



## Reducing variability of perceptual decision making with offline theta-burst TMS of dorsal medial frontal cortex

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### ABSTRACT

**Background:** Recent evidence suggests that the dorsal medial frontal cortex (dMFC) may make an important contribution to perceptual decision-making, and not only to motor control.

**Objective/hypothesis:** By fitting psychometric functions to behavioural data after TMS we tested whether the dMFC is critical specifically for the precision and/or bias of perceptual judgements. Additionally we aimed to disentangle potential roles of the dMFC in dealing with perceptual versus response switching.

**Methods:** A subjective visual vertical task (SVV) was used in which participants weight visual (and other, e.g., vestibular) information to establish whether a line is oriented vertically. To ensure a high perceptual demand (putatively necessary to demonstrate a dMFC involvement) SVV lines were presented inside pop-out targets within a visual search array. Distinct features of perceptual performance were analysed before as compared to following theta-burst TMS stimulation of the dMFC, a control site, or no stimulation, in three groups, each of 20 healthy participants.

**Results:** dMFC stimulation improved the precision of verticality judgments. Moreover, dMFC stimulation improved accuracy, selectively when response switches occurred with perceptual repeats.

**Conclusion:** These findings point to a causal role of the dMFC in establishing the precision of perceptual decision making, demonstrably dissociable from an additional role in motor control in attentionally demanding contexts.

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### Introduction

In studies of perceptual decision-making, two independent features can be disentangled, by fitting a psychometric function to behavioural data from two-alternative forced choice (2AFC) paradigms [1]: bias (i.e. how biased perception of a stimulus is in

relation to its actual properties) and precision (i.e. how reliable or variable perception of a stimulus is, also sometimes referred to as simply “threshold” or “sensitivity”). Although normally associated with lateral intraparietal cortex (LIP) or frontal eye fields (FEF), it is important to explore other areas [2], and dorsal medial prefrontal cortex in particular has been linked, including the presupplementary motor area (preSMA) [3]. In transcranial magnetic stimulation (TMS) studies, preSMA stimulation has modulated decision thresholds [4,5], in line with increased decision thresholds after preSMA inhibition [6]. Other work has elaborated the clear evidence for dMFC’s motor role [7–10]. Yet it remains unclear whether the human dMFC plays a causal role in controlling the precision of perceptual decision-making. Moreover, appropriate explanations

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about the behavioural consequences of TMS on neural activity by means of computational modelling of recorded data are needed [11].

The function of the dmFC in response control has conventionally been studied with exclusively visual stimuli. The integration of visual and vestibular information has attracted particular attention in terms of examining bias and precision [1,12–14]. Although a key visual-vestibular hub lies around inferior parieto-insular cortex [15–18], the network also encompasses medial frontal areas [16,19]. There are close connections between dmFC and core vestibular areas (e.g. inferior frontal gyrus and insula [8,20–24]). dmFC activity has been linked to the amount of body sway in patients with vestibular problems [25] and midline frontal effects were reported in a recent parietal TMS-EEG verticality perception study [26]. The dmFC is then a candidate for perceptual decision making during verticality judgments.

The present study employed a visual search paradigm combining verticality perception (SVV) with perceptual switches and response switches. The first hypothesis was that TMS of the dmFC would interfere with the precision of verticality judgments. Given that previous work demonstrated a dmFC TMS effect on response selection on trials with high perceptual load [9,10,27,28], verticality judgments were made in a visual search setting. An additional non-search SVV condition was included to establish participants' resting bias. Additionally, in the search blocks, target defining and response defining features were orthogonal: this allowed testing the second hypothesis that dmFC TMS would specifically affect performance in the attentionally demanding situations, according to whether the target-defining dimension or the related required response would repeat or switch from one trial to the next.

