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Psychophysical measurement of the effects and non-effects of TMS on contrast perception

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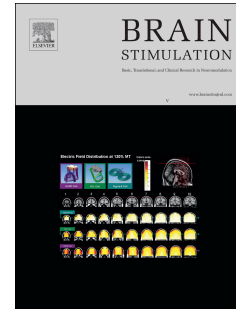
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1 **Title: Psychophysical measurement of the effects and**
2 **non-effects of TMS on contrast perception**

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18 Highlights

19

20 • Compared the effects of four TMS protocols on neural signals and
21 noise.

22 • Single pulse TMS suppressed neural signals and repetitive TMS
23 increased neural noise.

24 • Theta burst stimulation did not affect perceptual task performance.

25 • Participants differed in TMS susceptibility, determined by phosphene
26 perception.

27 • Findings suggest systematic inter-protocol and inter-participant
28 differences in TMS effects.

29

30

31 Key words

32 Sensory processing, neural effects, theta burst, online stimulation,

33 psychophysics

34 To the editor:

35

36 Transcranial magnetic stimulation (TMS) is widely used to establish causal
37 relationships between brain areas and behavior, but its effects on task
38 performance are not fully understood and have rarely been directly compared
39 between protocols. Decreases in performance on psychophysical tasks, such
40 as those observed when applying TMS, can be attributed to either
41 suppression of stimulus-related neural signals, increased random activity (i.e.
42 neural noise), or a combination of both [1,2]. Indeed, evidence for all three
43 hypotheses has been found when using differing methodologies and online
44 stimulation protocols [3–5]. Similarly, theta burst stimulation (TBS) has been
45 shown to have variable or bimodal effects between participants and between
46 exact stimulation protocols [6,7]. Despite different TMS protocols (e.g. online,
47 offline, repetitive, single pulse) potentially having vastly different effects, they
48 are often used interchangeably in sensory and cognitive research.

49

50 We directly compared the neural effects of four commonly used TMS
51 protocols: online single pulse (spTMS), online 3-pulse repetitive (rTMS; 50ms
52 between pulses), offline continuous theta burst (cTBS) and offline intermittent
53 theta burst (iTBS), during a well-understood neural computation – contrast
54 transduction. As a secondary objective, we investigated natural TMS-
55 susceptibility by comparing participants who could and could not perceive
56 phosphenes to address inter-participant variability in TMS effectiveness.

57

58 We tested all stimulation protocols using the same area (occipital cortex,
59 Supp. 2A) and a highly sensitive double-pass paradigm [8] to dissociate TMS
60 induced changes in stimulus-related neural signal strength (i.e. suppression)
61 and neural noise. On each trial (200 total per TMS condition) two luminance-
62 modulated stimuli (3 deg. vis. ang.) of randomly-selected contrast were
63 presented peripherally. Half of the trials contained a 4% contrast increment in
64 one of the intervals (see Supp. 1A,B for examples). The exact same trials
65 were then repeated with randomized interval order. Full details of stimuli and
66 the double-pass paradigm be found in [9]. Using standard protocols with a
67 Magstim Super Rapid² 'figure of 8' coil spTMS and rTMS (Supp. 2C, 70%
68 stimulator output) were applied 50ms after stimulus onset in each interval, and
69 offline TBS (Supp. 2D, 30% stimulator output) was applied before the start of
70 the task. Consistency between the first and second presentation of the trials
71 was calculated as a direct index of neural noise. Accuracy on the task was
72 calculated as a measure of stimulus-related signal strength.

73

74 During phosphene localization pre-screening, six participants (4 females, age
75 22-34) consistently perceived phosphenes and completed the main
76 experiment (a further 19 participants were screened but did not report seeing
77 phosphenes). Study was approved by YNiC ethics committee. All TMS
78 protocols were tested on different days (rTMS was tested over four days due
79 to high numbers of pulses). Phosphene localization was performed before
80 each testing session and the location of the phosphenes (as indicated with a
81 computer interface, Fig. 1A) was used to subsequently present stimuli.

