Causal evidence for frontal cortex organization for perceptual decision making

Dobromir Rahnev¹,², Dereck Evan Nee³, Justin Riddle⁴, Alina Sue Larson⁵, and Mark D’Esposito³,⁶

¹Department of Psychology, Georgia Institute of Technology, Atlanta, GA 30332; ²Helen Wills Neuroscience Institute, University of California, Berkeley, CA 94720; and ³Department of Psychology, University of California, Berkeley, CA 94720

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Although recent research has shown that the frontal cortex has a critical role in perceptual decision making, an overarching theory of frontal functional organization for perception has yet to emerge. Perceptual decision making is temporally organized such that it requires the processes of selection, criterion setting, and evaluation. We hypothesized that exploring this temporal structure would reveal a large-scale frontal organization for perception. A causal intervention with transcranial magnetic stimulation revealed clear specialization along the rostrocaudal axis such that the control of successive stages of perceptual decision making was selectively affected by perturbation of progressively rostral areas. Simulations with a dynamic model of decision making suggested distinct computational contributions of each region. Finally, the emergent frontal gradient was further corroborated by functional MRI. These causal results provide an organizational principle for the role of frontal cortex in the control of perceptual decision making and suggest specific mechanistic contributions for its different subregions.

Significance

The frontal cortex has long been understood as the seat of higher level cognition. Recent research, however, highlights its role in modulating perception. Here, we present a theoretical framework for frontal involvement in perceptual decision making and test it with the causal technique of transcranial magnetic stimulation. We find that progressively rostral regions of frontal cortex are involved in the control of progressively later stages of perceptual decision making. These causal findings are further corroborated by functional MRI and simulations of a dynamic model of decision making. Our results point to a crucial role of the frontal cortex in the control of perceptual processes and reveal its intrinsic organization in support of modulating perception.

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¹To whom correspondence should be addressed. Email: drahnev@gmail.com.

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tasks (12), and to test directly the necessity of each region for the control of each processing stage. Our task required subjects to deploy spatial attention to engage selection processes (6), follow speed/accuracy instructions to engage criterion setting processes (13), and provide metacognitive judgments to engage evaluation processes (14). We found clear evidence for frontal cortex organization such that progressively more rostral regions were necessary for controlling later stages of processing during perceptual decision making. This emergent gradient was corroborated by simulations derived from a dynamic model of decision making that suggested specific computational contributions of each frontal region, as well as functional MRI (fMRI) data that extended the TMS results.

Results
We designed a task in which the processes of selection, criterion setting, and evaluation could be clearly identified (Fig. 1). On each trial, subjects were instructed to attend selectively to one of two peripheral stimuli (selection). The task was to indicate the orientation (clockwise/counterclockwise) of a gratating embedded in noise while adjusting the decision criterion so as to emphasize either speed or accuracy (criterion setting). After making their choice, subjects indicated their level of confidence (evaluation).

A decreased ability to engage this selection process following TMS would manifest itself as a smaller RT difference between attended and unattended stimuli (6). We predicted that TMS to the most caudal frontal site (putative FEF) would exhibit this effect based on previous work (reviewed in 16). Consistent with this prediction, we found a significant difference in performance between different TMS sites (χ²(3) = 10.6; P = 0.01, mixed-effects model; Fig. 2 A). A planned post hoc t test confirmed that the RT difference between attended and unattended stimuli was significantly decreased after FEF stimulation compared with the control site [RT difference = 128 ms, t(16) = 8.52, P = 2 * 10⁻⁸]. A decreased ability to engage this selection process following TMS would manifest itself as a smaller RT difference between attended and unattended stimuli (6). We predicted that TMS to the most caudal frontal site (putative FEF) would exhibit this effect based on previous work (reviewed in 16). Consistent with this prediction, we found a significant difference in performance between different TMS sites (χ²(3) = 10.6; P = 0.01, mixed-effects model; Fig. 2 A). A planned post hoc t test confirmed that the RT difference between attended and unattended stimuli was significantly decreased after FEF stimulation compared with the control site [RT difference = 128 ms, t(16) = 8.52, P = 2 * 10⁻⁸].

TMS Evidence for Frontal Organization for Perception. TMS did not influence overall task performance as measured by overall accuracy, reaction time (RT), or confidence (P > 0.05 for all pairwise comparisons between any of the four sites; Table S1), suggesting it is unlikely that frontal cortex is necessary for the low-level visual processing. We now turn to the frontal cortex involvement in the control of selection, criterion setting, and evaluation processes.