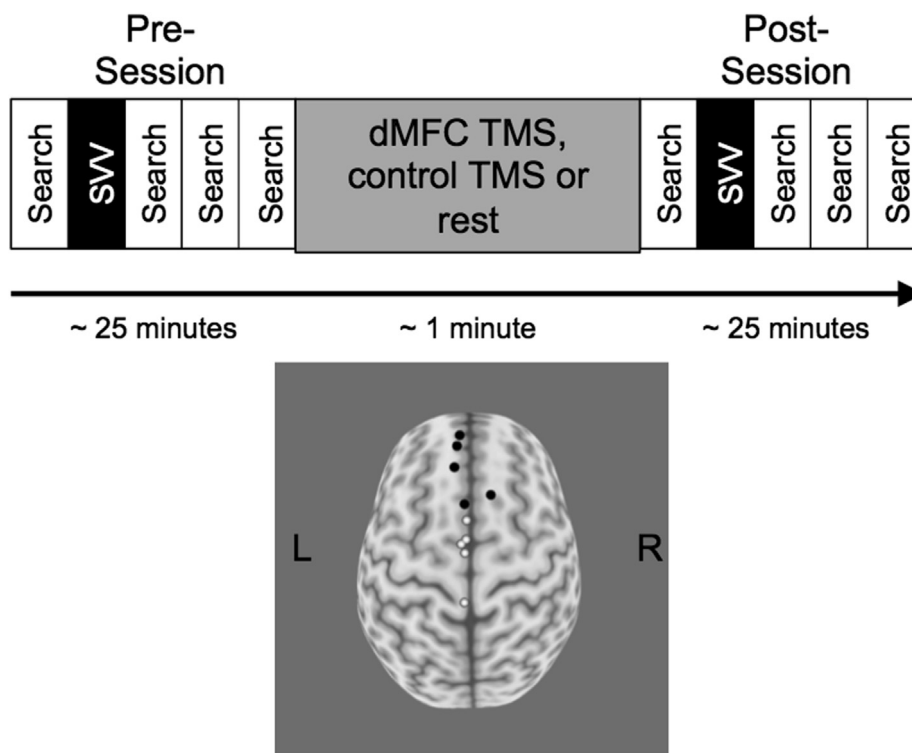
## Material and methods

### Participants

60 right-handed participants [29,30] took part (mean age:  $25.5 \pm 3.4$  years, 37 females). Participants were divided into three groups of 20. A first group received dmFC TMS (mean age:  $25.5 \pm 2.3$  years, range: 22–30 years, 14 females). To control for general alerting effects of TMS, and practice effects, a control TMS group underwent TMS stimulation over the vertex (mean age:  $24.5 \pm 2.0$  years, range: 21–29 years, 8 females) and a further group did not receive any TMS (mean age:  $26.7 \pm 4.8$  years, range: 23–41 years, 15 females). There was no overlap between participants in the three groups except one case between the dmFC and control TMS group and two cases between the control TMS and no TMS group. Note that although full cross-over designs help exclude population-based biases, they also are more sensitive to training effects over sessions or unblinding of the participants. All participants had normal or corrected-to-normal vision, and no history of any neurological disorders. Written informed consent according to established safety guidelines for TMS research [31] was obtained from all participants and the study was approved by the local ethics committee. Participants received monetary compensation.

### TMS

The two TMS groups received stimulation after the first half (i.e. after five out of ten blocks; "pre-session"; Fig. 1) of the experiment using a MagPro X100 (Magventure, Denmark) with a figure-of-eight coil (MCF-B70, outer winding diameter: 97 mm). TMS used the standard theta-burst TMS protocol used widely [32,33]: TMS lasted 47 s (200 bursts, each comprising three pulses at 50 Hz, repeated every 200 ms (5 Hz), 600 pulses in total) at 80% active



**Fig. 1.** Upper panel: experimental procedure. During the pre-session and post-session two task blocks were performed (SVV and visual search; block order counterbalanced). Between sessions participants received either dmFC TMS, control site (vertex) TMS or rested. Lower panel: location of the dmFC (black dots) and vertex (white dots) TMS sites for 5 participants from each group.

motor threshold (mean intensity:  $27\% \pm 6\%$  of maximal stimulator output; no intensity difference between the two groups:  $t(38) = 1.22, p = 0.23$ ; dMFC group:  $28 \pm 1\%$ , control TMS group:  $26 \pm 1\%$ ) to either the dMFC or the vertex. dMFC was defined as one and a half electrode positions anterior to electrode Cz according to the 10–20 International System [7,9]. A vertex control site, used in previous dMFC TMS studies [6,34] was chosen, because it is both near the active site and also over the midline, so that the two stimulation sites were well-matched for stimulation sensation – participants rate TMS over these regions similarly as low on scales of annoyance [35]. At the end of the experiment, coil positioning was confirmed for five participants in each TMS group using neuronavigation (Brainsight, Rogue Research, Canada, mean dMFC MNI (x,y,z) coordinates: 1, 36, 60; mean vertex MNI coordinates: 3, -12, 81). Despite variability of the stimulation sites in the y-axis within each TMS group the two groups did not overlap (Fig. 1). This target localisation method was based on previous dMFC TMS experiments [7,9,10]. One advantage of targeting midline areas is that the two hemispheres abut, meaning lower variability in the MNI x-axis than for other areas. Note the z co-ordinate of a TMS site does not imply the extent of stimulation depth. The TMS coil was held with the handle pointing backwards. Coil orientation was selected based on previous studies [7,9,10]. Note that with midline targets, holding the coil in any other way than parallel to the midline would lead to differential medial-lateral directions of induced current. During stimulation participants rested.

