the idea that the areas of anterior insula and DLPFC represent the twin demands of the Ultimatum Game task, the emotional goal of resisting unfairness and the cognitive goal of accumulating money, respectively. Further, our finding that activity in a region well known for its involvement in negative emotion is predictive of subsequent behavior supports the importance of emotional influences in human decision-making. We believe that these findings, and work that proceeds from them, will provide a more detailed characterization of specific emotional responses, their neural substrates, and the social circumstances under which they are elicited. Therefore, not only do our results provide direct empirical support for economic models that acknowledge the influence of emotional factors on decision-making behavior, but they also provide the first step toward the development of quantitative measures that may be useful in constraining the social utility function in economic models (*32*, *33*). Models of decision-making cannot afford to ignore emotion as a vital and dynamic component of our decisions and choices in the real world.

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12. We use the term "cognitive" here, in place of the term "rational" (as commonly used in the traditional economic literature), in recognition of the fact that emotional responses may also have a rational basis (e.g., to punish unfair offers). The term "cognitive" is perhaps also problematic, for similar reasons. Terms such as "proximal" and "distal" may be more accurate, respectively indicating the immediate and longer-term sources of gain associated with the behavior. However, until the field converges on a new set of accepted terms for designating these classes of motivation, we use the terms cognitive and emotional as intuitively accessible, if not technically accurate.
13. Materials and methods are available as supporting material on *Science* Online.
14. This methodology deviates somewhat from the standards of experimental economics, a field that generally proscribes the use of deception [see (*34*) for a summary of the issues, though there are some exceptions (*35*)]. We chose to use a limited amount of deception in the current study primarily because of the heavy logistic demands of an fMRI study, requiring a full distribution of offers in a constrained number of participants. Practical issues notwithstanding, we believe the use of deception had little if any impact on our results, and any effect was not likely to confound their interpretation. During the post-experiment debriefing, no subject gave any suggestion that they had been suspicious of the offers they received. Further, the behavioral results in the human partner condition replicate those found in versions of the game using no deception, with approximately half of offers of 20% or less of the total being rejected (*9*). Perhaps most importantly, if subjects suspected deception, this should have diminished emotional responses (i.e., if subjects suspected the offers to be fictitious, their emotional reactions to these offers, particularly unfair offers, should have been muted). The fact that we observed significant effects consistent with emotional responses suggests, once again, that the effects of deception were minimal and, if they were present, have simply caused an underestimate of the observed effects. Although we are sensitive to the issue of deception, we believe that the methodological constraints of fMRI justified our practice and that the findings do not appear to be tainted by subjects' possible perceptions of the deception used.
15. A common concern regarding the use of deception involves possible contamination of the participant pool. As mentioned previously, rejection rates in the current study replicate those typically reported from uncontrolled Ultimatum Game studies; therefore, we do not believe we suffered unduly from this. Furthermore, a comparison of rejection rates over the course of the experiment (i.e., longitudinally over participants) indicates no systematic trends in these rates (mean rejection rate of offers for first six participants was 32%; mean rate for last six participants was 35%).
16. After the conclusion of the Ultimatum Game with all partners, subjects then played a single round of the Prisoner's Dilemma (PD) game with each of the partners. This raises the possibility that subjects did not treat the Ultimatum Game as a true single-shot game. We do not believe playing the PD game affected their play in the Ultimatum Game in this study for several reasons. First, our behavioral results support the notion that the Ultimatum Game was played as a single-shot game. As noted above, the proportion of rejected offers in our study matches proportions reported in the experimental economic literature when the game is strictly controlled as single-shot. We would have expected much higher rejection rates in an iterated Ultimatum Game. Second, unpublished data of ours using a single-shot Ultimatum Game (with no subsequent task) produced rejection rates of unfair offers that are virtually identical to those reported here ($8:$2 split, 47% versus 49%; $9:$1 split, 61% versus 60%). We believe this evidence strongly suggests that subjects treated the Ultimatum Game as a single-shot game, as instructed.
17. We asked our participants as part of the debriefing process what they considered a "fair" offer to be irrespective of their decision to accept or reject, thus providing an indication of their standards of fairness. Of our participants, 58% considered any offer less than $5:$5 as unfair, with the remaining 42% deeming anything less than $7:$3 to be an unfair division.
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36. We would like to thank D. Kahneman, A. Scheres, and three anonymous reviewers for their helpful comments. This work was supported in part by grants from the Seaver Institute and the Mind, Brain, Body, and Health Initiative.

Supporting Online Material

www.sciencemag.org/cgi/content/full/300/5626/1755/DC1

Materials and Methods

Table S1

31 January 2003; accepted 15 April 2003

V1 Neurons Signal Acquisition of an Internal Representation of Stimulus Location

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A fundamental aspect of visuomotor behavior is deciding where to look or move next. Under certain conditions, the brain constructs an internal representation of stimulus location on the basis of previous knowledge and uses it to move the eyes or to make other movements. Neuronal responses in primary visual cortex were modulated when such an internal representation was acquired: Responses to a stimulus were affected progressively by sequential presentation of the stimulus at one location but not when the location was varied randomly. Responses of individual neurons were spatially tuned for gaze direction and tracked the Bayesian probability of stimulus appearance. We propose that the representation arises in a distributed cortical network and is associated with systematic changes in response selectivity and dynamics at the earliest stages of cortical visual processing.