Selection (spatial cue). The first critical component of the task was a requirement to control the way stimuli were processing: a cue indicated which of two stimuli to attend. Subjects successfully followed the spatial cue as demonstrated by faster RTs for attended compared with unattended stimuli during the fMRI session [RT difference = 128 ms, t(16) = 8.52, P = 2 * 10⁻⁸]. A decreased ability to engage this selection process following TMS would manifest itself as a smaller RT difference between attended and unattended stimuli (6). We predicted that TMS to the most caudal frontal site (putative FEF) would exhibit this effect based on previous work (reviewed in 16). Consistent with this prediction, we found a significant difference in performance between different TMS sites (χ²(3) = 10.6; P = 0.01, mixed-effects model; Fig. 2 A). A planned post hoc t test confirmed that the RT difference between attended and unattended stimuli was significantly decreased after FEF stimulation compared with the control site [RT difference = 128 ms, t(16) = 8.52, P = 2 * 10⁻⁸].

Criterion setting (speed/accuracy instruction). The second critical component of the task involved a requirement to set a perceptual criterion by emphasizing on different trials either speed or accuracy. Such adjustment of the response threshold has long been considered an important example of how decision criteria are set in perceptual decision making (5, 13). Subjects successfully followed the instructions as demonstrated by a large RT difference between accuracy and speed trials during the fMRI session [RT difference = 370 ms, t(16) = 5.19, P = 9 * 10⁻⁴]. A decreased ability to set the response criterion appropriately would manifest in a smaller RT difference between the two types of trials. We predicted that TMS to the middle of the rostrocaudal frontal gradient (DLPFC) would interfere with the control of the criterion setting process, based on previous work (5). Consistent with this prediction, we found a significant difference in performance between different TMS sites (χ²(3) = 15.3; P = 0.002, mixed-effects model; Fig. 2B). A planned post hoc t test confirmed that the RT difference between accuracy and speed instructions was significantly decreased following DLPFC TMS compared with the control site [RT difference = 55 ms, t(16) = 3.31,
partly due to the fact that DLPFC was localized in a very anterior part of frontal cortex improved metacognition. Indeed, we found a significant difference in Type 2 AUC between different TMS sites [\(t(16) = 3.61, P = 0.01\), mixed-effects model] between the TMS site (S1, FEF, DLPFC, and aPFC) and the task component (selection, criterion setting, and evaluation). However, because not all pairwise comparisons were significant for each measure, we cannot conclude the existence of a complete triple dissociation among these three regions.

**Simulating the TMS Effects with a Dynamic Model of Decision Making.** Our results suggest that caudal, middle, and rostral frontal cortex have differential contributions to perceptual decision making. To understand the functional role of each region better, we performed simulations using an adapted model of perceptual decision making introduced by Kepes et al. (21) and De Martino et al. (22), wherein evidence is accumulated separately for each of the two choices, and the decision is made when one of the accumulators reaches a bound (23). Confidence is then assigned as the noise-corrupted difference between the winning and losing accumulators (\(\Delta\), the difference in evidence; Fig. 3A) such that higher difference indicates higher confidence. The critical parameters of the model are (i) the drift rate, which determines how quickly evidence accumulates for each choice; (ii) the bound, which determines how much evidence is needed to make a decision; and (iii) the confidence noise, which determines the strength of the association between confidence and accuracy. This modeling framework provides a natural way to operationalize the processes of selection, criterion setting, and evaluation using the above parameters (Fig. 3A). First, selection is defined as the process of enhancing the sensitivity for one stimulus over another. In the framework of our model, this process is equivalent to boosting the drift rate for the correct choice for the attended, but not the unattended, stimulus. Second, the requirement to set the response criterion according to the speed/accuracy instructions is naturally modeled by an adjustment of the bound to be higher for accuracy compared with speed instructions. Third, we observed significant variability in the metacognitive scores (from 0.58 to 0.83 in the FMRI session), which points to the existence of confidence noise that varies between subjects (22). This confidence noise controls how tightly the metacognitive ratings follow a subject’s decision accuracy such that a greater amount of this type of noise leads to lower metacognitive scores.

Our simulations demonstrated that changes to these three parameters of the model can qualitatively reproduce our frontal
TMS effects. First, the smaller difference in RT between attended and unattended targets after FEF TMS is reproduced by a smaller difference in the drift rate between attended and unattended conditions (red arrows in Fig. 3A and results in Fig. 3B). Second, the smaller difference in RT between accuracy and speed instructions after DLPFC TMS is reproduced by a smaller difference in the bound between speed and accuracy focus (blue arrows in Fig. 3A and results in Fig. 3C). Finally, the unexpected finding of higher metacognitive scores after aPFC TMS is reproduced by a decrease in the confidence noise (Fig. 3D). Our simulations assumed that TMS to each of these regions affected only a single parameter of the model, which is why the simulated data do not perfectly reflect the empirical results (Fig. 2). For example, the metacognitive score after DLPFC TMS increased compared with our control site, but this increase is not reflected in the simulations. However, what is important here is the demonstration that the TMS effects on the processes of selection, criterion setting, and evaluation can be naturally understood computationally in the context of our model of dynamic decision making.