*Procedure*

Stimuli were presented on a 55.8 cm LCD monitor (1680 × 1050 pixel resolution, refresh rate of 60 Hz). Viewing distance from the screen was fixed to 50 cm using a chin rest and participants’ eye level was aligned with the screen centre. In order to avoid any environmental cues for verticality, the experiment was conducted in an extremely darkened room and the monitor edges were covered by a black paper 28 cm diameter circular cut-out [26].

Trials began with a white fixation dot (Fig. 2). After 1000 ms the target display appeared, showing either a single white line for 100 ms (Subjective Visual Vertical (SVV) blocks) or a visual search array for 200 ms (search blocks). The search array consisted of 8 white lines out of which 7 distractor lines were either placed inside white circles or red squares while the target line was always positioned inside a red circle. During the SVV condition participants had to indicate whether the flashed line was tilted in a counter-clockwise (CCW) or clockwise direction (CW) relative to true vertical. In the search condition the task was to judge the tilt direction of the target line. Next a blank screen was shown for 2000–3000 ms. Responses were given as quickly and accurately as possible with a button box. Participants pressed the left button with their right index finger for CCW tilts and the right button with their right middle finger for CW tilts.

Before the session, 24 practice trials of each condition were performed. For TMS groups participants’ motor thresholds were obtained after the practice block. Participants then performed the first five experimental blocks (“pre-session”; one SVV block of 60 trials and four search blocks of 50 trials each; block order counterbalanced between participants). Afterwards, either theta-burst TMS was applied, or participants were rested for 1 min. For the no TMS group, potential influencing factors were equated with those of the TMS groups, such as time taken between the first and second part of the experimental blocks and the lightning of the room. After the TMS stimulation or break, respectively, the second half of the experimental blocks was performed (“post-session”; one SVV block of 60 trials and four search blocks of 50 trials each; same block order as for the pre-session).

*Stimuli*

Stimuli were presented using Psychtoolbox [36]. In the SVV condition the target stimulus was a straight white line ( $23.2^\circ$  of visual angle long,  $1.2^\circ$  wide) shown on black background and on top of the central fixation point (diameter  $0.6^\circ$ ), which became black

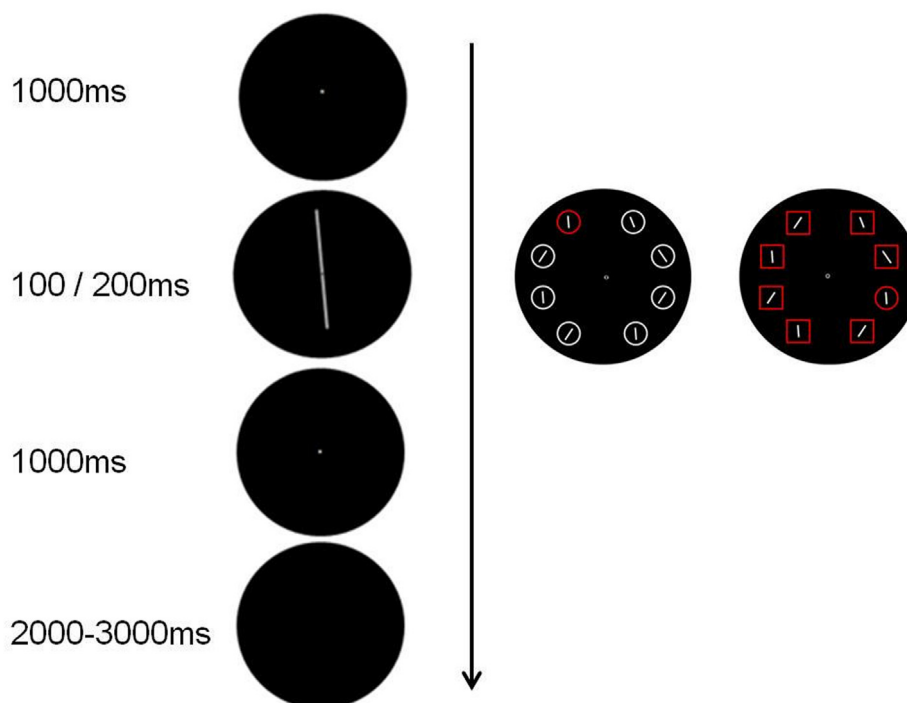


Fig. 2. Left: Schematic trial sequence SVV task. Right: Search task.

when the line was flashed. Tilt deviated up to  $\pm 2^\circ$  from true vertical, in steps of  $0.17^\circ$ . No true vertical ( $0^\circ$ ) trials were included.