To assess whether monkeys (*Macaca mulatta*) form an internal representation of stimulus location, we devised a task in which information about future stimulus locations could be acquired progressively with successive trials in one experimental condition but

not in another (Fig. 1A). Monkeys were trained to fixate a spot that appeared at one of three locations on a computer screen (*1*). In the "randomized" sequence, the location of the fixation spot varied randomly from trial to trial, whereas in the "grouped" sequence, the spot appeared repeatedly at the same location for a succession of trials. No cue was provided as to which sequence was in effect. We estimated the target probabilities by Bayesian updating, assuming equal prior probabilities of being in the randomized and grouped conditions (*2*) (supporting online text). We confirmed that the target probabilities were perceptible by human subjects by asking them to indicate where the target would appear next as trials progressed in either the randomized or the grouped sequence (supporting online text). The probability of successful prediction tracked the Bayesian target probabilities in both sequences (Fig. 1B). In monkeys, we monitored eye position and the latency to achieve fixation when a spot appeared (*1*). The saccade latency to a visual target is a sensitive indicator of the likelihood of the target's appearance (*3–5*). Fixation latency was approximately constant from trial to trial in the randomized condition but shortened significantly as trials progressed in the grouped condition (Fig. 2A; $P < 0.001$ comparing latencies in trials 1 and 2 with those in trials 4 to 10), as evident in the latency index (LI) derived for each trial from the difference between grouped and randomized latencies (*1*). The shortening of fixation latency with successive trials, particularly early in the grouped sequence, and its independence of trial order in the randomized sequence were robust findings in the two monkeys. Similarly, human subjects tracking the appearance of stimuli on a screen in an identical task showed a significant reduction in reaction time in grouped trials relative to randomized trials (supporting online text).

We reasoned that an internal representation of expected stimulus location would involve the integration of visual, decision, and motor signals and hence should be a distributed property of visual and visuomotor centers of the brain. Whereas the parietal and frontal cortex play a key role in saccade decisions and commands (*6–12*), responses in early visual areas such as the primary visual cortex (V1) are also robustly modulated by the position of the eyes in the orbits (*13–16*). Recent microstimulation studies suggest a marked role for V1 in the neural processes guiding target selection (*17*). We thus examined responses of V1 neurons as trials were presented in the grouped and in the randomized condition. Figure 2B shows the response of a cell to an optimally oriented stimulus recorded in 10 successive trials. When the stimulus was presented in one location in the grouped condition, there was an increase in response by the third and subsequent trials ($P < 0.01$, comparing responses in trials 1 and 2 with those in trials 4 to 10). This