Frontal Organization Corroborated by fMRI. Our TMS results and model simulation were consistent with our predictions that progressively rostral frontal regions are involved in progressively later processing stages during perceptual decision making. Because, as we noted above, the three stages are temporally organized, another prediction is that more rostral frontal regions will become active later in the course of each trial of our task. We tested this prediction by using the fMRI data from day 2 to characterize the activity in frontal cortex during the (i) instruction, (ii) stimulus/perceptual judgment, and (iii) confidence epochs of the task. We did not claim that the selection, criterion setting, and evaluation processes occur exclusively during the instruction, stimulus/perceptual judgment, and confidence epochs of the task, respectively. Instead, a temporal hierarchy exists whereby the stimulus needs first be selected before decision criteria can be applied, and both of these processes need to occur before evaluation can take place. This temporal hierarchy implies that each process should peak later than the previous one, even in the absence of one-to-one correspondence between the three processes and the three task epochs. The design of our task was optimized for the TMS effects rather than this particular analysis, but the results confirmed our prediction nonetheless. Specifically, we found a clear rostrocaudal gradient such that the activity in progressively rostral frontal regions peaked during progressively later epochs of our task (Fig. 4).

We first examined the brain activity during each of the three epochs of the task (Fig. 4A). The whole-brain activation patterns for each task epoch are shown and discussed in greater detail in Fig. S1 (we note that the pattern of activity in the left hemisphere was similar to the right hemisphere, and we provide a link to complete unthresholded maps, Materials and Methods). Here, we focus on the results in the frontal cortex. We found that frontal cortex activity during the instruction epoch was mostly constrained to a caudal region, activity during the stimulus/perceptual judgment epoch extended from caudal to midlateral frontal regions, and activity during the confidence epoch extended across the entire lateral surface of the frontal cortex.

Critically, we found that progressively rostral frontal regions were activated maximally during progressively later task epochs (Fig. 4B). Indeed, we observed a significant interaction between region (FEF, DLPFC, aPFC) and task epoch (instruction, stimulus/perceptual judgment, confidence) [F(4,40) = 22.16, P < 0.00001, repeated measures ANOVA]. Specifically, FEF activity was greatest early in each trial, DLPFC activity was greatest in the middle of the trial, and aPFC activity was greatest at the end of the trial. The most caudal frontal region, FEF, was more active during the instruction [t(20) = 2.09, P = 0.049, d = 0.46] and stimulus/perceptual judgment [t(20) = 4.31, P = 0.0003, d = 0.94] epochs, compared with the confidence epoch. FEF activity during the instruction and stimulus/perceptual judgment epochs was not significantly different (P = 0.99), which may be explained by the observation that FEF is responsive to stimulus presentation (16). The middle frontal region, DLPFC, was more active during the stimulus/perceptual judgment epoch compared with both the instruction [t(20) = 4.52, P = 0.0002, d = 0.99] and confidence [t(20) = 2.33, P = 0.03, d = 0.51] epochs. Finally, the most rostral frontal region, aPFC, was less active during the instruction epoch compared with both the stimulus/perceptual judgment [t(20) = 7.32, P = 4 × 10⁻⁷, d = 1.6] and confidence [t(20) = 6.88, P = 1×10⁻⁶, d = 1.5] epochs. aPFC activations during the stimulus/perceptual judgment and confidence epochs were not significantly different (P = 0.33), which may be partly due to the evaluation process starting immediately after making the perceptual decision internally, which is likely a few hundred milliseconds before the
button press that we used as an external indicator of the end of the stimulus/perceptual judgment epoch.

The above results were obtained by creating separate generalized linear model (GLM) models for each task epoch (SI Materials and Methods) to identify the full extent of activity during each task epoch. In a control analysis, we analyzed all three task epochs in the same GLM and obtained very similar results (Figs. S2 and S3).

**Discussion**

Despite numerous studies demonstrating the involvement of the frontal cortex in various high-level perceptual processes (2–5), the roles of distinct areas within frontal cortex during perceptual decision making remain underspecified. In this study, we provide a principle for frontal cortex functional organization based on the temporal organization of perception in the processes of selection, criterion setting, and evaluation. More specifically, convergent evidence from TMS and fMRI demonstrated that there are distinct frontal regions along a rostrocaudal (i.e., anterior-to-posterior) gradient that are necessary for the control of progressively later stages of the perceptual decision-making process.

