Dorsolateral prefrontal neurons mediate subjective decisions and their variation in humans

Mohsen Jamali1,8, Ben Grannan2,8, Keren Haroush2,8, Ziev B. Moses3, Emad N. Eskandar4, Todd Herrington5, Shaun Patel5 and Ziv M. Williams1,6,7*

Subjective decisions play an important role in human behavior because, while often grounded in fact, they are inherently based on personal beliefs that can vary broadly within and between individuals. While these properties set subjective decisions apart from many other sensorimotor processes and are of wide sociological impact, their single-neuronal basis in humans is unknown. Here we find cells in the dorsolateral prefrontal cortex (dIPFC) that reflect variations in the subjective decisions of humans when performing opinion-based tasks. These neurons changed their activities gradually as the participants transitioned between choice options but also reflected their unique point of conversion at equipoise. Focal disruption of the dIPFC, by contrast, diminished gradation between opposing decisions but had little effect on sensory perceptual choices or their motor report. These findings suggest that the human dIPFC plays an important role in subjective decisions and propose a mechanism for mediating their variation during opinion formation.

Results

Situational assessment task. A common framework for evaluating human subjective decisions is through situational assessments. In these tasks, for example, a participant may be given a naturalistic scene of a jogger running near a busy street or a person filling a cup of hot tea near its brim, and then be asked whether they believe the situation to be safe or unsafe. These and similar approaches have often been used in sociological and psychological studies because they allow one to follow the specific points at which individuals transition from one choice option to another as they form their opinions of the various scenes, and because they can be used to

1Department of Neurosurgery, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA. 2Department of Neurobiology, Stanford University School of Medicine, Palo Alto, CA, USA. 3Department of Neurosurgery, Brigham and Women’s Hospital, Boston, MA, USA. 4Department of Neurosurgery, Albert Einstein University, Bronx, NY, USA. 5Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA. 6Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, USA. 7Harvard Medical School, Program in Neuroscience, Boston, MA, USA. 8These authors contributed equally: Mohsen Jamali, Ben Grannan, Keren Haroush. *e-mail: zwilliams@mgh.harvard.edu
test the participant's subjective decisions under conditions in which there is no explicit correct or 'optimal' choice\textsuperscript{21,25}. Therefore, in our study, for each trial, the participants were presented with a visual scene followed by a brief delay period. They were then given two randomly positioned choice options used to indicate whether they believed the situation to be safe or unsafe. For generalizability and to further evaluate the point of equipoise at which the participants transitioned from one choice to the other, they were presented with seven prototypic scenes over the course of the session, each with its own unique situation and theme. For example, the participant may see a jogger running near a busy street in one scene but see a worker standing in a construction yard in another. Further, each of the prototypic scenes consisted of five different situations in which the relation between the subject and object within the scenes were covertly manipulated. For example, the position of the jogger (subject) in relation to the car (object) may vary from one scene to another (Fig. 1b and Fig. 2a). Second, all scenes were given in random order throughout the session and no feedback was given at any time to indicate which choice was 'correct'. On the far right are examples of different scenes, manipulations and choices made by a participant. As discussed in the main text, additional comparisons included scenes in which only an object was presented.
Behavioral performance. We evaluated the subjective decisions of the participants by first quantifying their probability of selecting one choice over the other across the different situations and scenes\(^{14,15}\). For example, the probability of making the same choice (for example, of safe) may gradually change as individuals transition, across equipoise, to the choice of unsafe. Therefore, when aligning trials in our task to the point at which the participants changed their choices from safe to unsafe per scene, choices aligned to the ‘left’ of equipoise would reflect situations that the participants subjectively believed to be progressively safer (ordinal positions from −1 to −4), whereas those aligned to the ‘right’ of equipoise would reflect situations that they believed to be progressively unsafe (ordinal positions from +1 to +4; Fig. 2d).

As expected, the participants displayed a gradual change in their probability of selecting one choice option over the other as they transitioned across equipoise (Lilliefors test, \(n = 11\) participants, \(P < 0.05\), Fig. 2b–d). Overall, when considered together across trials, the participants made the same choice selections 90.0 ± 3.3% of the time (\(\chi^2 = 127.6, P < 0.0001\)). However, when considering their choices in relation to equipoise, the participants made the same choice selection 84.4 ± 5.4% of the time when near equipoise (ordinal positions +1 and −1) and the same choice selection 94.4 ± 2.9% of the time when further away (ordinal positions +2 and −2 and above; \(\chi^2 = 54.36, P < 0.0001\)).

We also find that the participants gave the same choices when presented with similar situations. For instance, if the position of the jogger differed only slightly (for example, comparing manipulations 1 and 2 in the middle panel of Fig. 1b), one would expect the participant to hold a similar opinion. Overall, the participants were significantly more likely than chance to make the same choice selections when the situations were similar to each other across all ordinal positions (82.9 ± 3.5%; \(\chi^2 = 60.50, P < 0.0001\); Fig. 2c,d).

Finally, to confirm that the participants were indeed making appropriate choices, we evaluated their selections when asked to categorize individual objects as safe or unsafe in the absence of a situational assessment. Here, the participants agreed in their selection on 94.2 ± 3.5% of trials (\(\chi^2 = 142.3, P < 0.0001\)), meaning that essentially all participants agreed in their selections. Taken together, these findings suggested that the participants understood the task and that their choices accurately reflected their subjective evaluations of the scenes.

Neuronal responses when making subjective decisions. We initially recorded from 119 well-isolated units in Brodmann’s area 9 of...
the dlPFC. Here, a motorized microdrive and a temporary biodegradable buffer were used to provide stable unit isolation (Fig. 1a). Only units with a high degree of signal to noise, an adequate refractory period and stable waveform morphology over the course of recordings were included (Fig. 3a and Supplementary Fig. 1). This amounted to an average of 10.8 ± 2.8 units per participant across the 11 participants that performed the situational assessment task.

We first searched for neurons whose activities may be modulated by the task. Here, we centered our analyses on the time period 500–2,000 ms from scene onset to take into account the sensory response delay normally observed in the prefrontal cortex as well as the timespan over which the scenes were presented. Of the recorded population, we found that 26% of cells (n = 31) displayed a difference in response in trials in which the participants subsequently reported the scenes to be safe compared to unsafe (two-sided t-test, P < 0.05; Fig. 3b,c and Supplementary Fig. 2). Consistent with prior studies,16,24, only a few cells displayed a difference in response to the prototypic scenes themselves (n = 3; two-sided t-test, P < 0.05; Bonferroni corrected for the scene) or to the specific left/right movement (n = 4; two-sided t-test, P < 0.05).

To next examine whether and to what degree neuronal activity in the dlPFC correlates with the participant's subjective decisions as they varied from trial to trial, we aligned each of the trials to the points of equipoise at which the participants transitioned from making the choice of safe to unsafe (see Methods). As described above, trials aligned to the ‘left’ of equipoise reflected situations that the participants believed to be progressively safe (ordinal positions from −1 to −4), whereas those aligned to the ‘right’ of equipoise reflected situations that they believed to be progressively unsafe (ordinal positions from +1 to +4; Fig. 2d). Together, these psychometric curves constituted the participant’s ‘voting profile’18,23,31. Overall, 58% of the 31 neurons displayed responses that were positively correlated with the participants’ voting profiles, meaning that they displayed a gradual increase in their spiking rate as the participants transitioned from viewing the scenes from safe to unsafe (Fig. 3d,e). Forty-two percent displayed activity that was negatively correlated. Figure 3d illustrates two such representative dlPFC cells recorded from the same participant. The overall degree of correlation across neurons was r = 0.49 ± 0.03 (Supplementary Fig. 3). Neurons in the dlPFC therefore demonstrated gradual changes in their activity as the participants transitioned from one choice to the other across equipoise.