82 Control trials (no TMS) were performed before stimulation for each TMS
83 protocol separately.

84

85 We simulated predictions using a linear amplifier model (LAM). Simulations
86 showed that if TMS reduced neural signal strength (lowered sensitivity), we
87 would observe a steep drop in task accuracy but no change in double-pass
88 consistency. Alternatively, if TMS increased neural noise, we would see a
89 small reduction in accuracy and a larger drop in consistency. Finally, if TMS
90 both reduced stimulus-related signals and increased noise, we would observe
91 a large reduction in both measures (Supp. 1C-E).

92

93 We found a significant drop in accuracy ($t(5)=2.83$, $p=0.037$, Bayes factor
94 (BF)=2.83) when applying spTMS compared to the no TMS condition, but no
95 change in consistency ($p=0.601$, BF=0.29, Fig. 1B). This closely resembles
96 our LAM model predictions for an increase in neural suppression and
97 suggests that spTMS suppresses neural signals. Conversely, applying rTMS
98 showed a small non-significant change in accuracy ($p=0.848$, BF=0.33)
99 compared to the no-TMS condition, and a significant decrease in consistency
100 ($t(5)=2.74$, $p=0.041$, BF=2.38, Fig. 1C) – consistent with model predictions for
101 an increase in neural noise. Neither protocol produced data consistent with
102 change in both suppression and noise. This comparison between spTMS and
103 rTMS is consistent with previous research that tested these protocols
104 separately [4,3] and suggests suppressive and noise-inducing effects are
105 protocol-specific.

106

107 No effects on the accuracy ($p=0.790$, $BF=0.30$) or consistency ($p=0.132$,
108 $BF=0.93$) were observed when applying cTBS (Fig. 1D). Similarly, no
109 changes in accuracy ($p=0.773$, $BF=0.30$) or consistency ($p=0.244$, $BF=0.58$)
110 were observed when applying iTBS (Fig. 1E), indicating that neither protocol
111 changed the levels of neural noise or sensory signals. This may seem to
112 oppose the large number of successful TBS studies, particularly in the motor
113 cortex. However, most previous research into TBS effects measured motor
114 evoked potentials, which reflect an overall increase or decrease in neural
115 activity (e.g. [10]). It may be that TBS changes overall neural activation but
116 does not have particular effects on perceptually-relevant signals that would
117 affect sensory task performance. Alternatively, the effectiveness of TBS may
118 be overstated in the literature, as indicated by a recent large scale meta-
119 analysis [11] which found a large positive publication bias in the TBS
120 literature.

121

122 To investigate the effects of TMS susceptibility on task-relevant effects, a
123 further six participants (3 females, age 23-55) who did not report seeing
124 phosphenes also completed the experiment. For these participants, stimuli
125 were presented at the mean location of phosphenes experienced by the other
126 group. None of the four TMS protocols had any significant effect on accuracy
127 or consistency scores in these individuals, indicating that the participants who
128 did not perceive phosphenes during phosphene localization were not affected
129 by TMS during the task. Anatomical differences in cortical folding and skull
130 thickness may explain these individual differences in TMS susceptibility.

131

132 The inter-participant and inter-protocol differences in TMS effects found here
133 shed light on the interpretation of findings in the existing TMS literature and
134 inform future methodological choices. The individual differences in
135 susceptibility and the use of different stimulation protocols in the literature
136 may be some of the major factors in the TMS 'replication crisis' [12]. The
137 effects of TMS are subtle and can often only be detected in reaction time data
138 rather than task performance [13]. In this respect, the sensitivity and precision
139 of the double-pass paradigm is a valuable tool for further investigating TMS
140 inter-protocol and inter-participant variability in other brain areas and with
141 larger samples.