For the search condition, stimuli consisted of 8 white, straight lines ( $3.0^\circ$  long and  $0.2^\circ$  wide) drawn within the either circles (diameter:  $3.4^\circ$  visual angle) or squares (side length:  $3.4^\circ$  visual angle), at eight equidistant locations around fixation (distance from the centre:  $12^\circ$  visual angle). To adjust for the smaller stimuli compared to the SVV condition, a larger tilt range of  $\pm 4^\circ$  from true vertical, in steps of  $0.33^\circ$ , was used, and truly vertical lines were included. Tilt angles of the 8 lines were different. The target stimulus always appeared within a red circle, with equal likelihood at any one of 8 possible locations, and could be different from the other seven distractor stimuli in one of two dimensions: either shape or colour. For shape pop-out trials, the red circular target was presented among lines within red, square distractors. For colour pop-outs, the red circular target was presented among lines within white, circular distractors. Search trials were classified relative to the preceding trial: same dimension (sD): the dimension of the distracting stimuli on the current trial matched the preceding trial; different dimension (dD): the dimension of the distracting stimuli on the current trial switched (i.e. either from shape to colour or from colour to shape); same response (sR): participants responded with the same button press; different response (dR): the participant's response switched (either from CCW to CW tilt judgment or vice versa). These conditions were then combined into four trial types: sDsR, sDdR, dDsR, and dDdR (Fig. 3). For each of these types 100 trials were performed in a randomized order across blocks.

Data analysis

Psychometric fitting of the observed data was used to derive individual SVV performance [1,12,37–39]. The point of subjective equality (PSE, reflecting the individual SVV bias) and the steepness of the slope of the sigmoid (i.e. standard deviation of the curve, which gives a measure of the participant's discrimination threshold, in that way reflecting response variability or precision) were computed for both tasks. Please note we use the term bias and not “accuracy” to reflect the PSE to make it more easily distinguishable from other analyses: In addition, the impact of dmFC TMS on performance in the two different tasks was investigated in terms of reaction times, accuracy, and perceptual versus response switching, analysed using ANOVA and post-hoc t-tests, with alpha set to 0.05 and effects sizes supplied when present. Effects were only considered as demonstrating group-specific TMS effects if supported by both ANOVA interactions involving the factor “group” and also by follow-up t-tests comparing pre-sessions with post-sessions, all using Bonferroni correction for multiple comparisons (i.e. correcting by 15 tests for analyses of precision and accuracy and by 24 tests for analyses of trial context). Comparisons were made between pre and post session within group (as opposed to comparisons across groups within session) because we had chosen a between-groups design to minimise additional variance that might arise from training effects with multiple sessions per participant [40].