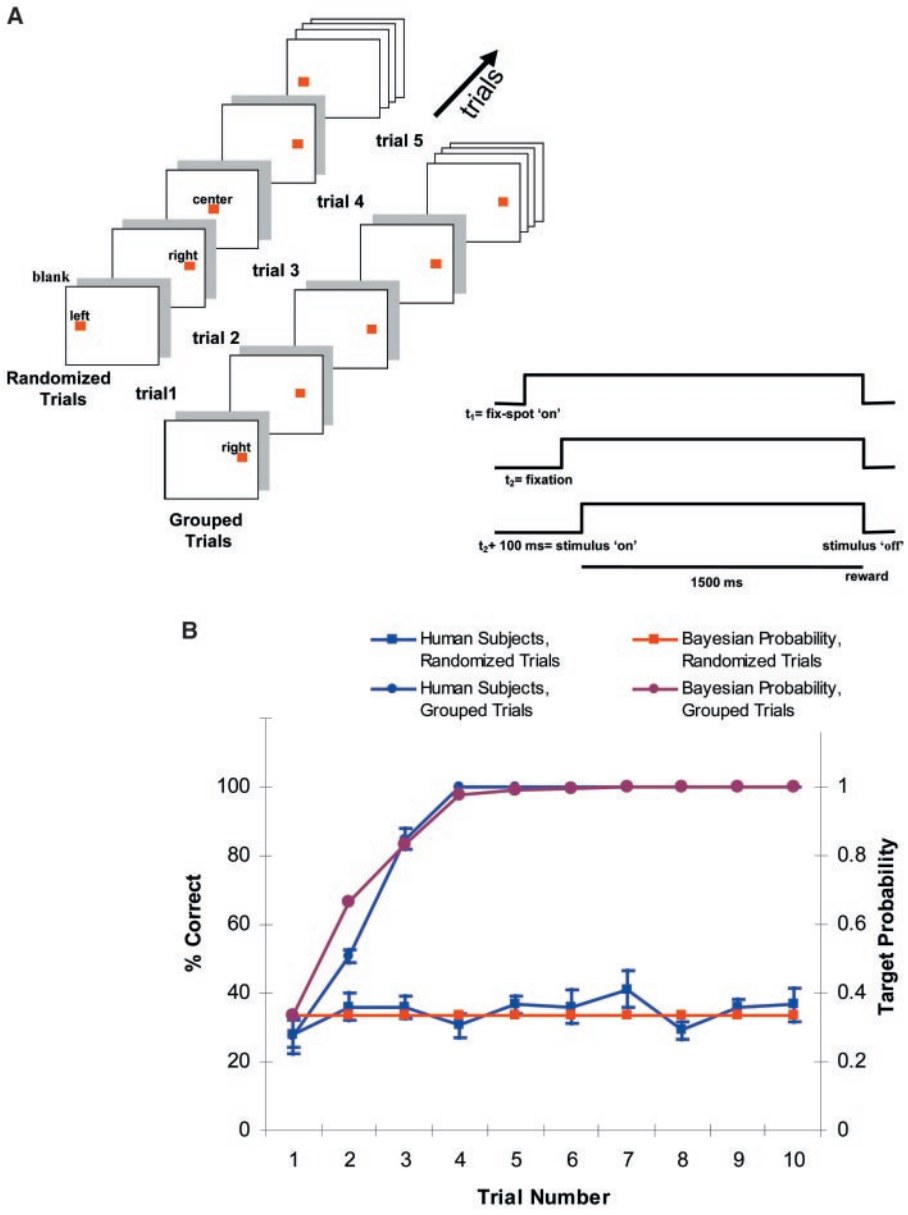

Fig. 1. Experimental task for examining an internal representation of stimulus location and the Bayesian probabilities associated with the task. (**A**) Grouped and randomized trials. Trial sequence on the left shows an example of randomized trials. In successive trials, the fixation spot (red) appeared randomly in one of three locations (left, right, or center). Sequence on the right shows an example of grouped trials, in which the spot appeared at the same location for a succession of trials. When the fixation spot appeared on a previously blank screen (time t_1), the monkeys made a saccade to the spot (time t_2) and held fixation for 100 ms (time t_2 + 100 ms), after which a stimulus consisting of drifting sinusoidal gratings appeared within a window centered on the fixation spot. The monkeys were required to hold fixation throughout the stimulus presentation (1500 ms) to earn a juice reward (*1*). (**B**) The performance of human subjects tracks the Bayesian estimate of target probability in the two task conditions. Subjects were asked to predict the location of target appearance in a randomized or grouped sequence of trials. In the grouped sequence, the Bayesian estimate of the target probability (right ordinate) rises from 1/3 in trial 1 to a value close to 1 by trial 4, whereas in the randomized sequence, the estimated probability of the target appearing at any location is (on average) 1/3, regardless of trial number (supporting online text). Percentage of correct predictions (mean ± SEM) in randomized and grouped trials (left ordinate) demonstrates probability matching.

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increase was consistent with the change in the monkey's fixation latency during the same set of trials (Fig. 2A). Conversely, there was no sustained effect of stimulus location on responses when trials were presented in the randomized condition, consistent with the lack of an effect on fixation latency in the same set of randomized trials. We calculated an index of response difference in the two conditions, termed an internal representation index (IRI) (*1*). The IRI for this cell rose sharply as trials progressed in the grouped sequence and then remained high, in a manner parallel to the LI.

The modulation in neuronal responses or in saccade latency was not related to the stimulus or its location: A grating of the same orientation, presented at the same stimulus location and hence subtending the same angle of gaze, led to a modulation of responses when the stimulus was presented in a grouped sequence but not in a randomized sequence. Of 67 neurons, 28 (42%) showed a significant difference in responses between grouped and randomized trials in at least one of the three gaze directions ($P < 0.05$, paired t test, comparing responses on a trial-by-trial basis). The mean IRI of these 28 neurons, together with the mean LI derived from saccades in the same trials as those in which neuronal responses were recorded, is shown in Fig. 2C. There was significant correlation between the IRI and LI, as also between the two indices and the Bayesian probability of target appearance (Pearson's correlation coefficient $r > 0.8$ for each pairwise comparison of IRI, LI, and the Bayesian probability, $P < 0.01$ with a two-tailed paired t test of significance). A two-way analysis of variance (ANOVA) between LI and IRI with group and trial number as factors suggested a great deal of overlap between the two curves. Both values showed an increase with trial number ($P < 0.01$), and there was no overall difference between them (group, $P > 0.32$). There was a significant interaction between the factors ($P < 0.05$), but post hoc contrasts showed that the values differed for trials 2 and 3 only (Fig. 2C). This is because the IRI (along with the Bayesian target probability) begins to increase on trial 2, whereas the LI does not increase significantly until trial 3. Monkeys appear to adjust their fixation strategy in proportion to the estimated probability of being in the grouped condition, whereas the responses of V1 neurons appear to reflect the estimated probability of stimulus appearance at particular locations (supporting online text).