Individually, the spiking activities of these neurons were best described by a logistic function. Using a modeling approach to evaluate the activity profile of each neuron, we fit their firing rates to either a constant, linear, binary, logistic or U-shaped function (Fig. 4a). Thus, for example, whereas neuronal responses that are best fit by a binary function can be used to describe differences in the participants’ binary choices, a logistic function (that is, one that gradually changes from one choice to the other) can also be used to additionally describe the relation between their choices and equipoise. Calculating the residuals of each fit, we found that neural responses were best explained by a logistic fit (1.9-fold Δ in variance accounted for; two-sided paired t-test, t(30) = 5.35, P < 0.0001; Fig. 4c).

These changes in activity did not reflect differences in choice uncertainty that peaked or fell as the participants approached equipoise. For example, an increase in spiking activity near equipoise could be explained by a non-specific increase in uncertainty14,28–30 or change in ‘value’ (for example, when based on reward14,31) assigned to a choice. Here, however, we found that the spiking activities of the neurons were significantly better explained by a logistic compared to a U-shaped function (Δ variance accounted for; two-sided paired t-test, t(30) = 9.05, P < 0.0001; Fig. 4d). Consistent with these observations, there was also no difference in averaged population activity for trials lying near versus far from equipoise (1.06 ± 0.05 spikes s−1 versus 1.07 ± 0.04 spikes s−1, respectively; two-sided paired t-test, t(30) = 0.18, P = 0.87; Supplementary Fig. 4). We also find no behavioral difference in reaction times on trials lying near equipoise compared to those that did not (1,206 ± 46 versus 1,283 ± 43 ms; two-sided t-test, t(1023) = −1.17, P = 0.24), and no correlation between the participants’ reaction times and firing rate on a trial-by-trial basis (Pearson correlation; n = 4723, r = 0.004, P = 0.78; Supplementary Fig. 5) to suggest a difficulty- or demand-related effect.

As noted above, a choice selection made near equipoise (for example, ordinal position +1) and a choice selection made further away (for example, ordinal position +2 or above) reflected differences in the degree to which the participants believed the scenes to be unsafe (that is, even though the choice selections themselves are the same). Therefore, to further evaluate for neural modulation by these variations across the population, we used a two-way analysis of variance (ANOVA, P < 0.01) that considered the interaction between terms describing the participant’s choices (safe versus unsafe) and their relation to equipoise (near versus far). Using this evaluation, we found that the interaction between terms describing the participant’s choice report and their relation to equipoise was significant (two-way ANOVA, F(1,120) = 24.5, P < 1 × 10−5; choice × equipoise; Supplementary Table 4). Further post-hoc analyses demonstrated a significant effect for both variables (choice; F(1,120) = 35.6, 1 × 10−5 and equipoise; F(1,120) = 12.3, P < 0.0011; Fig. 4b). Therefore, taken together, the activities of these neurons appeared to reflect the participant’s subjective decisions and their variation when considered across scenes.

Lack of neuronal modulation during sensory perceptual choices.
Unlike neuronal responses observed during the situational assessment task, neurons in the dlPFC displayed little modulation during performance of an analogous sensory perceptual task34–36. For example, it is possible that similar results may be observed under any condition that requires selection between two binary choice options. Therefore, to test for this, we next used a perceptual control task that involved small changes in the orientation of a Gabor17–19 (Fig. 5a). The Gabor’s orientation varied from −3 to 3° across vertical and the participants were allowed to make two-forced choices on whether the Gabor was oriented to the left or the right. Here, we used this task because, similar to the situational assessment task, it was based on a two force-choice selection and because small variations in Gabor’s orientation produced psychometric profiles that gradually transitioned from one choice to the other (Fig. 5c).

Of the 71 neurons recorded from the dlPFC during the performance of this task, we found that 32% (n = 23) of the neurons responded to the Gabor presentation, meaning that they displayed either an increase or decrease in firing activity compared to baseline (that is, before image presentation; paired t-test, P < 0.05). Figure 5b illustrates an example of such a neuron. Of this population, however, only one cell displayed a difference in the firing activity when the participants perceived the Gabor as tilting to the right (clockwise) versus left (counterclockwise; Fig. 5b, middle and bottom panels). In other words, only 4.2% (n = 3) of the neurons displayed a difference in response to the Gabor as the participants transitioned from one choice to the other across the equipoise (Fig. 5c). This difference between the situational assessment task and the sensory perceptual task was significant (3/71 versus 31/119 modulated cells respectively; χ² = 9.4, P = 0.0012).

Next, we also considered whether neuronal responses reflect the participant’s upcoming motor report. Subjective decisions are thought to be formulated early on during opinion formation and before making the motor selection15–16. Using a linear discriminant, we find that decoding accuracy for the population (n = 31) was
Fig. 3 | Neuronal responses in the dlPFc correlate with variations in the participant’s subjective decisions. a, A representative neuron recorded from the dlPFC (total population \( n = 119 \)). The raw voltage tracings are displayed above, and the waveform morphology and interstimulus interval (ISI) are displayed below (the inset is on a log scale to emphasize the refractory period; the red line is at 1 ms). Supplementary Fig. 1 provides additional illustration of the waveforms’ stability over time and their isolations. b, Peristimulus spike histogram and trial heatmap of the same cell during task performance for trials reported as safe (green line) versus unsafe (red line). The shaded bands represent the s.e.m. The first vertical dashed line (0 s) represents scene presentation onset and the second vertical dashed line (3 s) represents the choice option presentation. The grayed area represents the time period considered for neuronal analysis and was chosen to reflect the corresponding stimulus–response delay and scene presentation times. See Supplementary Fig. 2 for additional examples. c, Peristimulus histogram of neural activity ± s.e.m. over time across different scene manipulations for the same cell displayed in Fig. 3b. The five figures represent the five main manipulations from 1 to 5 (43 trials). These figures do not take into account the participant’s specific choices or the point of equipoise. d, Average spiking activity ± s.e.m of two representative cells aligned to equipoise. The corresponding voting profile of the participant is shown in black. For the x axis, ordinal values below zero represent scenes that the participants believed were progressively safe and values above zero represent scenes that the participants believed were progressively unsafe (43 trials). Neural activity of the cell on the left is negatively correlated with the participant’s voting profile (with logistic \( \beta \) regression coefficient of \(-3.40\)) and the cell on the right is positively correlated (13.21). e, The \( \beta \) coefficients describing the correlations for all recorded cells. Left inset: scatter plot of activity during reported safe versus unsafe trials. Right inset: distribution of changes in neuronal activity. FR, firing rate.
Variations in subjective decision between individuals. A second core feature of subjective decisions is that they often vary from person to person, even when presented with the same sensory information. For example, one participant may view a particular situation as safe, whereas another may view that same precise situation as unsafe (Fig. 2c)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\). Therefore, we next examined how closely neuronal activity may correlate with the participant’s own unique voting profile when compared to that of the other participants. To do this, we performed a permutation procedure, similar to that described previously\(^6\), in which we compared the same choice selections of safe and unsafe, but now substituted the recorded participant’s voting profile with that of another participant (Fig. 7a). In other words, the same choice selections were evaluated, but their unique relation to the equipoise within the voting profiles varied.