142

143 **Conflict of Interest**

144 There is no conflict of interest relating to this manuscript.

145

146 **References**

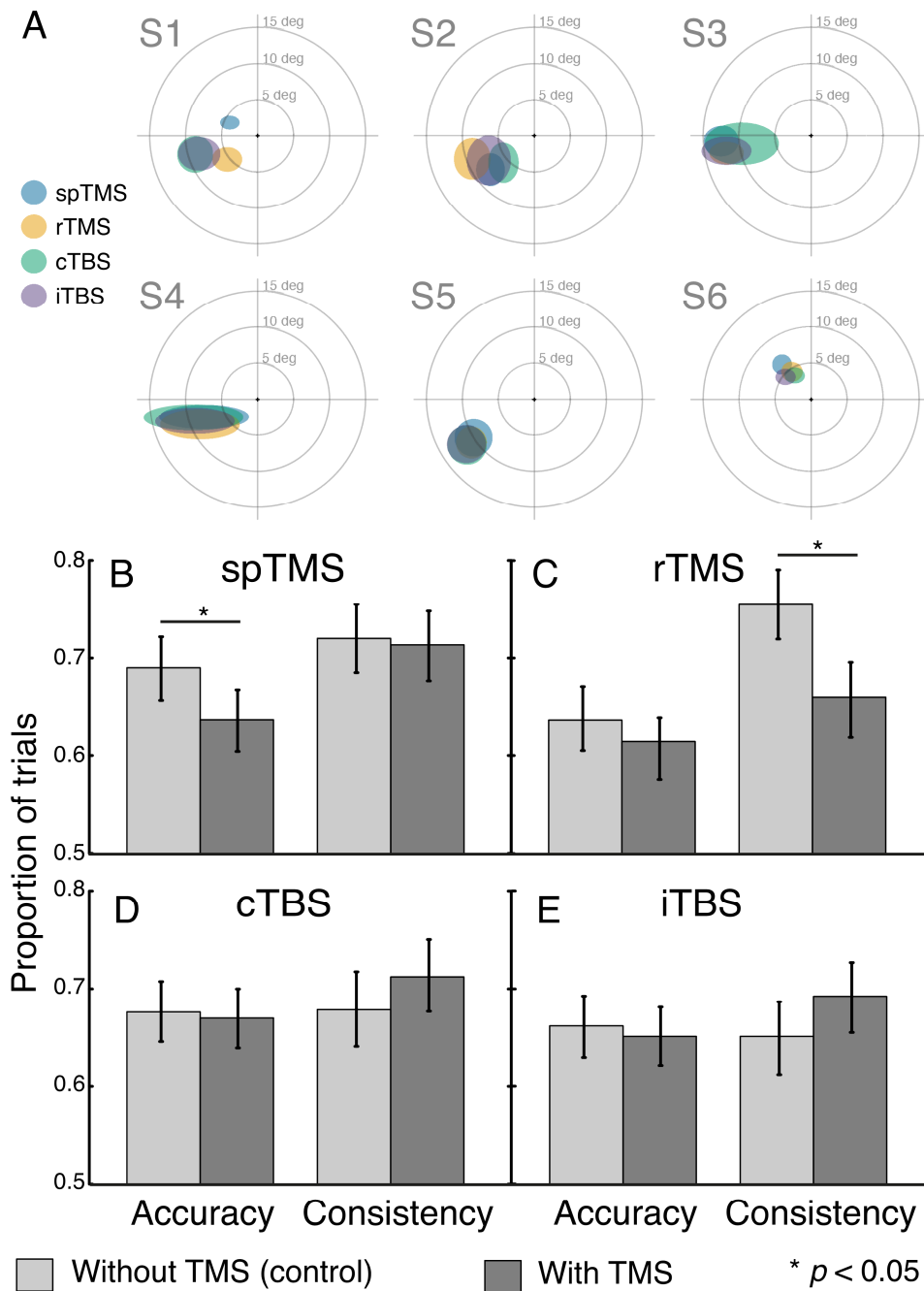
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191 **Figures**