Significant modulation of responses in the grouped condition was commonly observed for a preferred direction of gaze. Figure 3A illustrates orientation tuning curves of the same neuron shown in Fig. 2B, obtained at different gaze directions. The tuning curves of the neuron in all gaze directions were similar during randomized trials, with similar peak response rates and preferred orientations. (This also demonstrates that the retinal stimulation in different gaze directions was similar.) In the grouped trials there was a significant increase in response when gaze was directed to the right compared with the center or left. This effect is prominent in our population of neurons (Fig. 3B). Normalized peristimulus time histograms of cells that increased their firing in grouped trials relative to randomized trials (Fig. 3C) indicated that the response difference peaked 300 ms after stimulus presentation and was maintained through much of the stimulus period.

Figure 4A shows a neuron that decreased its response in the right or left gaze directions in grouped trials but showed no effect of gaze direction in randomized trials. The trial-by-trial IRI plots (Fig. 4B) show an effect similar to that shown in Fig. 2B, namely, a rapid change in response during the initial trials when stimuli were presented in the grouped condition in the left or right gaze directions but not in the center direction (*18*). The animal's fixation latency also decreased significantly in the grouped condition (Fig. 4B). From the two representative neurons shown

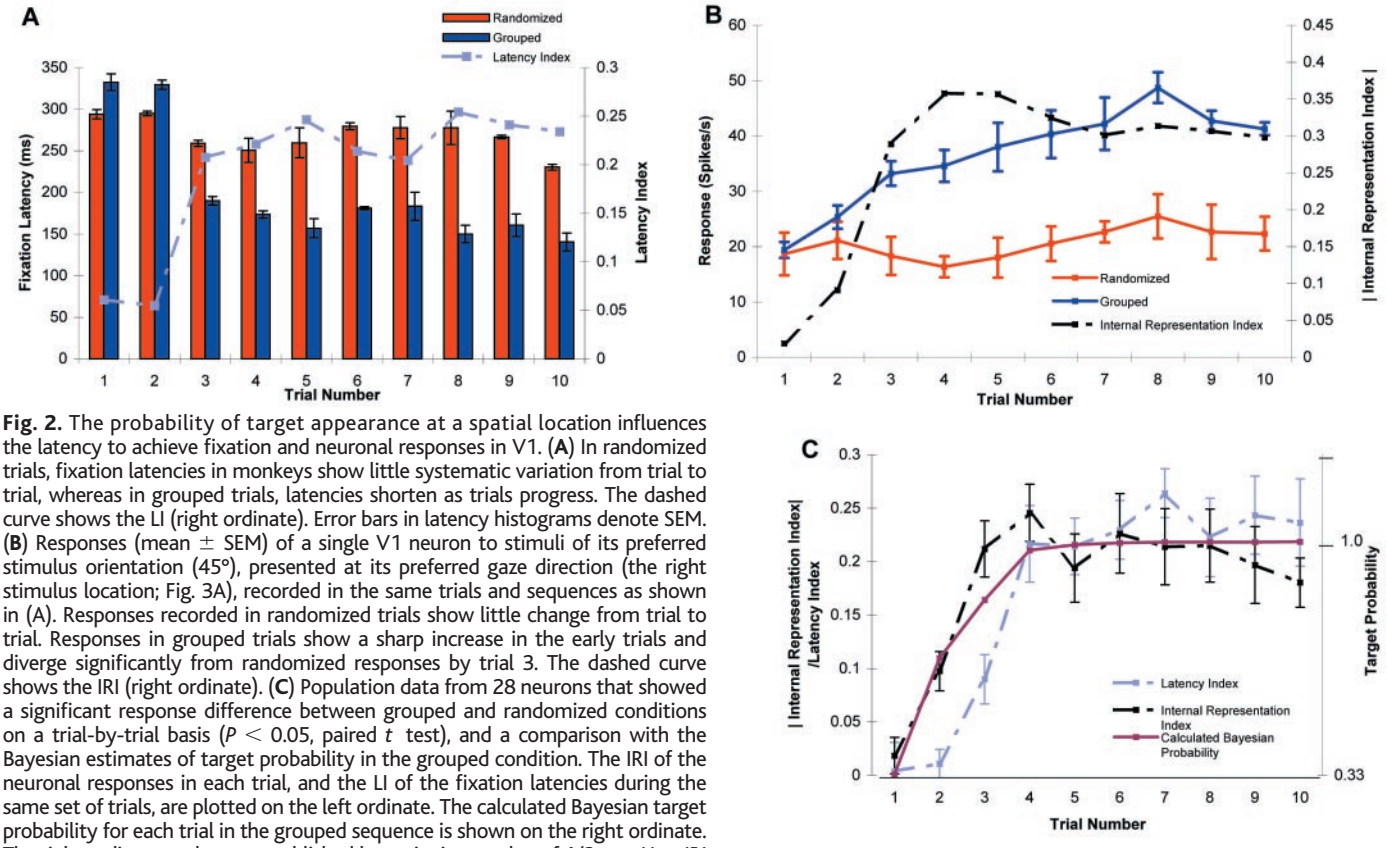

Fig. 2. The probability of target appearance at a spatial location influences the latency to achieve fixation and neuronal responses in V1. (**A**) In randomized trials, fixation latencies in monkeys show little systematic variation from trial to trial, whereas in grouped trials, latencies shorten as trials progress. The dashed curve shows the LI (right ordinate). Error bars in latency histograms denote SEM. (**B**) Responses (mean ± SEM) of a single V1 neuron to stimuli of its preferred stimulus orientation (45°), presented at its preferred gaze direction (the right stimulus location; Fig. 3A), recorded in the same trials and sequences as shown in (A). Responses recorded in randomized trials show little change from trial to trial. Responses in grouped trials show a sharp increase in the early trials and diverge significantly from randomized responses by trial 3. The dashed curve shows the IRI (right ordinate). (**C**) Population data from 28 neurons that showed a significant response difference between grouped and randomized conditions on a trial-by-trial basis ($P < 0.05$, paired t test), and a comparison with the Bayesian estimates of target probability in the grouped condition. The IRI of the neuronal responses in each trial, and the LI of the fixation latencies during the same set of trials, are plotted on the left ordinate. The calculated Bayesian target probability for each trial in the grouped sequence is shown on the right ordinate. The right ordinate scale was established by assigning a value of 1/3 to a LI or IRI value of 0, and a value of 1 to the mean of the LI and IRI values in trials 4 to 10. Error bars denote SEM.