Here, we found that, when neuronal activity was taken from the participant recorded from but correlated with the voting profile of the other 10 participants, the fitted coefficients that described the regression were significantly lower (absolute 35% lower, permutation test, \(P = 0.005\); Fig. 7b). We also examined the choice selections themselves in which the trials were permuted across the participants. This maintained the same net choice comparisons of safe/unsafe, but produced a mismatch between the participant’s subjective decision and the particular situation and scene in which it was made. Using this procedure, we similarly found that the difference in firing activity between the choices was 21% lower following permutation (permutation test, \(P = 0.043\); Fig. 7a). Therefore, when considering the same choice selections, the spiking activities

![Image](image-url)
of these neurons accounted for much of the variation in choice between individuals.

Effect of localized dlPFC disruption on subjective decision-making. While the above observations suggested that neural responses in the dlPFC may reflect the participants’ subjective decisions and their variation during situational assessments, they did not reveal whether or what causal contribution the dlPFC may have. Therefore, to next test this, we searched for additional subjects who had previously undergone focal resection of frontal cortical lesions for clinical reasons and whose resection cavities were localized to Brodmann’s area 9 of the dlPFC. Using these criteria, we identified four such participants (Supplementary Table 1). Their resection cavities measured $11.1 \pm 2.7$ cm$^2$ and were centered within the mid-portion of Brodmann’s area 9 (Fig. 8a). We then compared the performance of these ‘lesioned’ participants to that of the 11 control participants who had previously undergone neurosurgical access to the dlPFC by neuronal recordings but no lesion resection.

Individuals with focal dlPFC resections made largely similar choice selections to that of control. Specifically, the lesioned participants reported 42% of the scenes as safe, whereas the controls reported 41% of the scenes as safe (1% difference in choice probability, with both groups having a slight bias towards reporting the scenes as unsafe, $\chi^2 = 0.041$, $P = 0.83$; Fig. 8b). Moreover, when comparing choices during the object presentations, the lesioned participants made the same selections as the control on almost all trials (95%, $\chi^2 = 0.66$, $P = 0.42$). In other words, essentially all the participants from both groups agreed that a ‘gun’ is unsafe and that a ‘shirt’ is safe. The lesioned participants therefore appeared to understand the task and make largely appropriate choice selections.

Fig. 5 | Neuronal responses and the effect of dlPFC lesions on sensory perceptual decisions. a, Gabor stimuli were presented to the participants and varied in orientation from least ambiguous ($+3.0^\circ$ and $-3.0^\circ$) to most ambiguous ($\pm 0.2^\circ$). b, Peristimulus spike histogram and trial heatmap of an example cell during task performance. The shaded bands represent s.e.m. While the firing activity of this neuron increased during the presentation of Gabors (top), the neuron was not modulated by variations in the participant’s choice of left or right (middle and bottom). The first vertical dashed line (0 s) represents Gabor presentation onset, and the second vertical dashed line (3 s) represents the choice option presentation (left or right). The grayed area represents the time period considered for neuronal analysis. c, Average spiking activity $\pm$ s.e.m. of the representative cell as a function of the Gabor orientation (29 trials). The corresponding psychometric function of the participant is superimposed (black curve and gray circles). d, Psychometric profiles with performances for dlPFC lesioned ($n = 4$) and non-lesioned ($n = 14$) participants across the different Gabor orientations were similar, displaying no difference in the slope (two-sided Wilcoxon ranked-sum test, $P = 0.96$). The inset shows the median (red line), quartiles (boxes) and the range (whiskers) of the slopes for lesioned and non-lesioned subjects. NS, not significant.
the lesioned participants (two-sided Wilcoxon ranked-sum test, \( z = 1.74, P = 0.04 \)). We also found a significant increase in slope when compared to the control participants who had undergone neuronal recordings but not lesioning (one-sided Wilcoxon ranked-sum test, \( z = 2.25, P = 0.01 \); Supplementary Fig. 8b). Lesions in the dlPFC therefore appeared to lead to a consistently diminished gradation in the participant’s voting profile when comparing these two tasks.

Unlike the opinion-based tasks, lesions in the dlPFC did not appear to affect the participants’ choices when performing a sensory perceptual task. Using the same Gabor task described above\(^\text{15}\), we found that the five participants with dlPFC lesions displayed no difference in the slopes of their psychometric curves when compared to those of the participants with no lesion (two-sided Wilcoxon ranked-sum test, \( P = 0.96 \); Fig. 5d). Therefore, unlike for the opinion-based tasks, focal lesions in the dlPFC did not appear to affect the participants’ ability to make sensory perceptual choices or enact their motor report.

Controls for motor-related behavior and neuropathology. Next, we also considered whether these findings could have been explained by other, more generalized, sensorimotor deficits related to surgical resection or underlying disease state. Overall, the lesioned participants demonstrated that they understood the task and made similar choice selections when compared to participants without dlPFC lesions. They also displayed no difference when performing the object evaluations or when performing the sensory perceptual task suggesting that the effect of lesions in this area was selective. Nonetheless, to cast a wide net and to consider other possible deficits, we further performed four additional controls.

First, we examined the participants’ choices at the extremes of the curve, at which the situations were most obviously safe or unsafe (for example, ordinal positions \( \pm 2 \) or above). If differences between the lesioned and control groups were due to simple unintended ‘errors’ or difference in choice consistency, we would expect selections for these manipulations to differ as well. However, we found no difference in selection on these trials between the participants (96.8 \( \pm 1.4 \% \) versus 94.4 \( \pm 2.9 \% \), two-sided \( t \)-test, \( t(46) = 1.06, P = 0.29 \)). We also found no difference in performances between the population that had undergone intra-operative neuronal recordings and healthy controls during these trials (95.2 \( \pm 1.5 \% \) versus 94.4 \( \pm 2.9 \% \), two-sided \( t \)-test, \( t(66) = 0.58, P = 0.56 \)). In other words, the patients displayed little variation in report when presented with the same scene on ‘obvious’ trials.

Second, we searched for differences that could be potentially explained by non-specific variations in task difficulty or demand. As mentioned before, the point of transition at equipoise was defined by the participant’s own subjective evaluation of the scenes rather than by an extrinsic change in required response or attended scene feature (for example, such as in a conflict monitoring- or countermand-type task\(^\text{19,40} \)). Nonetheless, to test for possible differences related to task difficulty, we examined whether the lesioned participants may be taking more time to make their selections and, therefore, be displaying evidence of demand-related changes near equipoise. However, we found no difference in response times between the lesioned participants and controls in face features taken from a validated database\(^\text{39} \) produced psychometric profiles that gradually transitioned from the choice selection of trustworthy to untrustworthy across equipoise (Supplementary Fig. 8a). Therefore, like the situational assessment task, there were no explicitly correct choices under any condition. Unlike it, however, this task did not involve elements of safety or danger.

Here, we tested 5 participants with dlPFC lesions and 14 individuals with no lesions (Supplementary Table 2). Similar to our original task, we found that the participants with dlPFC lesions displayed a significant increase in the slope of their psychometric curves when compared to the healthy participants (one-sided Wilcoxon ranked-sum test, \( z = 1.74, P = 0.04 \)). We also found a significant increase in slope when compared to the control participants who had undergone neuronal recordings but not lesioning (one-sided Wilcoxon ranked-sum test, \( z = 2.25, P = 0.01 \); Supplementary Fig. 8b). Lesions in the dlPFC therefore appeared to lead to a consistently diminished gradation in the participant’s voting profile when comparing these two tasks.