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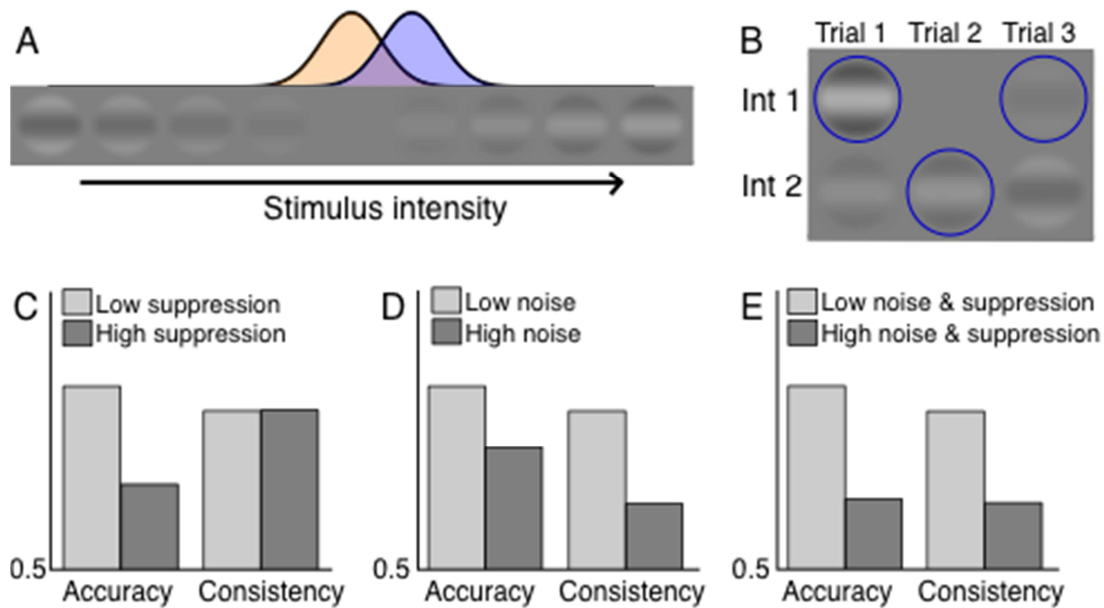
193

194 **Figure 1. Phosphene locations, mean accuracy and consistency scores for the**
 195 **individuals seeing phosphenes.** Phosphene locations were similar for all six
 196 participants, centered around the midline of the left visual field (A), within 15 degrees
 197 of the fixation cross. Phosphene locations were consistent across the four
 198 experiments using different stimulation protocols: spTMS (blue), rTMS (yellow,

199 averaged over four sessions), cTBS (green) and iTBS (purple), as indicated by filled
200 ovals. In Exp 1, single pulse TMS (B) significantly reduced the mean accuracy scores
201 (dark bars) compared to the no-TMS condition (light bars) but not consistency scores
202 which indicates increased suppression resulting from TMS stimulation. Repetitive
203 TMS (C) significantly reduced task consistency but not task accuracy, indicating a
204 TMS-induced increase in neural noise. Neither cTBS (D) nor iTBS (E) produced any
205 significant change in task performance. Error bars indicate bootstrapped 95%
206 confidence intervals.