in Figs. 2 to 4, we note that although the animal's behavioral fixation latency decreased when the stimulus was presented at any of the three gaze directions in the grouped condition, these particular neurons altered their responses only for one (Figs. 2B and 3A) or two (Fig. 4B) of the three gaze directions in the grouped condition.

We calculated a gaze direction index (GDI) (*1*) for each neuron to describe its response modulation by eye position in grouped and randomized trials. Cells showed significantly greater modulation in the grouped condition compared with the randomized condition ($P < 0.001$, chi-square test) (Fig. 4C). When peak firing rate was taken as an independent variable and plotted against GDI, the distribution was again significantly biased toward the grouped condition ($P < 0.01$). To ascertain the robustness of modulation in the grouped or randomized condition, we tested cells ($n = 67$) by repeating the first task condition. Thus, cells were tested in blocks consisting of randomized-grouped-randomized or grouped-randomized-grouped conditions (Fig. 4A). There was no significant difference ($P > 0.8$) in the GDI from initial versus repeat blocks of trials regardless of task condition (Fig. 4D).

The neurons that showed significant gaze modulation in grouped trials were roughly equally distributed over the entire range of orientations and the three gaze directions. There was no systematic relation between the location or size of receptive fields and their response modulation, or any difference in the accuracy of fixation between grouped and randomized trials (supporting online text). There was no systematic change in neuronal responses when monkeys fixated passively during trials that were not presented as part of either a randomized or a grouped sequence (supporting online text). To address potential artifacts due to retinal disparity at different locations, we recorded a subset of cells ($n = 27$) in monocular as well as binocular stimulation conditions. Monocular stimulation also led to significantly greater modulation in grouped trials compared with randomized trials ($P < 0.01$, two-tailed paired t test) (supporting online text; fig. S1). Finally, we recorded responses with the fixation spot at 6° and at 11° of eccentricity in both randomized and grouped conditions. We did not find a significant change in the magnitude of modulation with the extent of gaze angle in our cell population ($P > 0.1$, $n = 22$).

To determine whether the orientation selectivity of individual neurons was affected in the grouped condition, we compared the orientation selectivity index (OSI) of each cell in grouped and randomized trials, for the most modulated gaze direction (*1*). The 28 (of 67) cells that were significantly modulated in the grouped condition showed a mean change in OSI of 37.5% between grouped and randomized conditions. This result was significantly different ($P < 0.01$) from the mean OSI change of 10.0% in the remaining 39 cells.

These data demonstrate that V1 neurons can signal an internal representation of expected stimulus location on the basis of the probability of stimulus occurrence. The response modulation during grouped trials is specific in two ways: It is associated with restricted gaze directions and with a neuron's selectivity to stimulus orientation. Al-