**Fig. 6 | Temporal dynamic of neuronal response.** Peak population prediction timing distribution and means (indicated by arrows). The light blue arrow corresponds to trial predictions of choices made near equipoise (ordinal positions \( -1 \) and \(+1 \)) and the dark blue arrow corresponds to those made far from equipoise (ordinal positions \( -4 \) and \(+4 \)). The inset illustrates the prediction profile (mean \( \pm \) s.e.m. for 1,000 repetitions) obtained from an example cell during the image presentation.
Third, we considered cortical areas other than the dlPFC. Specifically, we examined whether reselection in an upstream area that is broadly interconnected with the dlPFC and associated with higher-level sensory perceptual processing\(^{44,45}\) could produce a similar effect. Here, we searched for subjects who had previously undergone wide resection of the anterior temporal lobe (ATL; inferior/middle/superior gyri including amygdala and anterior hippocampus) and found three such participants (Supplementary Table 1). As with the control participants, individuals with ATL lesions displayed a range of voting profiles (Fig. 8c). Yet, unlike those with dlPFC lesions, the participants with ATL lesions displayed no difference in the slope of their voting profiles compared to control (68 ± 12 % change versus 72 ± 12 % change; two-sided Wilcoxon ranked-sum test, P = 0.23). The slopes of the voting profiles for the ATL lesioned participants were also lower than those of participants who had undergone dlPFC lesion resection (that is, compared to 117 ± 4 % change; one-sided Wilcoxon ranked-sum test, P = 0.03).

Last, we considered whether differences in the underlying disease state itself could have contributed to these results. Of the 11 patients who had undergone neuronal recordings during the situational assessment task, 2 had Parkinson’s disease (PD), 7 had essential tremor (ET) and 2 had primary dystonia or chronic pain (OTHER). While the number of patients may be too small to find definitive trends, we observed no significant difference in psychometric slopes between patients with PD and ET (slopes of 85 ± 17 % change versus 57 ± 15 % change, respectively, two-sided Wilcoxon ranked-sum test, P = 0.50). We also found a largely similar proportion of neurons that were modulated by the task across the three participant groups (27%, 26% and 33% of cells, for PD, ET and OTHER, respectively; Kruskal–Wallis test, H(2,8) = 0.778, P = 0.68; Supplementary Fig. 9). Comparisons between individuals with different underlying dlPFC pathologies before resection also revealed similar results (for example, glial versus non-glial lesions; see Supplementary Fig. 10).

Discussion

What neuronal processes underlie subjective decisions and what makes us change from one choice to another when forming opinions have long been intriguing questions in cognitive neuroscience, psychology and sociology\(^{1,4,37,43}\). Here, we found neurons in the dlPFC that displayed spiking activities that changed gradually as the participants transitioned from one choice to another and that varied non-linearly, in a logistic manner, as the participants transitioned between choice options. In other words, the absolute difference in their activity for choices made near equipoise was proportionally larger than for choices made further away. Together, these observations are notable because they appear to be consistent with behavioral observations of how humans probably form their opinions and describe how even small differences in a situation can dramatically tip your opinion of them (for example, as gluttonous even though, calorically, adding a small piece of desert accounts for only a minor proportion of the meal). Here, changes in the spiking activities of these neurons appeared to reflect both this subjective point of transition as well as the specific decision being made.

Supporting these observations, individuals with focal lesions of the dlPFC displayed a loss of gradation in their psychometric profiles and near-unitary transition across equipoise. By comparison, they displayed little difference in their choice selections or motor responses when compared to non-lesioned participants, suggesting that these changes were not explained by a non-specific sensory or motor deficit. This dissociation was also not explained by difficulty with task switching or in adaptively changing between choices\(^{40,45}\), as these transitions occurred randomly throughout the task and were not instructed.
Subjective decisions and perceptual choices are probably processed in the human dIPFC. Prior animal studies, for instance, have shown differences in the activities of neurons in frontal and parietal areas when making sensory perceptual choices on the apparent motion of stimuli, their tactile discrimination or source location. They have also shown differences in activity that correlate with the proportion of dots moving coherently in one direction over another or the amount of auditory clicks coming from a particular location, as predicted from signal-detection theory. Opinion-based tasks such as the ones tested here, by comparison, test for variations in subjective judgment or valuation, where there is no intrinsic correct choice for any situation (whether the participant’s choices lie near equipoise or not). Consistent with this, we found that neurons in the human dIPFC gradually changed their activities in relation to equipoise during the situational assessments even though the choice reports were the same. Moreover, they displayed a notable difference in response and lesion effects when comparing the situational assessment to the sensory perceptual Gabor task.

Collectively, our data suggest a neuronal process in the dIPFC that may support subjective decision-making in humans. In particular, they suggest a process that could allow single neurons to encode both a graded evaluation of the available choice options as well as their unique point of transition at equipoise and, therefore, allow them to reflect an individual’s complete voting profile. Disrupting this process, in turn, would lead to a loss of gradation between opposing choice options but would not impact the primary mechanisms by which sensory information is processed or motor selections are made. It would also not impact more generalized cognitive processes, such as demand adaptation or sensory perceptual processing. These observations on how subjective decisions are made during opinion formation could help improve our understanding of the mechanisms that underlie human behavior and its variability.

Collectively, our data suggest a neuronal process in the dIPFC that may support subjective decision-making in humans. In particular, they suggest a process that could allow single neurons to encode both a graded evaluation of the available choice options as well as their unique point of transition at equipoise and, therefore, allow them to reflect an individual’s complete voting profile. Disrupting this process, in turn, would lead to a loss of gradation between opposing choice options but would not impact the primary mechanisms by which sensory information is processed or motor selections are made. It would also not impact more generalized cognitive processes, such as demand adaptation or sensory perceptual processing. These observations on how subjective decisions are made during opinion formation could help improve our understanding of the mechanisms that underlie human behavior and its variability.

Online content
Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41593-019-0378-3.

Received: 25 October 2018; Accepted: 8 March 2019; Published online: 22 April 2019

Fig. 8 | Focal dysfunction of the dIPFC leads to a loss of gradation between opposing decisions but does not influence the participant’s motor report. a, A sagittal T1-weighted MRI of a participant (total population n = 4) that had previously undergone focal neurosurgical resection of a small lesion localized to the dIPFC. b, Left: the net proportion of trials in which the participants made the choice of safe versus unsafe ± s.e.m. Right: the slope of their voting profiles (that is, the rate of change in the participants’ choices of safe to unsafe at the inflection of the curve; see Methods). The values shown are the median (red line), quartiles (boxes) and the range (whiskers) for the control (n = 11) and lesioned (n = 4) subjects. c, Averaged voting profiles of dIPFC lesioned and control participants aligned to equipoise. Supplementary Fig. 7 displays the individual performances from which the psychometric curves were constructed separately for clarity. d, Scatter plot depicting the rate of change in choice (slope) versus average choice at the plateaus of the curves. Curves for individuals with dIPFC lesions (n = 4) are displayed in red and those of control subjects (n = 11) are displayed in black. The shaded areas represent the centroid and standard deviation for each respective group. e, Scatter plot for individuals with ATL lesions (n = 3) and control (n = 11). The shaded areas represent the centroid and standard deviation for each respective group.

Such behavior, in turn, whereby there is little gradation between opposing choice options, is often referred to in decision theory as false dichotomous or black-and-white thinking. Individuals with such a tendency commonly consider choice options unambiguously as ‘right and wrong’ or ‘good and evil’ and have difficulty in considering intermediate possibilities, especially under circumstances in which there is no explicit correct choice. While such a deficit would not be apparent when examining individual choices, they are apparent when evaluating the participant’s complete voting profiles. The ability of humans to consider choice options in a continuous or non-dichotomous manner and to allow for variability in their decisions are important features that define human decision-making and the process by which opinions are probably formed. Here, our findings suggest that the human dIPFC plays an important role in this process and explains how it may contribute to this choice variability.