Our results based on a causal intervention with TMS provide a critical addition to the literature on the contribution of frontal cortex to perceptual decision making that is largely based on correlational studies. Using correlational techniques, some studies claimed that relatively caudal regions of the frontal cortex are important for some of the later perceptual stages of processing. For example, speed/accuracy signals were found in FEF neurons (24), and confidence signals were found in supplementary eye field neurons (25). However, in our study, disruption of caudal frontal cortex function with TMS did not have a significant effect either on speed/accuracy or on confidence. It is possible that these differences are due to interspecies variation in the organization of frontal cortex and/or the substantial difference in the tasks used. Another important possibility is that because the perceptual decision was indicated via a saccade in both of these studies, the speed/accuracy and confidence signals were passed to the eye movement effector system but were nevertheless computed in more anterior areas of frontal cortex. This possibility is consistent with a recent study in which monkeys indicated the perceptual decisions using their hands and speed/accuracy signals were present in the primary motor cortex even though it is unlikely that these signals originated there (26).

More studies that use causal interventions in both humans and monkeys are needed to determine the etiology of the discrepancies between our and these previous studies.

The functional gradient revealed in our data has strong implications regarding the general organization of the frontal cortex. A critical mass of studies has suggested the existence of a rostrocaudal gradient in the frontal cortex (1, 7–10). Although these studies differ in the details of the type of processes or representations being linked to each PFC subregion, each proposes a hierarchical organization with more rostral regions involved in the processing of more abstract representations (1, 7). Other studies, however, have proposed that the lateral frontal cortex is homogeneous in function without a functional gradient (12, 27, 28). This debate is complicated by the correlational nature of most previous studies. However, two previous studies of patients with focal brain lesions found causal support for a rostrocaudal gradient in frontal cortex (9, 10). The current results extend these previous patient studies by providing causal evidence from healthy human subjects in support of a rostrocaudal functional organization of frontal cortex.

Simulations based on a dynamic computational model of perceptual decision making (21–23) were able to reproduce the observed empirical TMS effects. The decrease in the RT advantage for attended stimuli following FEF TMS could be reproduced by decreasing the difference in drift rate between attended and unattended stimuli. Thus, one possibility is that the caudal frontal cortex biases the processing of visual information such that one stimulus is favored over another through a process akin to gain amplification (16, 29). This possibility is further corroborated by the known connectivity of FEF to early visual areas that respond to the visual stimulus (30). The decrease in the RT difference between accuracy and speed focus following DLPFC TMS could be reproduced by decreasing the difference in the decision bound between the two conditions. One possibility is that DLPFC is involved in the adjustment of the decision criterion. Such a role is facilitated by the wide connectivity of DLPFC with higher visual and parietal (as well as premotor and subcortical) areas (5). Finally, the improved metacognitive performance after aPFC TMS could be reproduced by decreasing the noise term in confidence decisions, consistent with a role of aPFC in metacognitive evaluations. This type of metacognitive process likely requires communication only with other high-level regions, such as frontal and parietal cortices, which is consistent with the connectivity pattern of aPFC (31). In summary, even though our simulations were intended as, and should only be seen as, a proof of concept, they are consistent with a rostrocaudal organization of frontal cortex function in relation to visual perception. A similar idea has been put forth in the context of linking perception with action (1).

Surprisingly, we found improvement in metacognition after aPFC TMS. Despite the unexpected nature of this result, it is actually in line with a pair of recent studies. The first one reported similar metacognitive enhancement after aPFC TMS on a memory task (32). The second one showed that monkeys with lesions to
rostral frontal cortex showed behavioral improvements on certain tasks (33). Specifically, they remained more focused in exploiting the current task when faced with various interruptions, potentially suggesting a role for rostral frontal cortex in reallocating cognitive resources for new purposes. Nevertheless, metacognitive impairment after TMS to a more posterior site in middle frontal gyrus has also been reported (34). Critically, in our study, average confidence ratings were not affected by aPFC TMS; instead, what was improved was the correspondence between the trial-by-trial confidence ratings and accuracy. Several types of explanations have been provided for TMS-induced performance improvements. For example, if TMS suppresses the noise more than the signal, behavioral performance would improve rather than decline (35).

Another possibility is that behavioral performance can improve if TMS suppresses the noise more than the signal, which could have contributed to the improvements in metacognition. Nevertheless, in the absence of direct neural evidence, each of these explanations remains speculative. Regardless of the explanation of our finding, it does support a critical role for aPFC in metacognition, and is consistent with the existence of a rostrocaudal gradient in frontal cortex for perception.

### Materials and Methods

Forty-one subjects were tested in an initial screening session. Twenty-one of these subjects were able to perform the task appropriately by following both the attentional and speed/accuracy instructions, and were therefore invited to participate in the five additional days of testing. Four subjects were unable to complete all six sessions; thus, a total of 17 subjects completed the study (11 females and 6 males, average age = 23.06 y, age range: 21–30 y). All participants had normal or corrected-to-normal vision. They received detailed information about the potential side effects of TMS and provided written informed consent. All procedures were approved by the University of California, Berkeley Committee for the Protection of Human Subjects.

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