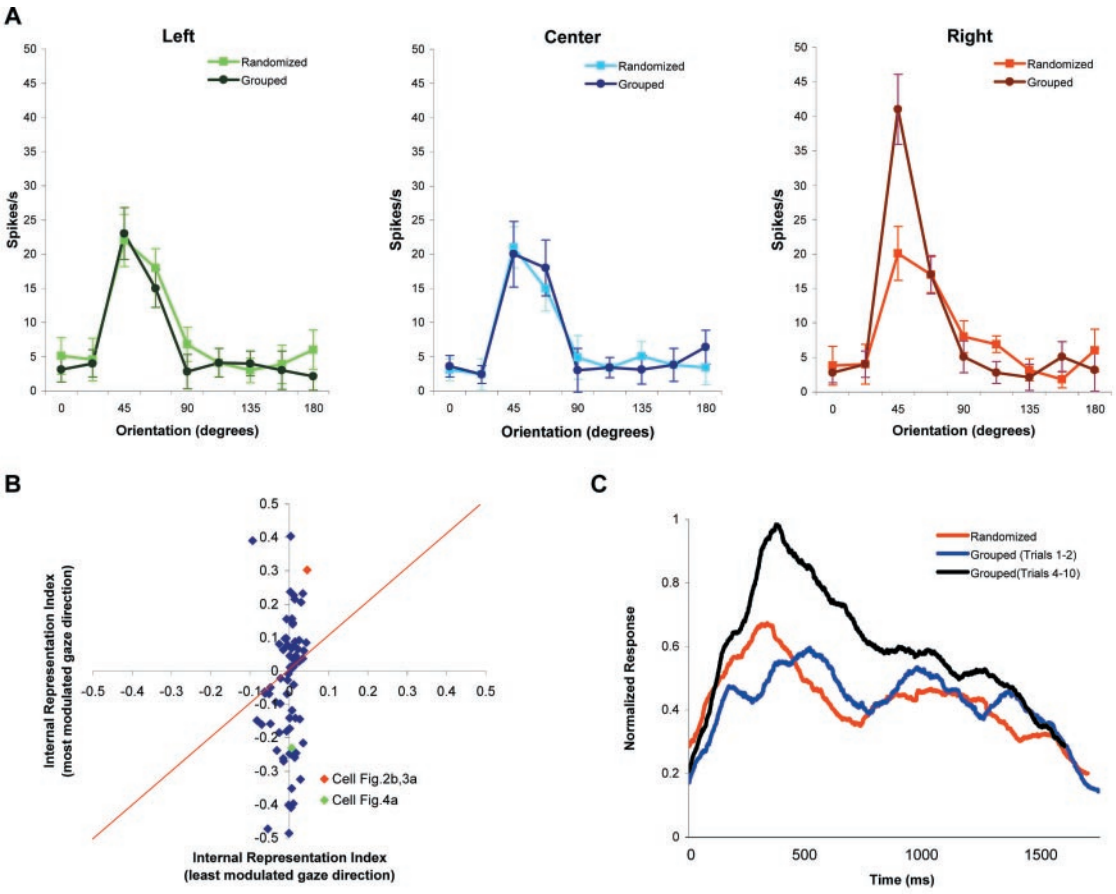

Fig. 3. Influence of task conditions on gaze-related modulation of V1 neurons. (**A**) Orientation tuning curves of a neuron in grouped and randomized trials in the three gaze directions: left, center, and right. This neuron's trial-by-trial responses in the right gaze direction are shown in Fig. 2B. Significant gaze-related modulation was seen in grouped trials when gaze was directed to the right, whereas no significant modulation occurred in the two trial conditions when gaze was directed toward the left or the center. (**B**) Scatterplot of the IRI of individual cell responses ($n = 67$) for the least modulated compared with the most modulated gaze direction. The neurons shown in Figs. 2B and 3A, and in Fig. 4, A and B, are marked in red and green, respectively. The diagonal line of slope 1 represents indices for cells that would be equally modulated in all gaze directions in grouped versus randomized conditions. Positive IRI values indicate response facilitation in the grouped condition; negative values denote response suppression. (**C**) Averaged peri-stimulus time histograms (bin width, 1 ms) of the normalized responses of 11 neurons that showed a significant response increase in the grouped sequence. Responses in trials 4 to 10 of the grouped sequence are compared with those in trials 1 and 2 of the grouped sequence and with all trials of the randomized sequence.

though modulation of neuronal responses in V1 by the direction of gaze has been described previously (*13*–*16*), our findings add new elements to the role of V1 in signaling eye-position information. Even when the retinal stimulus or the gaze direction associated with it remained the same, the changes in fixation latency and evoked responses occurred as the task proceeded, and hence were observed "online" in one condition but not in another. It is unlikely that the effects were due to passive inputs from extraocular muscles (*19*), oculomotor habituation, or priming [e.g., (*13*)], because the response change in grouped trials occurred most sharply during early trials, as an internal representation was acquired.

V1 responses are modulated by nonvisual influences (*20*–*26*), and top-down pathways to V1 (*27*–*29*) can convey signals for an internal model of stimulus location. Indeed, the modulation of V1 responses at specific gaze directions in the grouped condition of our task is reminiscent of gaze-related gain fields described in parietal cortex (*30*, *31*). The tight coupling between fixation latency and postsaccadic response argues for a common distributed network that underlies both oculomotor and neural responses. The extent of involvement of network components and their influence on V1 may depend on the task. Although a number of areas in the dorsal cortical stream may globally encode tasks related to spatial location and spatial working memory (*32*–*34*), the frontal eye fields may be preferentially engaged only under conditions similar to those in the grouped sequence of our task (*35*). An increase or a decrease in V1 responses during grouped trials is also consistent with known saccadic influences of upper- and lower-layer V1 neurons: Stimulation of deep-layer neurons increases the probability of saccades to a target within a neuron's receptive field, whereas stimulation of superficial-layer neurons reduces the probability (*17*). Finally, the modulation of V1 responses by stimulus probability is not simply a passive scalar change. Instead, top-down signals nonlinearly modify bottom-up visual inputs to actively shape emergent orientation-selective responses of V1 neurons (*36*, *37*). The dynamic changes in orientation selectivity that we observed are consistent with the psychophysical finding that visual sensitivity is influenced by uncertainty in target location (*4*). The influence on V1 responses of an internal model of stimulus location demonstrates that such representations arise in distributed cortical networks yet lead to specific changes in response selectivity and dynamics at the earliest stages of cortical processing.