These findings also reveal an important distinction between how subjective decisions and perceptual choices are probably processed in the human dIPFC.
10. Kim, J. N. & Shadlen, M. N. Neural correlates of a decision in the dorsolateral prefrontal cortical macaque. *Nat. Neurosci.* 2, 176–183 (1999).

11. Odegaard, B. et al. Superior colliculus neuronal ensemble activity signals optimal rather than subjective confidence. *Proc. Natl Acad. Sci. USA* 115, E1588–E1597 (2018).

12. Romo, R. & de Lafuente, V. Conversion of sensory signals into perceptual decisions. *Prog. Neurobiol.* 103, 41–75 (2013).

13. de Lafuente, V. & Romo, R. Dopamine neurons code subjective sensory experience and uncertainty of perceptual decisions. *Proc. Natl Acad. Sci. USA* 108, 19767–19777 (2011).

14. Padoa-Schioppa, C. & Assad, J. A. Neurons in the orbitofrontal cortex encode economic value. *Nature* 441, 223–226 (2006).

15. Cai, X. & Padoa-Schioppa, C. Contributions of orbitofrontal and lateral prefrontal cortices to economic choice and the good-to-action transformation. *Neuron* 81, 1140–1151 (2014).

16. Koenigs, M. et al. Damage to the prefrontal cortex increases utilitarian moral judgments. *Nature* 466, 908–911 (2007).

17. Chung, D., Christopoulos, G. I., King-Casas, B., Ball, S. B. & Chiu, P. H. Social signals of safety and risk confer utility and have asymmetric effects on observers’ choices. *Nat. Neurosci.* 18, 912–916 (2015).

18. Kable, J. W. & Glimcher, P. W. The neural correlates of subjective value during intertemporal choice. *Nat. Neurosci.* 10, 1625–1633 (2007).

19. Shenhar, A. & Greene, J. D. Moral judgments recruit domain-general valuation mechanisms to integrate representations of probability and magnitude. *Neuron* 67, 667–677 (2010).

20. Sternberg, R. J. Cognitive Psychology 3rd edn (Thomson/Wadsworth, 2003).

21. Weekley, J. A. & Plohjart, R. E. Situational Judgment Tests: Theory, Measurement, and Application (Lawrence Erlbaum Associates, 2006).

22. Nowinski, W. L., Gupta, V., Qian, G., Ambrosius, W. & Karmerski, R. Population-based stroke atlas for outcome prediction: method and preliminary results for ischemic stroke from CT. *PLoS One* 9, e102048 (2014).

23. Ndode-Ekane, X. E., Kharatishvili, I. & Pitkanen, A. Unfolded maps for cognitive Psychology (Lawrence Erlbaum Associates, 2006).

24. Patel, S. R. et al. Studying task-related activity of individual neurons in the human brain. *Nat. Protoc.* 8, 949–957 (2013).

25. Zedeck, S. & American Psychological Association. *APA Handbook of Industrial and Organizational Psychology* 1st edn (American Psychological Association, 2011).

26. Rainer, G., Asaad, W. F. & Miller, E. K. Selective representation of relevant information by neurons in the primate prefrontal cortex. *Nature* 393, 577–579 (1998).

27. Haroush, K. & Williams, Z. M. Neuronal prediction of opponent’s behavior during cooperative social interchange in primates. *Cell* 160, 1233–1245 (2015).

28. Kepcecs, A., Uchida, N., Zarivach, H. A. & Mainen, Z. F. Neural correlates, computation and behavioural impact of decision confidence. *Nature* 455, 227–231 (2008).

29. Hanes, D. P., Patterson, W. F. II & Schall, J. D. Role of frontal eye fields in countermanding saccades: visual, movement, and fixation activity. *J. Neurophysiol.* 79, 817–834 (1998).

30. Freeman, E., Sagi, D. & Driver, J. Lateral interactions between targets and flankers in low-level vision depend on attention to the flankers. *Nat. Neurosci.* 4, 1032–1036 (2001).

31. Padoa-Schioppa, C. & Assad, J. A. The representation of economic value in the orbitofrontal cortex is invariant for changes of menu. *Nat. Neurosci.* 11, 95–102 (2008).

32. Summerfield, C., Behrens, T. E. & Koechlin, E. Perceptual classification in a rapidly changing environment. *Neuron* 71, 725–736 (2011).

33. Williams, Z. M., Elfar, J. C., Eskandar, E. N., Toth, L. J. & Assad, J. A. Parietal activity and the perceived direction of ambiguous apparent motion. *Nat. Neurosci.* 6, 616–623 (2003).

34. Mian, M. K. et al. Encoding of rules by neurons in the human dorsolateral prefrontal cortex. *Cereb. Cortex* 24, 807–816 (2014).

35. Rigotti, M. et al. The importance of mixed selectivity in complex cognitive tasks. *Nature* 497, 585–590 (2013).

36. Fusi, S., Asaad, W. F., Miller, E. K. & Wang, X. J. A neural circuit model of flexible sensorimotor mapping: learning and forgetting on multiple timescales. *Neuron* 54, 319–333 (2007).

37. Zuckerman, M. *Psychobiology of Personality* 2nd edn (Cambridge Univ. Press, 2005).

38. Porter, K. R., McCarthy, B. J., Freels, S., Kim, Y. & Davis, F. G. Prevalence estimates for primary brain tumors in the United States by age, gender, behavior, and histology. *Neuro Oncol.* 12, 520–527 (2010).

39. Sofer, C., Dotsch, R., Wiggoldus, D. H. & Todorov, A. What is typical is good: the influence of face typicality on perceived trustworthiness. *Psychol. Sci.* 26, 39–47 (2015).

40. Sheth, S. A. et al. Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. *Nature* 488, 218–221 (2012).

41. Freiwald, W. A., Tsao, D. Y. & Livingstone, M. S. A face feature space in the macaque temporal lobe. *Nat. Neurosci.* 12, 1187–1196 (2009).

42. Hirabayashi, T., Takeuchi, D., Tamura, K. & Miyashita, Y. Microcircuits for hierarchical elaboration of object coding across primate temporal areas. *Science* 341, 191–195 (2013).

43. Siddique, Z., Anand, S. & Lewis-Greene, H. *Situational Judgment Tests for Dentists: the DF1 Guidebook* (Wiley, 2017).

44. Eysenck, H. J. *The Psychology of Politics* (Routledge and Kegan Paul, 1954).

45. Rushworth, M. F., Hadlan, K. A., Gaffan, D. & Passingham, R. E. The effect of cingulate cortex lesions on task switching and working memory. *J. Cogn. Neurosci.* 15, 358–353 (2003).

46. Williams, Z. M., Bush, G., Rauch, S. L., Cosgrove, G. R. & Eskandar, E. N. Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nat. Neurosci.* 7, 1370–1375 (2004).

47. Wenzel, A., Chapman, J. E., Newman, C. F., Beck, A. T. & Brown, G. K. Hypothesized mechanisms of change in cognitive therapy for borderline personality disorder. *J. Clin. Psychol.* 62, 503–516 (2006).

48. Eysenck, H. J. *The Psychology of Politics* (Transaction Publishers, 1999).

49. Asaad, W. F., Rainer, G. & Miller, E. K. Neural activity in the primate prefrontal cortex during associative learning. *Neuron* 21, 1399–1407 (1998).

50. Green, D. M. & Swets, J. A. *Signal Detection Theory and Psychophysics* (Krieger, 1974).

Acknowledgements
Z.M.W. is supported by NIH grant nos. R01HD059852 and R01NS091390, the Presidential Early Career Award for Scientists and Engineers and the Whithead Foundation. M.I. is supported by the Banting Foundation, B.G. is supported by the NREF and Z.B.M. is supported by the NREF and NIH NRSA. K.H. is supported by the Simonson’s foundation. E.N.E. is supported by grant nos. NIH R01NS086422 and NIH UH3NS100548.

