters, even though they reported that they did not consciously perceive the letters. “Such reports hint at a dual process, the first registering the letters at an unconscious level and the second rapidly entering consciousness but more susceptible to the MC pulse” (Amassian et al., 1989, p. 460). This remark foreshadowed the current interest in the role of EVC in conscious awareness versus unconscious information processing. Only recently have TMS masking studies begun to incorporate multiple measures of visual processing, including direct subjective report of conscious perception, forced-choice behavioral tasks, and (un)conscious priming effects.

Ro et al. (2004), Jolij and Lamme (2005), and Boyer et al. (2005) first addressed the issue systematically, optimizing the TMS masking paradigm to simulate ‘blindsight’. Blindsight patients have lesions in the primary visual cortex, resulting in scotomas, or conscious blind spots, in their visual field (Weiskrantz, 1996). Even in the absence of conscious perception these patients can relatively accurately process some information about stimuli presented in the blind areas, such as motion direction or the location of stimuli. Ro et al. (2004) showed in normal participants that, when TMS pulses to early visual cortex successfully masked visual stimuli, these stimuli could still affect saccades (see Christensen et al. (2008) and Ro (2008) for effects on reaching movements). Jolij and Lamme (2005) showed that TMS suppression of the visibility of emoticons (subjects could not localize the emotional emoticon in an array of neutral emoticons) did not necessarily abolish processing of the emotional content (subjects could still indicate whether the emoticon was ‘sad’ or ‘happy’), demonstrating ‘affective blindsight’ in normal observers. Boyer et al. (2005) directly assessed the subjective experience of subjects (“did you see the orientation of the bar, yes or no”) on every trial, and assessed in trials without subjective awareness of the stimuli to what extent objective information processing was effective (“forced-choice guess: was the bar horizontal or vertical?”). Five subjects performed highly accurately on the forced-choice task, even though they reported no conscious percept of the orientation on those trials. The same was found for color judgments (Boyer et al., 2005).

These results seemed to emulate blindsight, suggesting that early visual cortex is necessary for conscious perception but not unconscious processing of orientation and color stimuli. But the experimental paradigm in Boyer et al. (2005) has since been extended in terms of experimental controls and behavioral measures. It has been suggested that some additional control conditions could more clearly demonstrate whether discrimination performance without reported awareness was affected by TMS (Koivisto et al., 2010). Indeed, in our own efforts concerning this issue, we have been able to replicate the finding that subjects perform above-chance on trials where they do not consciously report seeing the stimulus (de Graaf et al., 2011a; Jacobs et al., 2012b). Yet, we generally found above-chance performance without reported consciousness also for no-TMS trials and SHAM (placebo) TMS trials. Such observations illustrate the need for further control

conditions. Without them, TMS-induced blindsight results may be explained by a difference in sensitivity of the two measures of visual processing. In fact, a very recent investigation used signal detection theory analysis to directly address this issue. In a series of experiments, Lloyd et al. (2013) showed that when a response bias-free measure such as d -prime (d') was used, no dissociation remained between forced-choice task performance (‘objective measure of vision’) and yes-no awareness reports (‘subjective measure of vision’). When it comes to judging the possibility of TMS-induced blindsight, it would be good to confirm this null result in further studies using a variety of experimental parameters and stimuli. Moreover, it is unclear what to make of studies that found condition-dependent ‘TMS-induced blindsight’. Either way, Lloyd et al. (2013) clearly demonstrated that response bias needs to be considered and eliminated in this type of work. A very recent contribution did indeed control for response bias, and nevertheless found above-chance visual task performance to be dissociated from conscious vision (Allen et al., 2014). They moreover used two sets of stimuli, of which one could bypass the retinotectal pathway sometimes thought to underlie TMS-induced blindsight. This clever experiment demonstrates how these questions remain of interest today, and how innovations in the masking paradigm still yield new insights.

Thus, the earlier pioneering reports inspired future studies to incorporate multiple measures of visual processing. We have generally employed two measures of vision, one subjective (e.g. a stimulus visibility rating on a four-point scale) and one objective (e.g. 2-alternative forced-choice—2AFC). We evaluated across SOAs (de Graaf et al., 2011b, 2012; Jacobs et al., 2012a,b), or TMS pulse intensities (de Graaf et al., 2011a; Jacobs et al., in press), whether TMS differentially affected subjective reports or objective performance. We have generally found a strong correspondence between TMS effects on both the objective and subjective measures (see also Koivisto et al., 2014), suggesting that TMS pulses affect visual processing holistically. We hypothesized that perhaps objective-subjective disruption dissociations would only become apparent at certain TMS intensities, for example if conscious-related processes in EVC are more susceptible to TMS disruption than unconscious-related processes. Yet, for TMS at -25 ms and $+90$ ms (de Graaf et al., 2011a) as well as -50 ms and -20 ms (Jacobs et al., in press), effects were nearly identical for both measures of vision across a wide range of intensities.