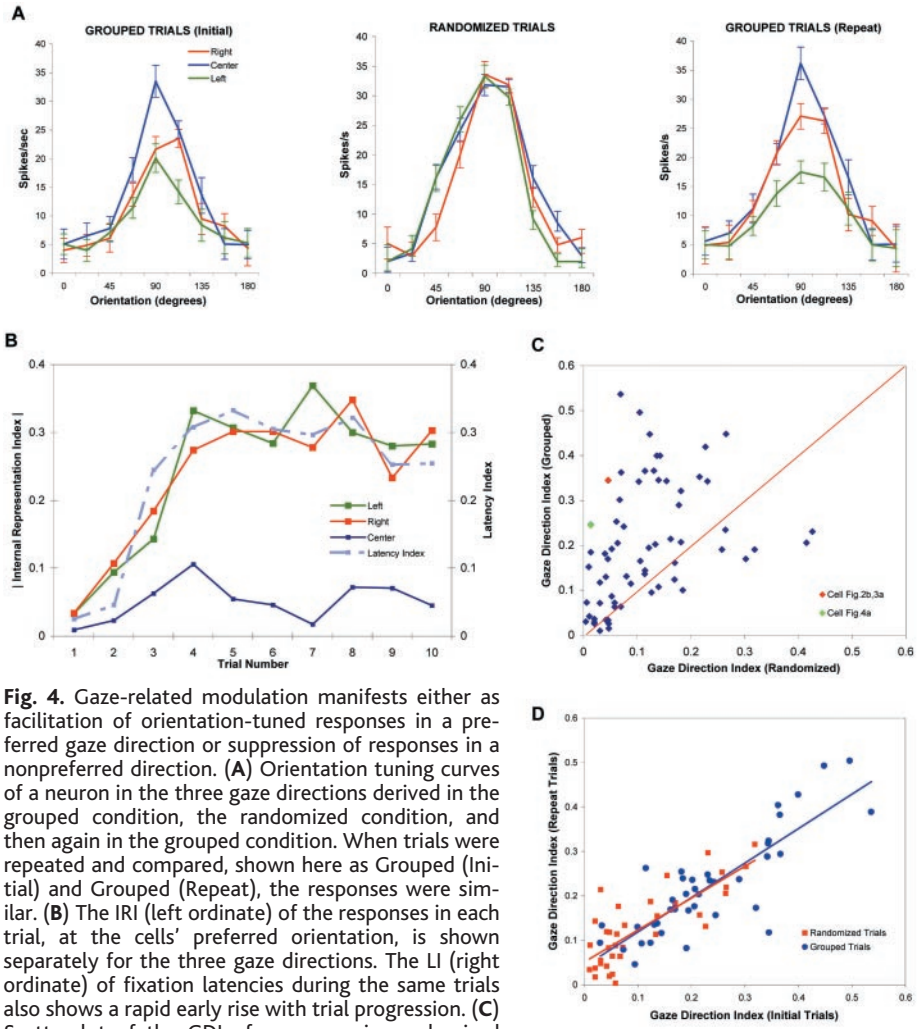

Fig. 4. Gaze-related modulation manifests either as facilitation of orientation-tuned responses in a preferred gaze direction or suppression of responses in a nonpreferred direction. (**A**) Orientation tuning curves of a neuron in the three gaze directions derived in the grouped condition, the randomized condition, and then again in the grouped condition. When trials were repeated and compared, shown here as Grouped (Initial) and Grouped (Repeat), the responses were similar. (**B**) The IRI (left ordinate) of the responses in each trial, at the cells' preferred orientation, is shown separately for the three gaze directions. The LI (right ordinate) of fixation latencies during the same trials also shows a rapid early rise with trial progression. (**C**) Scatterplot of the GDI of responses in randomized trials and grouped trials (n = 67). Neurons above the diagonal line of slope 1 show greater modulation in grouped trials in a particular gaze direction. The neurons shown in Figs. 2B and 3A, and in Fig. 4, A and B, are marked in red and green, respectively. (**D**) Scatterplot of the GDI for individual neurons during initial and repeat trials of the same task condition. In 41 (of 67) neurons, grouped trials were repeated, whereas in 34 neurons, randomized trials were repeated (numbers include 8 neurons in which trials were repeated in both conditions).