Author contributions
M.I. performed the analyses, helped obtain neuronal recordings and co-wrote the manuscript. B.G., Z.B.M., K.H., S.P. and E.N.E. helped perform the neuronal recordings and task set up. S.P. and T.H. helped program the task presentation. Z.M.W. conceived and designed the study, performed the neuronal recordings and wrote the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41593-019-0378-3.

Reprints and permissions information is available at www.nature.com/reprints.

Correspondence and requests for materials should be addressed to Z.M.W.

Journal peer review information: *Nature Neuroscience* thanks Romy Paz, Philip Starr, and other anonymous reviewer(s) for their contribution to the peer review of this work.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Methods

Study subjects and enrollment. All aspects of the study were approved by the Massachusetts General Hospital Institutional Review Board and were held in strict accordance with Harvard Medical School ethical guidelines. For neuronal recordings, participants underwent intra-operative neurophysiology and their planned deep brain stimulator (DBS) placement. Before consideration, candidates for the study were evaluated by a multidisciplinary team of neurologists, neurosurgeons and neuropsychologists and decisions for surgery were unrelated to study participation. After surgical consent was obtained and the participants were scheduled for surgery, an independent member of the research team approached the patient for study participation. They then filled a separate research consent if they wished to participate in the study. At any point in the study, including during the intra-operative phase, patients were freely able to withdraw from the study without any consequence to their clinical care. Participants included for lesion evaluation were identified retrospectively. Decisions for lesion resection were made for clinical reasons and had no relation to the present study. All of the participants demonstrated a focal neurological deficit on neurological examination (for example, paraplegia) or demonstrated a language or comprehension deficit. A total of 39 participants were included in the study (Supplementary Table 1 and Supplementary Table 2). Evaluation of the relationship between underlying pathology, task performance and neuronal recording results are described further in Supplementary Figs. 7–10.

Neurophysiology and DBS targeting. Acute neuronal recording. Subjects partaking in planned DBS at our institution normally also undergo standardized micro-electrode recordings to optimize DBS targeting. The micro-electrodes sometimes traverse the dorsal lateral surface of the prefrontal cortex on the way to the target nucleus (for example, the subthalamic nucleus or thalamus) and, therefore, provide the opportunity to brieﬂy study neuronal responses in the area. These recordings do not perturb the planned operative approach or alter clinical care. To perform single-neuronal recordings from the dIPFC, we ﬁrst incorporated a US Food and Drug Administration approved, biodegradable, ﬁbrous sealant (Tisseal) between the cortical surface and the inner table of the skull. The sealant is normally used after DBS placement but, in our setting, placement before electrode targeting further allowed for cortical pulsations to be locally mitigated (Fig. 1a). Second, we incrementally advanced the micro-electrodes along the cortical ribbon at 10–100 μm increments to identify and isolate individual units (that is, rather than focusing on the subcortical structures alone). Here, we employed the same array of ﬁve tungsten micro-electrodes (500–1,500 kΩ) normally used for deep targeting (Alpha Omega Engineering). The micro-drive did not have independent control over each electrode. Once putative neurons were identiﬁed, the micro-electrodes were held in position for 4–5 min to conﬁrm signal stability (we did not screen putative neurons for task responsiveness). Lastly, we used the intra-operative multi-electrode recording system (Alpha Omega Engineering) and data acquisition card (Texas Instruments) that allowed us to precisely time-stamp task events (1 kHz) and sample the neuronal data (44.1 kHz) in a second resolution. Neuronal signals were amplified, bandpass filtered (300 Hz and 6 kHz) and stored off-line (Alpha Omega Engineering). After recording from the dIPFC, subcortical neuronal recordings and DBS placement proceeded as scheduled.

Single-unit isolation. Single units were identiﬁed and sorted off-line through a Plexon work station (Plexon Inc.). To ensure the identiﬁcation of single, well-isolated units, we ﬁrst constructed a histogram of peak heights from the raw voltage tracings on each channel. A minimum threshold of 3 s.d.s was used to differentiate between neural signals from background noise. Next, template matching and principal component analysis (PCA) were used to classify action potentials and sorting. An ANOVA was performed on the ﬁrst three PCA components used to discriminate between waveform morphologies in which more than one unit was present. Candidate clusters of putative neurons needed to clearly separate from channel noise, display a voltage waveform consistent with that of a cortical neuron and have at least 99% of action potentials separated by an interspike interval of at least 1 ms (although some neurons display an ISI of 0.2 ms or more; Fig. 3a inset). Finally, any units that did not demonstrate waveform stability over the course of the trial were excluded from analysis (Supplementary Fig. 1a). No multi-units were used. Considering each patient underwent an average of two recording sessions, we recorded from an average of 1.6 ± 0.2 well-isolated single units per micro-electrode. Supplementary Fig. 1b illustrates two examples of spike waveform morphologies and associated PCA clusters. In the ﬁrst example, only a single unit was isolated from the recorded trace. In the second example, two units were isolated (red and green; the baseline noise is displayed in gray). Any putative units that displayed signiﬁcant overlap in their PCA distributions by multivariate ANOVA (P < 0.01) or overlapped with the baseline signal to noise were considered multi-units and excluded from further analyses.

Recording and lesion site conﬁrmation. All subjects involved in neuronal recordings underwent high-resolution 1.5–3 T magnetic resonance imaging (MRI) and computed tomography scans before surgery. Post-operatively, the same subjects underwent a repeat computed tomography scan to conﬁrm placement of the DBS electrodes. To conﬁrm recording locations, we referenced the location of the burr hole and DBS lead. Recording sites for all participants in which neuronal recordings were made were within the middle frontal gyrus of Brodmann’s area 9 of the dIPFC (Fig. 1).

Subjects with focal dIPFC lesions were identiﬁed by retrospecively reviewing patient charts of those who had previously undergone concomitant resections for fronto-temporal tumors. Following the deﬁnition of our inclusion criteria, participants were included in the study if MRI and/or lesion resection cavities were that were associated with subtotal resection (that is, the lesion was not entirely removed), the resection cavities were clearly separate from a subset of four individuals with solitary, focal resection cavities localized to the dIPFC. These individuals underwent complete resection of the entire anterior superior, middle and inferior temporal gyrus. Description of lesion location and underlying pathologies for all participants can be found in Supplementary Tables 1 and 2.

Behavioral tasks. Subjective situational assessment. Each trial began with a blank screen (Fig. 2a) and a base in which the participant responded with a blank screen delay for another 1 s. After this, two targets representing the choice options of ‘safe’ and ‘unsafe’ were presented in a random order on each of the screen (Fig. 2a). The subject had up to 10 s to select his or her choice by moving the joystick towards the safe or unsafe target option (Fig. 1b). For example, if the target option of safe was presented at the bottom of the screen and the participant was more likely to represent the safe situation, then he or she would move the joystick downwards. However, if the target option of safe was presented at the top of the screen, then he or she would move the joystick upwards. All scenes and target locations were given pseudorandomly and in a counterbalanced order across the course of the session. No feedback was given at any point during the trial.