But the fact that vision as a whole is affected by TMS does not preclude the possibility that unconscious processing remains when conscious perception is wholly abolished. To investigate this issue, behavioral performance in trials without conscious perception must be evaluated as in Ro et al. (2004), Jolij and Lamme (2005), and Boyer et al. (2005). In one recent report, we found significant above-chance performance in unconscious trials for some SOAs (-40 ms, $+80$ ms, $+100$ ms) but not in others, suggesting that perhaps the ‘TMS-induced blindsight’ effect may depend on the timing of TMS pulses (Jacobs et al., 2012b). Koivisto et al. (2010) examined the issue for motion stimuli. Replicating the core findings from Silvanto et al. (2005b), they stimulated early visual cortex in the ‘early’ and ‘late’ time windows, with hMT in-between, finding again that early visual cortex was functionally relevant in both time windows. But while Silvanto (2005b) implemented only a subjective ‘conscious’ measure, now an objective ‘unconscious’ 2AFC discrimination task was included as well. Interestingly, performance on trials in which visual awareness of motion direction was absent was above-chance for no-TMS trials and for an ‘early’ masking window (i.e. 20 ms stimulus offset asynchrony), but was at chance-level for a ‘late’ masking window (i.e. 60 ms stimulus offset asynchrony; on average 127 ms SOA), suggesting that in this paradigm the feedback was required for both conscious and ‘unconscious’ processing of motion.

Some studies include still another measure of visual processing. Sack et al. (2009) presented subjects with symbolic arrow primes (pointing to the left or to the right), which were meta-contrast masked. Even when thus not consciously perceived, the arrow primes generally improve performance when subjects discriminate the pointing-direction of the target arrows (Vorberg et al., 2003). If TMS in the classical masking window affects only conscious processing, this symbolic response priming effect should remain unaffected by TMS. Yet, TMS at SOAs from 60 to 100 ms abolished response priming. Koivisto et al. (2012) in a similar paradigm tested a wider range of SOAs. They could show that TMS over EVC reduced unconscious priming at SOAs from 30 to 90 ms, whereas conscious recognition of (unmasked) primes was impaired at SOAs from 30 to 180 ms. Importantly, TMS over lateral occipital cortex (LO) impaired unconscious priming at SOAs from 90 to 120 ms (although only when the task was fresh), suggesting that unconscious priming relied on a linear feedforward sweep from V1 to higher areas. These results suggest that the end part of the classical dip (around 120 ms) was, at least in this particular study, related specifically to conscious perception, and that this late part may have reflected feedback processing from higher areas because LO was functionally relevant well before the classical dip had ended. A recent study by Persuh and Ro (2013) provided further support for the dependence of unconscious shape priming on EVC within the time frame of the classical dip.

Railo et al. (2012) studied processing of colors and found no consciousness-specific suppression of chromatic stimuli by occipital TMS in TMS windows up to 100 ms. Conscious color detection, forced-choice color discrimination, and unconscious color priming were all abolished by TMS over EVC. Lastly, Koivisto et al. (2011b) tested the effects of occipital TMS on subjective (conscious) and objective (forced-choice) processing of two types of stimuli, symbolic arrow stimuli and orientation stimuli. TMS affected both conscious and unconscious processing of symbolic stimuli in the same classical time windows (from 60 to 120 ms). But for the orientation stimuli, TMS specifically suppressed conscious processing from 90 to 120 ms, thus again at the 'later part' of the classical masking window. In a different paradigm, we also noted that occipital TMS in late classical SOAs (110–130 ms) affected the processing of one type of visual stimulus (faces) but not orientation stimuli (gratings). Here, both types of stimuli were superimposed and only the task differed (experiment 2 in de Graaf et al., 2012). An idea set forth in Koivisto et al. (2011b) could similarly explain both datasets, as well as several related findings discussed above. That idea requires reinterpretation of the classical dip.