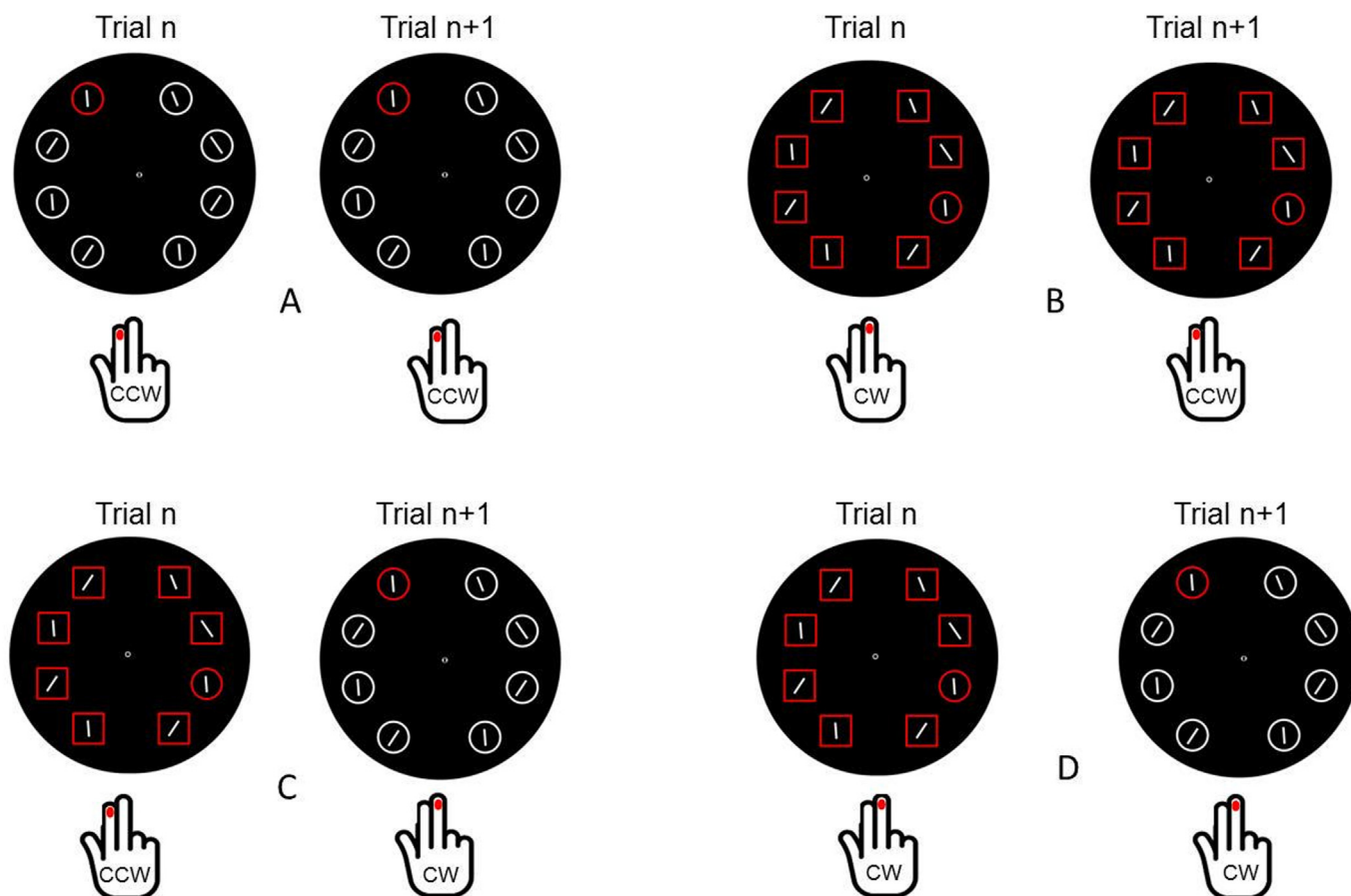


Fig. 3. Schematic of the four switch trial types of the search task: A: same dimension, same response (sDsR), B: same dimension, different response (sDdR), C: different dimension, different response (dDsR), D: different dimension, same response (dDdR).

## Results

### TMS effects on precision

Precision in the post-session differed from the pre-session according to both TMS and task (interaction Session (pre/post) x experimental group (dMFC, control, no TMS) x task (SVV, search):  $F(2,57) = 6.57, p < 0.01, \eta^2 = 0.19$  Fig. 4). This pattern was driven by dMFC TMS decreasing the variability of responses compared to the pre TMS session (i.e. improved precision of SVV judgments;  $t(19) = 3.97, p < 0.01, \text{Cohen's } d = -0.83$ ) with no such effects following control TMS ( $t(19) = 1.49, p = 0.15$ ) or no TMS ( $t(19) = -0.83, p = 0.42$ ). This could not be explained by any baseline (pre TMS/break) differences between the three groups ( $F(2,59) = 1.68, p = 0.20$ ). There were no between group effects using post-hoc t-tests. Moreover, the dMFC TMS effect was specific to the search task and did not occur in the SVV task ( $F(2,57) = 0.23, p = 0.79$ ).

### TMS effects on bias

No changes regarding SVV bias were observed in either of the two tasks or for any of the three experimental groups (all  $p$ 's  $> 0.44$ ). This was also true when participants were split on the basis of their performance in SVV blocks into those with a resting clockwise or counterclockwise bias (ANOVAs testing Session (pre/post) x experimental group (dMFC; control, no TMS) x SVV baseline bias subgroup (CW/CCW) all  $p$ 's  $> 0.57$ ).

### TMS effects on accuracy

There were no statistically significant effects on SVV accuracy in this psychometric fitting analysis, either at the level of the group interactions nor of dMFC TMS, control TMS or noTMS considered separately and compared between pre and post sessions. This included no differences in baseline accuracy levels between the three groups in search ( $F(2,59) = 1.68, p = 0.20$ ) nor in the SVV task ( $F(2,57) = 0.20, p = 0.82$ ) Accuracy was significantly higher in the SVV task as compared to the search task both in the pre-session ( $t(59) = 6.69, p < 0.01, \text{Cohen's } d = -0.85$ ) and the post-session ( $t(59) = 3.42, p < 0.01, \text{Cohen's } d = -0.40$ ) (Fig. 5).

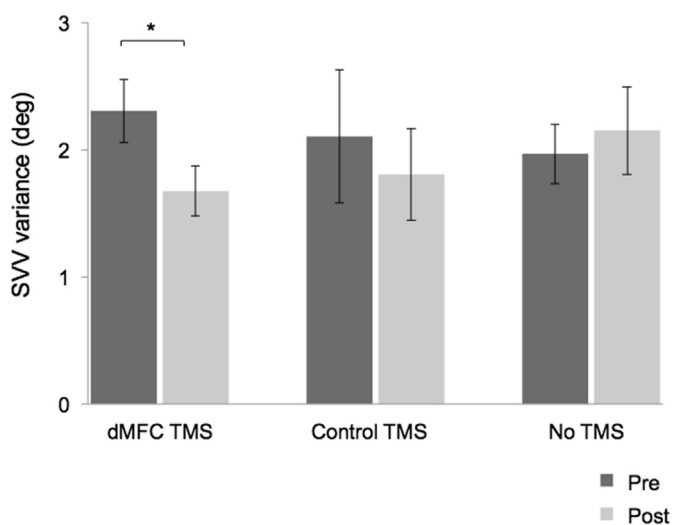


Fig. 4. Variability of SVV responses in the search task before TMS/break (pre) vs. after TMS/break (post) for the three experimental groups showing that dMFC TMS reduced variability (i.e. increased precision).