A common pool of 70 images was used in the study and constructed of three main variations. First, 35 of the 70 images were divided into seven distinct prototypic scenes, each with their own unique situation and theme. For example, the participant may see a jogger running near a car in one scene but may see a person standing in a construction yard in another (Fig. 1b). Second, each of the prototypic scenes consisted of a subject that varied in relation to the object. For example, the relationship between the subject (e.g. a dog, a cat), the target option of safe or unsafe, and the car (object) on the street may vary from trial to trial for a total of five variations per prototypic scene (Fig. 1b). Finally, the other 35 images consisted of scenes in which the object itself was identiﬁable as safe or unsafe. For example, the participant may be given the image of a gun. In total, these variations were introduced to allow us to test the participant’s choices across a variety of real-world scenarios, still allowing the regular points at which the participant transitioned from one choice to another across scenes and compare variations in the choices of the different participants.

Subjective trustworthiness assessment. While the main task used situational safety assessment to evaluate for variability in opinion, it is possible that variations in trustworthiness may have been specific to tasks that only involve safety or danger. Therefore, to further test for this possibility, we included an additional control task that required the participants to render an opinion on trustworthiness. Guided by prior literature, the participants were shown faces taken from a validated database, whereby small variations in the features of the faces produced psychometric proﬁles that gradually transitioned from trustworthy to untrustworthy (Supplementary Fig. 8a). The faces presented to the participants were taken from a common pool of 15 faces. These faces were created from four pairs of prototypic faces that varied both in gender and facial features (see ref. 10 for additional detail). Each pair was then manipulated to produce three additional intermediates for a total of ﬁve variations per face pair (three sets of ﬁve faces). Faces were then presented in a pseudorandom and in a counterbalanced order (with approximately three repeats on average) across the course of the session. The trial sequence was also similar to the subjective situational assessment task. Here, each trial began with a blank screen for 1 s. A face was then presented for 2 s followed by a blank screen delay for another 1 s. After this, two targets representing the choice options of ‘trustworthy’ and ‘non-trustworthy’ were presented in random order on each end of the screen. The subject had up to 10 s to select his or her choice by moving the joystick towards one of the two options (Fig. 1b). No feedback was given at any point during the trial.

Sensory perceptual Gabor task. To further evaluate for selectivity of effect, we included an additional control task that required the participants to perform a sensory perceptual task. Here, the participants were presented with a Gabor image that was slightly rotated in a leftward (clockwise) or rightward (counterclockwise) direction (Fig. 5a). The Gabor’s orientation varied from −3° to +3° across the vertical and the participants were allowed to make forced choices on whether the Gabor was rotated to the left or the right. While this task produced...
similar psychometric profiles as in the situational assessment task (Fig. 5c), the participant's choices were explicitly correct or incorrect. Similar to the main task, each trial began with a blank screen for 1 s followed by a Gabor for 2 s and then a blank screen delay for another 1 s. Finally, two targets representing the closest options of 'left' and 'right' were randomly presented on each end of the screen. The subject then had up to 10 s to select his or her choice by moving a joystick. Overall, the participants were presented with eight Gabors of different orientations (Fig. 5a), which were given in a pseudorandom fashion (each Gabor was presented four times on average) during the course of each session. These ranged from most ambiguous (±3.0°) to least ambiguous (±0.2°). No feedback was given at any point during the trial.

Participant instruction. For participants undergoing neuronal recordings, the subjects were familiarized with the task on the morning of surgery. For healthy participants, the task was performed with dIPFC/ATL lesions present. The participants were required to work with the task before testing. All subjects were given instruction before practice. For example, for the situational assessment task, they were told that: "(1) You will be shown a series of images on the computer screen displaying a scene or an object. (2) You will need to decide whether each scene or object is safe or unsafe. (3) To indicate your choice, please wait for the target choice to appear at the end of each trial and move the joystick to the displayed 'safe' target if you believe the scene or object is safe and to the displayed 'unsafe' target if you believe it is unsafe." Each subject practiced for 5–10 min before performing the task. All behavioral tasks were performed and recorded using customized software written in MATLAB (MathWorks, Inc.).

Statistical analysis. Psychometric curves and voting profile analysis. The voting profiles of the participants were constructed in three steps. For the situational assessment task, we constructed a psychometric curve based on the choices of the participant for each specific scene and manipulation. For example, as can be seen in Fig. 6, the choice responses of one of the participants to prototypic scene no. 1 were safe-safe-safe-unsafe-unsafe across the five manipulations no. 1–5. Second, in Fig. 2b, the choice responses of one of the participants to prototypic scene no. 5 were safe-safe-safe-unsafe-unsafe across the five manipulations no. 1–5. Second, the choices of each participant across the seven prototypic scenes were aligned to the point at which the participant's choices transitioned from safe to unsafe. This point of transition was determined through a two-point moving average function (that is, neighboring choices) in which the smoothed value was closest to 0.5. Essentially identical results were obtained through a formal space–state approach. Thus, for example, if the manipulations 1–5 for prototypic scene 1 lead to choices of safe-safe-safe-unsafe-unsafe, whereas the manipulations 1–5 for prototypic scene 2 lead to choices of safe-unsafe-unsafe-unsafe-unsafe, their point of equipoise would be between manipulations 3 and 4 and 1 and 2, respectively. For certain cases, there was variation in choice for adjacent manipulations (for example, safe-safe-unsafe-unsafe-unsafe) or on control duplicate manipulations (for example, safe-safe-unsafe-safe-unsafe) within a particular prototypic scene. Here, the point of transition was calculated in the same fashion as above. In other words, the point of transition was based on the net 'weight' of all choice selections, such that the most equal set of selections laid on the 'left' and 'right' of equipoise. Last, we aligned these points of transition across all the prototypic scenes per participant and calculated their average to obtain the psychometric curve. This represented the participant's voting profile across the different manipulations; ordinal positions above zero represented scenes that the participant believed were progressively less safe, and ordinal positions below zero represented scenes that the participant believed were progressively unsafe (Fig. 2d). For the figures, psychometric profiles are displayed with each of the participant's data points. The box-and-whisker plots display the median and quantiles.

To further evaluate the differences in the participants' voting profiles, we fit their choices to

\[ y = B + \frac{A - B}{1 + e^{k(x - c)}} \]

where \( y \) is the overall probability of the participant choosing 'unsafe'; \( A \) and \( B \) are the asymptotic values of \( y \) in the extreme 'unsafe' and 'safe' domains of the logistic curve, respectively; \( k \) is the steepness of the curve; and \( c \) represents the point of inflection at equipoise. As done previously, these fits were optimized to minimize the root mean square error between the simulation and the experimental data for each participant.

For further validation, we also calculated \( k \) from the raw behavioral data. Here, we considered the participant's choice probability at ordinal positions \(-1\) and \(+1\) (that is, the values closest to equipoise) and calculated the slope of the curve simply as the mean difference in their values. The values of \( A \) and \( B \) were calculated as the raw choice probability at the two plateaus of the curve.

Task modulation and neurometric analysis. Peri-stimulus histograms and rasters were constructed for all units that displayed stable waveform parameters, adequate refractory periods and morphology. To allow for comparisons between cells with different firing rates, trial activity was normalized (divided by) the average firing rate for the cells at baseline (1,000 ms before image onset). Because of the known temporal delay of frontal neurons to sensory stimuli and the variability in the participants' reaction times, we focused on a 1,500 ms window starting 500 ms from the onset of scene presentation and lasting for the duration of scene presentation. Differences in the firing rates of the cells to the choices of safe/unsafe were made through a standard two-sided Student's \( t \)-test (\( P < 0.05 \); with Bonferroni correction). A two-way ANOVA was used to examine differences in the firing rates of the cells in relation to choice (safe/unsafe) and equipoise (near/far; two-way ANOVA, \( P < 0.05 \)). For simplicity and to provide an identical number of trials to compare, we defined 'near' equipoise as ordinal positions \([-2, -1, +1, +2] \) and 'far' from equipoise as ordinal positions \([-4, -3, +3, +4] \) (although largely identical results were obtained by comparing \([-1, +1] \) to the other positions).