5. Revisiting the classical masking dip

We observed several times above that the classical dip, spanning as broad a period as 60–140 ms SOAs, may not reflect a single stage of processing. Our current hypothesis is that the classical masking dip essentially contains two stages (Koivisto et al., 2011b; de Graaf et al., 2012; Miyawaki et al., 2012). The first part of the masking curve (i.e. until 90–100 ms) represents a feedforward stage of activity, in which early processing stages relevant for both conscious and unconscious vision, and presumably relatively independent of stimuli, tasks and context take place. But soon after this, local recurrent activity within EVC and between EVC and extrastriate areas commences, in the second part of the classical masking dip (i.e. ~100 ms to ~130 ms), potentially determining the contents of visual awareness (Koivisto et al., 2011b) and potentially susceptible to attentional/task demands (de Graaf et al., 2012). The involvement of feedforward activity in the early part and recurrent processing in the late part of the masking curve is supported also by the study of Emmanouil et al. (2013) who found that bottom-up (saliency)

and top-down (attentional set) factors influenced differently the early and late parts of the masking curve that resembled the classical masking dip. In addition, the TMS studies (Koivisto et al., 2010, 2012, 2014; Silvanto et al., 2005b) which have stimulated EVC and higher cortical areas across SOAs during the same task have shown that the higher areas start to play a functional role around 90 ms after stimulus-onset, that is, in the middle of the classical dip. This pattern indicates that the hierarchically higher areas are activated before the critical contribution of EVC has been accomplished, suggesting that it temporally plausible that the higher areas modulate the EVC activity in top-down manner during the time-window of the classical dip.

Electrophysiological recordings in animals (Lamme and Roelfsema, 2000) and humans (Boehler et al., 2008; Liu et al., 2009) show that the feedforward sweep reaches the highest extrastriate areas within about 100 ms and is immediately followed by recurrent processing in V1 about 100–120 ms after the onset of visual stimulus. It is possible that these recurrent processes may be involved with 'high-resolution' vision (e.g. Bullier, 2001; Hochstein and Ahissar, 2002). If the stimulus or task requires such high-resolution information, the latter part of the classical masking dip will appear (the crucial recurrent processes are disrupted), while it is 'missing' when these recurrent processes are not necessary for a given stimulus/task. Alternatively, or in addition, recurrent processes taking place around 100–130 ms may be required for the establishment of conscious vision but not for forced-choice task performance (as in the results of Koivisto et al., 2011b, 2012) although this may depend on the stimuli used (e.g. Koivisto et al., 2010, 2011b).

More generally, a two-stage classical suppression effect was proposed on the basis of numerical simulations using computational models of local circuits in early visual cortex (Miyawaki et al., 2012). Miyawaki et al. (2012) showed that TMS effects on feedforward activity (neurons responsive to the visual stimulus) could explain the early (approximately around 70–80 ms SOA) suppression, but not the later (approximately after 100 ms SOA) suppression found since Amassian et al. (1989). When the model was adapted to include sustained excitation and/or strong excitatory recurrent connections, the temporal pattern of TMS suppression in the model started to include the later suppression effect. These results also support a reconceptualization of the classical masking effect as containing TMS disruption of two distinct neural mechanisms (Miyawaki et al., 2012).

It thus appears that much can still be gained by using TMS to investigate even the 'classical masking dip', using different stimuli/tasks in the same subjects, and using concurrently different measures of vision (subjective, forced-choice behavioral, response priming). In any case, different groups and different methods are converging on the conclusion that the classical masking effect is not as simple as it may have seemed.

6. Conclusions and future directions

It is somewhat ironic that we currently see so much promise, when it comes to further insights in the context of TMS masking, in a deeper probing of what is actually the most established TMS masking result: the classical masking dip. It is exactly because it is so established that it may be very meaningful to study and 'use' this effect more. One approach here is the use of different kinds of stimuli or different tasks on the same stimuli. If TMS over EVC has differential effects depending on a particular task or condition, this could mean that EVC is functionally relevant specifically in one or the other task. This strategy can be applied whenever the hypothesis involves engagement of early visual regions in the tasks at hand. There has for example been recent interest in the role of

early visual cortex in memory (e.g. van de Ven and Sack, 2012). But also, the classical masking dip can be probed further with new paradigmatic approaches, such as the simultaneous measurement of multiple subjective and objective measures of visual processing, the combined variation of TMS SOA and intensity, and (f)MRI based modeling of TMS effects in/on the brain. Results to date have been considered above. We must conclude that not only there is more to learn from the classical masking dip, all the other ‘dips’ introduced over the years are far from established, though a pattern is beginning to emerge. Until we can further elucidate when and why some of these masking effects are obtained some of the time, an accurate depiction of the chronometry of early visual processing remains difficult.

But TMS masking as a field is still young. The abolishment of visual perception by a magnetic pulse to the back of the head remains one of the most tangible and impressive effects in the TMS literature. This review suggests that early visual cortex plays a causal role in conscious and unconscious visual perception during the classical masking window, but probably indeed also in various other stages, up to hundreds of milliseconds after stimulus onset and even before the stimulus appears. The exact nature of the functional role of early visual cortex in all these different time windows remains surprisingly obscure, though results appear to depend on stimulus and task parameters. By expanding on these issues, there is definitely more to learn using the TMS masking paradigm.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neubiorev.2014.06.017>.

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