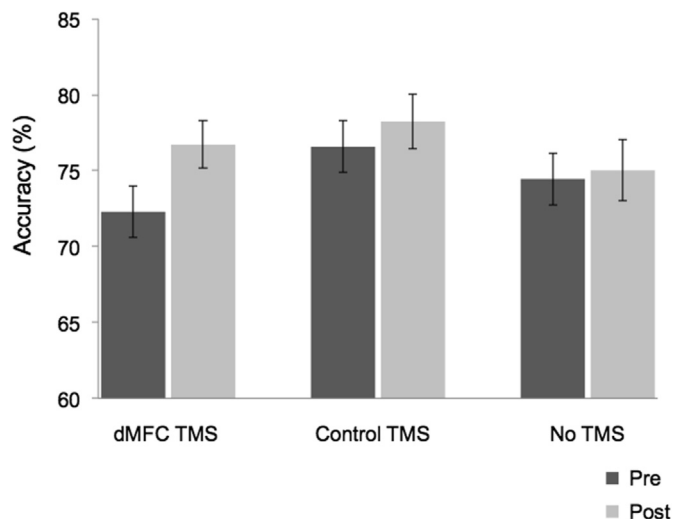


Fig. 5. Accuracy (% correct responses) in the search task before TMS/break (pre) vs. after TMS/break (post) for the three experimental groups.

### TMS effects on perceptual versus response switching: reaction times

Reaction times were faster after TMS or a break, as compared to baseline ( $F(1,57) = 74.22, p < 0.01$ ), regardless of experimental group or task ( $F(2,57) = 1.20, p = 0.31$ ) (Fig. 6). To assess to what extent this speeding of reaction times was dependent on the type of information switch from one trial to the next, TMS effects on reaction times in the four different switch conditions of the search task (sDsR, sDdR, dDsR, & dDdR) were analysed. There were no statistically significant interactions in the global analysis looking at all groups nor within groups. The overall effect of response switch was highly significant ( $F(1,57) = 20.49, p < 0.01$ ). As before, there were no baseline reaction times differences between the three groups (independent t-tests: all  $p$ 's  $> 0.13$ ).

### TMS effects perceptual versus response switching: accuracy

Accuracy was also calculated in terms of percent correct and not psychometric fitting (due to the subdivision of data into 8 different trial types per block). This revealed a general response switch cost (main effects of response switch, sR vs. dR;  $F(1,57) = 33.83, p < 0.01, \eta^2 = 0.37$ ). Critically, interactions involving experimental group (dMFC TMS, control TMS, no TMS) (Session x experimental group:  $F(2,57) = 11.46, p < 0.01, \eta^2 = 0.29$ ; Session x response switch x experimental group:  $F(2,57) = 10.25, p < 0.01, \eta^2 = 0.27$ ) showed that accuracy was affected by TMS. There was no 4-way interaction (TMS x dimension switch x response switch x experimental group:  $F(2,57) = 0.04, p = 0.96$ ) nor any other main effects or interactions. A post-hoc t-test (corrected for multiple comparisons as with all analyses) confirmed that the effect seen in the three-way interaction was driven by dMFC TMS improving accuracy selectively for the response switch trials, on which the dimension of the target repeated from one trial to the next (sDdR trials,  $t(19) = -4.67, p < 0.01, \text{Cohen's } d = 1.13$ ) (Fig. 7).

### TMS effects on switch conditions of the SVV task

Investigating RT response switch costs in the SVV task (as with search above), omnibus ANOVA including Session (pre/post) x response switch (sR vs. dR) x experimental group did not show an interaction ( $F(2,57) = 0.68, p = 0.51$ ). However, if anything there was a marginally significant trend in the opposite direction from in