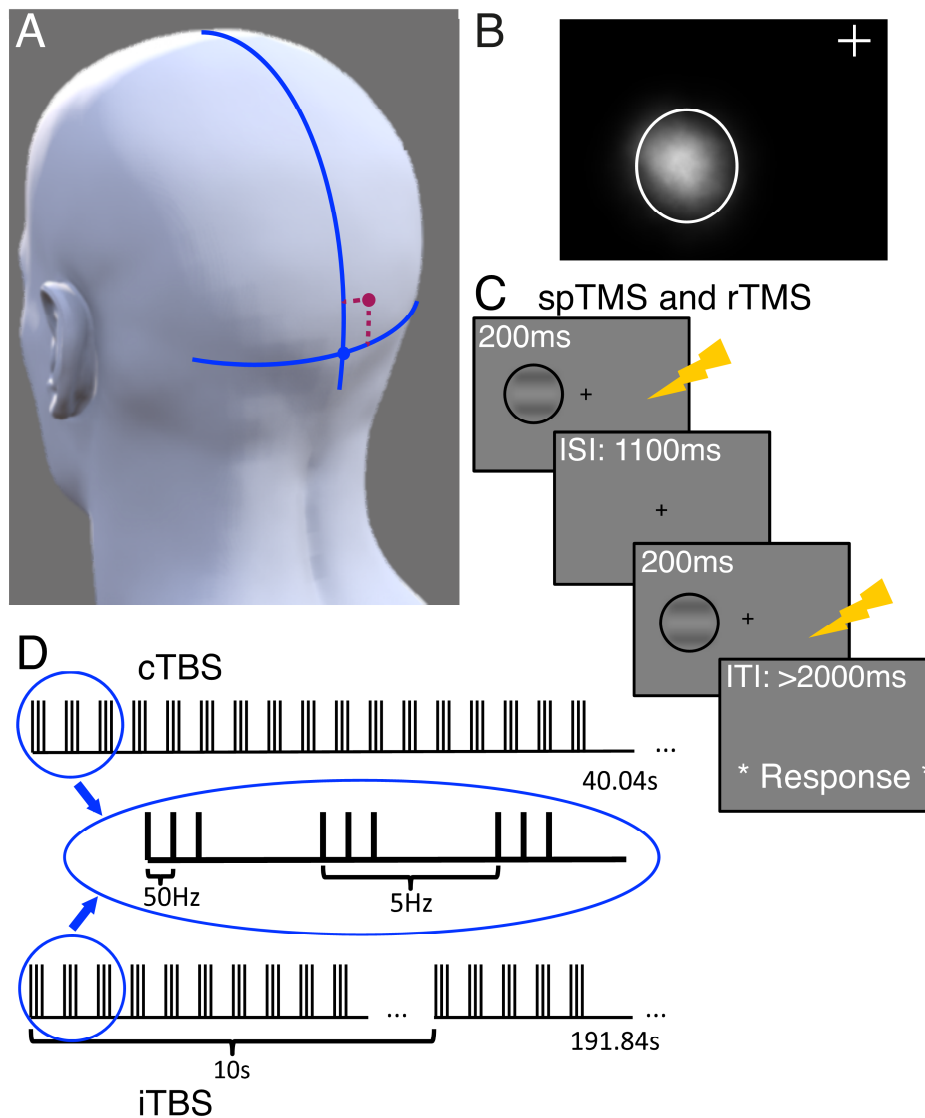
207 **Supplementary materials**

208



209

210 **Supplementary figure 1.** Each interval during a trial was drawn from the target
 211 (blue) and non-target (yellow) stimulus distributions (A). Participants were asked to
 212 choose the interval with the more positive contrast (B; example correct intervals are
 213 shown with a blue circle). Stochastic simulations were used to generate model
 214 predictions of double-pass data (C-E). Light bars in all panels indicate a system with
 215 low neural noise and low suppression (high sensitivity) in the system. Dark bars
 216 model an increase in either suppression, noise, or both. If TMS suppresses neural
 217 signals (lowers sensitivity) then we should expect double-pass data to be similar to
 218 the prediction in panel C. On the other hand, if TMS increases neural noise the data
 219 should resemble panel D. If both suppression and neural noise are increased we
 220 would expect data to be similar to panel E.



221

222 **Supplementary figure 2.** The TMS coil was positioned (red dot) approximately 2cm
 223 above and 1cm to the right of the inion (blue line intersection) to induce phosphenes
 224 (A). Before phosphene localization participants were trained to indicate the location
 225 and shape of a simulated phosphene on the screen (B; see section 2.3). During
 226 spTMS and rTMS protocols either one or three pulses (50ms apart) were delivered
 227 50ms after stimulus onset (C). Pulses during offline cTBS and iTBS were delivered
 228 as shown in D.