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Coronavirus Main Proteinase ($3CL^{pro}$) Structure: Basis for Design of Anti-SARS Drugs

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A novel coronavirus has been identified as the causative agent of severe acute respiratory syndrome (SARS). The viral main proteinase (M^{pro}, also called $3CL^{pro}$), which controls the activities of the coronavirus replication complex, is an attractive target for therapy. We determined crystal structures for human coronavirus (strain 229E) M^{pro} and for an inhibitor complex of porcine coronavirus [transmissible gastroenteritis virus (TGEV)] M^{pro}, and we constructed a homology model for SARS coronavirus (SARS-CoV) M^{pro}. The structures reveal a remarkable degree of conservation of the substrate-binding sites, which is further supported by recombinant SARS-CoV M^{pro}-mediated cleavage of a TGEV M^{pro} substrate. Molecular modeling suggests that available rhinovirus $3C^{pro}$ inhibitors may be modified to make them useful for treating SARS.

Human coronaviruses (HCoVs) are major causes of upper respiratory tract illness in humans; in particular, the common cold (*1*). To date, only the 229E strain of HCoV has been characterized in detail, because it used to be the only isolate that grows efficiently in cell culture. It has recently been shown that a novel HCoV causes severe acute respiratory syndrome (SARS), a disease that is rapidly spreading from its likely origin in southern China to several countries in other parts of the world (*2*, *3*). SARS is characterized by high fever, malaise, rigor, headache, and nonproductive cough or dyspnea and may progress to generalized interstitial infiltrates in the lung, requiring intubation and mechanical ventilation (*4*). The fatality rate among people with illness meeting the current definition of SARS is presently around 15% [calculated as deaths/(deaths + surviving patients)]. Epidemiological evidence suggests that the transmission of this newly emerging pathogen occurs mainly by face-to-face contact, although other routes of transmission cannot be fully excluded. By 9 May 2003, more than 7000 cases of SARS had been diagnosed worldwide, with the numbers still rapidly increasing. At present, no efficacious therapy is available.

Coronaviruses are positive-stranded RNA viruses featuring the largest viral RNA genomes known to date (27 to 31 kb). The gene for the human coronavirus 229E replicase, encompassing more than 20,000 nucleotides, encodes two overlapping polyproteins [pp1a (replicase 1a, ~450 kD) and pp1ab (replicase 1ab, ~750 kD) (*5*)] that mediate all the functions required for viral replication and transcription (*6*). Expression of the C-proximal portion of pp1ab requires (–1) ribosomal frameshifting (*5*). The functional polypeptides are released from the polyproteins by extensive proteolytic processing. This is primarily achieved by the 33.1-kD HCoV 229E main proteinase (M^{pro}) (*7*), which is frequently also called 3C-like proteinase ($3CL^{pro}$) to indicate a similarity of its cleavage-site specificity to that observed for picornavirus 3C proteinases [$3C^{pro}$ (table S1)], although we have recently shown that the structural similarities between the two families of proteinases are limited (*8*). The M^{pro} ($3CL^{pro}$) cleaves the polyprotein at no less than 11 conserved sites involving Leu-Gln↓(Ser,Ala,Gly) sequences (the cleavage site is indicated by ↓), a process initiated by the enzyme's own autolytic cleavage from pp1a and pp1ab (*9*, *10*). This cleavage pattern appears to be conserved in the M^{pro} from SARS coronavirus (SARS-CoV), as we deduced from the genomic sequence published recently (*11*, *12*) and prove experimentally here for one cleavage site (see below). The SARS-CoV polyproteins have three noncanonical M^{pro} cleavage sites with Phe, Met, or Val in the P2 position, but the same cleavage sites are unusual in other coronaviruses as well. The functional importance of M^{pro} in the viral life cycle makes this proteinase an attractive target for the development of drugs directed against SARS and other coronavirus infections.

Here we report three three-dimensional (3D) structures of coronavirus M^{pro}s, which together form a solid basis for inhibitor design: (i) the crystal structure, at 2.54 Å resolution, of the free enzyme of human coronavirus (strain 229E) M^{pro}; (ii) a homology model of SARS-CoV M^{pro}, based on the crystal structure of HCoV 229E M^{pro} described here and on that of the homologous enzyme of the related porcine transmissible gastroenteritis (corona)virus (TGEV), which we determined previously (*8*); and (iii) the 2.37 Å crystal structure of a complex between TGEV M^{pro} and a substrate-analog hexapeptidyl chloromethyl ketone (CMK) inhibitor. Comparison of the structures shows that the substrate-binding sites are well conserved among coronavirus main proteinases. This is supported by our experimental finding that recombinant SARS-CoV M^{pro} cleaves a peptide corresponding to the N-terminal autocleavage site of TGEV M^{pro}. Further, we find the binding mode of the hexapeptidyl inhibitor to be similar to that seen in the distantly related human rhinovirus 3C proteinase ($3C^{pro}$) (*13*). On the basis of the combined structural information, a prototype inhibitor is proposed that should block M^{pro}s and thus be a suitable drug for targeting coronavirus infections, including SARS.

The 2.54 Å crystal structure of HCoV 229E M^{pro} (*14*) shows that the molecule comprises three domains (Fig. 1A). Domains I and II (residues 8 to 99 and 100 to 183, respectively) are six-stranded antiparallel β barrels and together resemble the architecture of chymotrypsin and of picornavirus 3C proteinases. The substrate-binding site is located

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