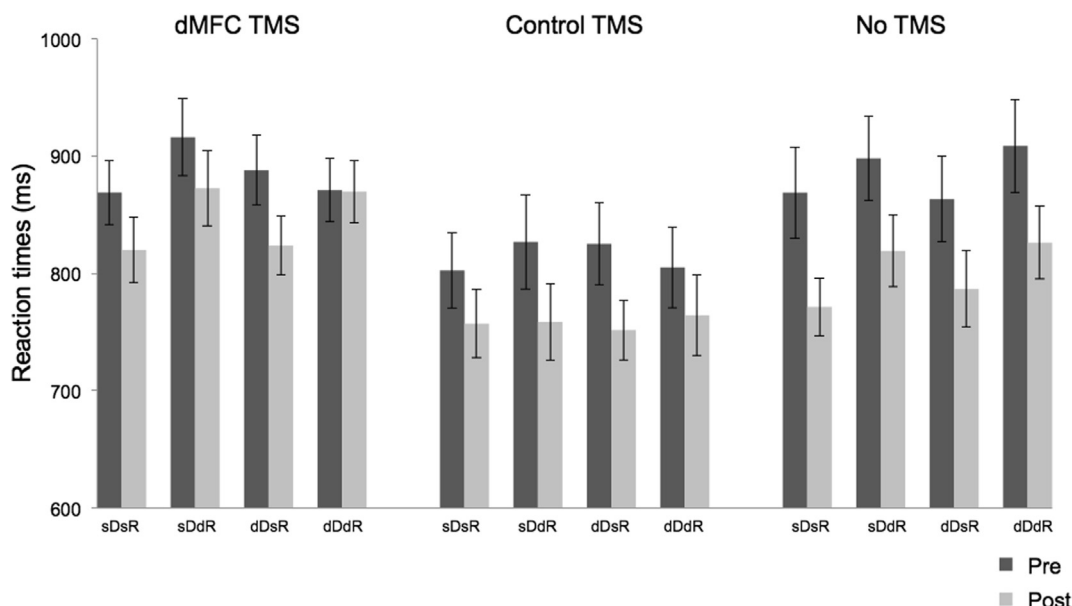


Fig. 6. Reaction times in the search task before TMS/break (pre) vs. after TMS/break (post) for the four different switch conditions of the search task for the three experimental groups.

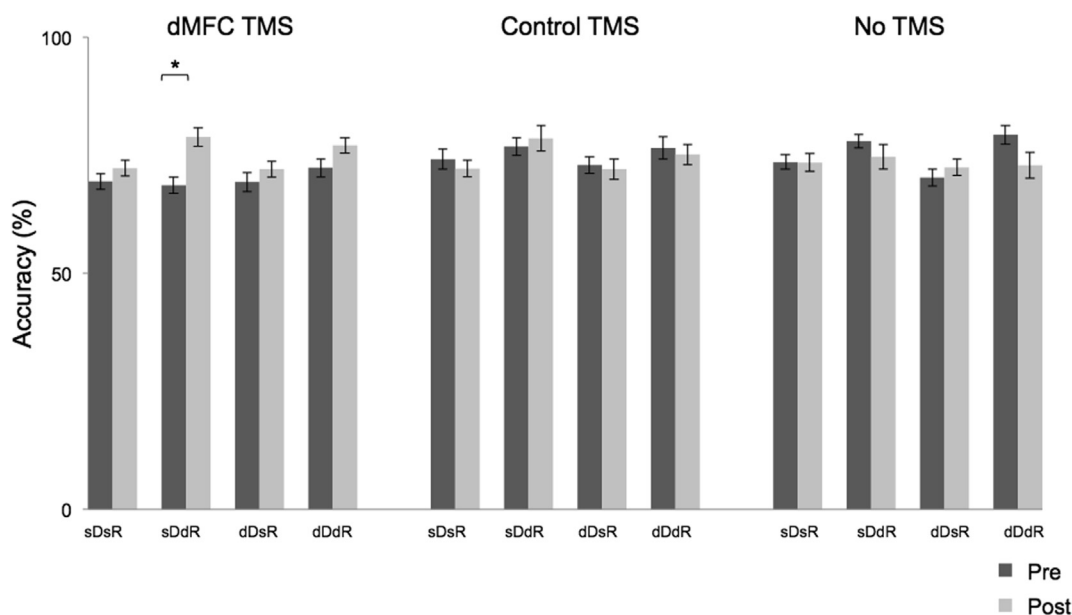


Fig. 7. Accuracy (% correct responses) in the search task before TMS/break (pre) vs. after TMS/break (post) for the four different switch conditions of the search task for the three experimental groups.

the search task, albeit only significant with uncorrected post-hoc *t*-tests and not supported by intermediate ANOVAs. dMFC TMS seemed to induce a speeding rather than a slowing of dR reaction times ( $t(19) = 5.15, p < 0.01$ , Cohen's  $d = -1.12$ ). Regarding accuracy there were no interactions between Session x response switch x experimental group nor between Session x response switch nor between response switch x experimental group (all  $p$ 's  $> 0.11$ ).

**Discussion**

*dMFC in the precision of perceptual decision making and the subjective visual vertical*

Dorsal medial frontal cortex (dMFC) activity correlates with trial-to-trial variations in response caution [41] and the dMFC has

been proposed to be a part of a brain network for sensory evidence integration [42,43]. dMFC TMS can increase or decrease perceptual decision thresholds [4,6]. Here our task design allowed extending this previous work to investigate precision versus bias of perceptual decision-making. Proficient observers are both precise and unbiased. Higher precision reflects more reliable discrimination by the observer. Precision is a measure of variance in responses corresponding to the steepness of the fitted sigmoid, calculated as the 'sigma' of the cumulative Gaussian fit of the psychometric function [1]. "Bias" in this sense is the bias of the percept compared to the true stimulus value. dMFC TMS did not affect bias. A simple SVV task (without search) was used primarily to classify participants according to their resting baseline bias and to check for bias-specific effects during search: online parietal TMS has affected bias depending on participants' resting bias [26]. However, while

the dMFC is involved in establishing the precision of verticality judgments, particularly under situations of high perceptual load (such as during a search task setting), we did not find evidence that it plays a crucial role in the bias of verticality perception.

dMFC lies outside the conventional network related to vestibular processing and the SVV [15–18], yet it is a main hub in a network that is responsible for perceptual decision making in which it exerts top-down control to other nodes such as the intraparietal sulcus (IPS) or insula [24,44], areas which form the human core vestibular region [15–17]. Moreover, dorsal medial frontal cortex may contribute to the processing of vestibular information [16,19]. A functionally relevant interaction between the right IPS and dMFC during verticality judgments should not be ruled out. Rather, future work should address the involvement of the frontal dorsal spatial attention network with its cortical core regions located in the posterior parietal and frontal cortices [45,46] more closely. This may help illuminate a proposed broader relationship between the classical attentional and vestibular networks giving rise to higher vestibular cognition [47–49].

#### *dMFC in response control when attentional demands are high*

dMFC is activated in visual search in the attentionally demanding situation where switches in the target-defining dimension occur, and more so than during within-dimension feature switches [27]. dMFC TMS affects action reprogramming only when the stimulus discrimination is hard and not easy [28]. The dMFC may be particularly critical for response selection if attentional demands are high [50]. This was generally the case here during the search task, but also in particular during the “sDdR” trials where response selection had to be made when the target-defining dimension had repeated and the correct response had switched from the previous trial. Previous studies of compound tasks support the view that the cognitive system links dimension and response expectancies [51,52]. If the target dimension repeats it is implicitly expected that the response repeats too [53], but if that assumed correlation is breached and the required response switches (i.e. sDdR trials) then in this context attentional demands are more challenging and response selection takes longer [51]. Previous TMS work using different tasks also supports a function for dMFC for resolving response conflicts in situations where the cognitive system is not prepared for them, such as in a flanker task on incongruent trials following congruent trials [9,10]. dMFC TMS studies reporting effects on response selection only under high perceptual load [28] have in common with the current effects (on SVV precision only during search, and on accuracy of response switch trials only on target dimension repeats) that the attentional demands have to be high for dMFC TMS effects to be evident.

#### *Limitations and outlook*

Future work could directly compare several areas with different tasks and protocols. Previous heterogeneous effects of dMFC TMS on decision threshold may be attributed to task difficulty [4–6,32]. The first continuous theta burst TMS study produced inhibitory effects, with excitation after intermittent bursts [54]. There may however be no direct 1:1 mapping between continuous/intermittent and inhibitory/facilitatory theta burst TMS: modelling suggests that continuous protocols elicit inhibitory and facilitatory effects simultaneously with different time-courses [55]. Accordingly there is now high variability evident in the literature [56]. Here, continuous theta burst facilitated performance. TMS effects may be highly task-specific: future work dMFC TMS studies should use tasks that do not require orientation judgements. By using two sites and two different tasks, one with multiple switch types, we were able to

dissociate between multiple hypotheses regarding dMFC function – this did necessarily increase the number of statistical tests performed which we addressed using Bonferroni multiple comparison correction. Future studies with simpler designs - only examining one task, site, or switch type - may allow replicating the core findings here with fewer tests. Additionally no effects on bias were found here with offline theta TMS as were found previously with an online 10 Hz TMS protocol [26] and this could be addressed directly by comparing both areas with both protocols.

#### **Author contribution:**

Lina Willacker: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Visualization; Writing - original draft; Writing - review & editing

Marco Rocco: Formal analysis; Investigation

Beril Nisa Can: Formal analysis; Investigation

Marianne Dieterich: Conceptualization; Writing - review & editing

Paul Taylor: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing - original draft; Writing - review & editing

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#### **Declaration of competing interest**

none.

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