To analyze differences in firing rate as they relate to the participant's voting profile, we used two principal procedures. For the first, we fit three distinct functions to the neuronal activities: (1) a logistic function similar to what we used above for the psychometric curves where \( y \) is the neuronal activity, \( A \) and \( B \) represent the minimum and maximum firing rates respectively, \( k \) is the steepness of the curve and \( x \) represents the point of inflection; (2) a binary step function that only included \( B \) and \( A \), representing the minimum and maximum neuronal activity, respectively, on each side of equipoise; and (3) a U-shaped (that is, parabolic) function. Here, the U-shaped function was defined by

\[ y = c(x - a)^2 + m \]

where \( y \) is the neuronal activity, the parameter \( c \) determines the steepness of the parabola as well as its direction (upward if \( c > 0 \) and downward if \( c < 0 \)) and \( m \) represents the participant's maximum (or minimum) probability of choosing unsafe depending on whether the parabola is upward or downward. Lastly, \( x_0 \) represents the neutral ordinal position (that is, equipoise).

These fits were optimized to minimize the root-mean-square error between the simulated and the experimental data for each neuron. The goodness of fit was evaluated using the variance accounted for (VAF),

\[ \text{VAF} = 1 - \frac{\text{var}(A - \hat{A})}{\text{var}(A)} \]

where \( \text{var} \) is the variance, \( A \) is the actual neuronal activity and \( \hat{A} \) is the estimated neuronal activity using either the logistic or the binary step function.

For the second approach, we performed a model selection procedure that progressively considered the neuronal activity, point of inflection and slope to fit the experimental data. These successively included a unitary fit (which was essentially \( A + B)/2 \) in equation 1, a linear fit (which described the linear slope between \( A \) and \( B \) and contains a constant and a slope parameter), a logistic fit (which included \( e^{-k[x-c]} \) in equation 1) and a U-shaped fit according to the equation 2. To determine which model best fits the data, we used both an AIC and a Bayesian information criterion (BIC) that penalize models containing more parameters (Supplementary Table 3). AIC was computed as \( \text{AIC} = 2k - 2\ln(L) \), where \( L \) is the maximum value of the likelihood function of a given model and \( k \) is the number of free parameters in the model. Similarly, BIC was calculated as \( \text{BIC} = \ln(n) - 2\ln(L) \), and \( n \) is the number of data points.

Substitution analysis. A substitution analysis was performed to quantify the degree to which neural activity correlated with each participant's own unique voting profile. This procedure was done in four parts. First, we would identify neuronal activity recorded in one participant (for example, participant no. 1) when he or she was viewing a particular scene and then determine when, during the session, another participant (for example, participant no. 2) was viewing the same precise scene. Second, we would maintain the trial-by-trial relation between the neuronal activity and the specific manipulation (that is, manipulations 1–5 in Fig. 1b) per prototypic scene from the recorded participant no. 1, but the choice reports to those manipulations would now be assigned to the choice reports of participant no. 2. Third, to ensure an even sample across participants and an identical net proportion of safe/unsafe selections comparison, we pseudorandomly repeated this procedure 1,000 times (that is, the choices were preserved on average across all 1,000 shuffles). Thus, for example, participant no. 1 may view manipulation 2 of scene 1 as safe, whereas participant no. 2 may view that same manipulation/scene as unsafe. However, whereas participant no. 2 may view that manipulation/scene as unsafe, participant no. 3 may view it as safe, and so on. Therefore, even though we were comparing the same choice of ‘safe’ across shuffles, the participant's subjective evaluation of the scenes, as inferred from their psychometric profiles, differed. Lastly, to examine the degree to which neural activity correlated with the participant's unique voting profiles, we calculated the \( \beta \) logistic regression coefficient that describes the correlation between neuronal activity and the original and substituted voting profiles. We also examined for differences in raw firing rates for the safe/unsafe choices between the original and substituted trials (permutation test, \( P < 0.05 \)).

Neuronal population decoding. A Fisher's discriminant was used to quantify the degree to which population activity was informative of the participant's upcoming choice. As described previously, we quantitatively measured the ratio of the variance in neuronal activity between the two groups of options 'safe' and 'unsafe' to the variance within the groups based on \( S_\text{between} = \frac{\sum S_\text{between}}{n} \), where \( S_\text{between} \) and \( S_\text{within} \) are the
within group scatter matrices and between group scatter matrices, respectively. The prediction vector \( \mathbf{v} \) corresponds to the largest eigenvalue of the matrix on the left-hand side of the equation. The prediction vector defines a projection of the recorded activity into a scalar unit that is then compared to a threshold, \( \theta \), and if greater than \( \theta \) then the trial choice was predicted to be safe and if less than \( \theta \) then it was predicted to be unsafe. For validation, we divided the data into a training set consisting of 75% of the trials and tested the accuracy of the prediction on the remaining 25% of trials. This operation was repeated 1,000 times using a random sampling of the total trials. Finally, to examine the timing of maximum decoding accuracy, we used a 1,500-ms sliding window advanced in 100 ms increments.

Statistics. Throughout the paper, we report mean and s.e.m. unless otherwise noted. Correlation analyses were conducted using Pearson’s \( r \) value. Testing for differences of means of distributions was performed using non-parametric Wilcoxon ranked sum test, unless parametric \( t \)-test or ANOVA testing is specified. No data points were excluded from analyses unless otherwise stated. Parametric testing was used when data were assumed to be normally distributed. However, this was not formally tested. If data were not assumed to be normally distributed, non-parametric tests were used. When box-and-whisker plots are displayed, the central line represents the median of the distribution, box limits represent the 25th and 75th quantiles, and whisker limits represent the full range of data. Sample sizes were not predetermined using power analysis or other statistical tests, but the sample sizes acquired are comparable to those in previously reported work. Data collection and analysis were not performed in a blinded fashion.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability
The primary codes used to analyze the data are available from the corresponding author upon reasonable request.

References
51. Amirnovin, R., Williams, Z. M., Cosgrove, G. R. & Eskandar, E. N. Experience with microelectrode guided subthalamic nucleus deep brain stimulation. *Neurosurgery* **58**, ONS96–ONS102 (2006).
52. Gross, R. E., Krack, P., Rodriguez-Oroz, M. C., Rezai, A. R. & Benabid, A. L. Electrophysiological mapping for the implantation of deep brain stimulators for Parkinson’s disease and tremor. *Mov. Disord.* **21**, S259–S283 (2006).
53. Theodosopoulos, P. V., Marks, W. J. Jr., Christine, C. & Starr, P. A. Locations of movement-related cells in the human subthalamic nucleus in Parkinson’s disease. *Mov. Disord.* **18**, 791–798 (2003).
54. Asaad, W. F. & Eskandar, E. N. Achieving behavioral control with millisecond resolution in a high-level programming environment. *J. Neurosci. Methods* **173**, 235–240 (2008).
55. Wasserman, L. *All of Statistics: A Concise Course in Statistical Inference* (Springer Texts, 2005).
Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a

- **Confirmed**

  - The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
  - A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
  - The statistical test(s) used AND whether they are one- or two-sided
    - *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
  - A description of all covariates tested
  - A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
  - A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
  - For null hypothesis testing, the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P value noted
    - *Give P values as exact values whenever suitable.*
  - For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
  - For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
  - Estimates of effect sizes (e.g. Cohen's d, Pearson's r), indicating how they were calculated

_Our web collection on statistics for biologists contains articles on many of the points above._

Software and code

Policy information about availability of computer code

| Data collection | Plexon offline sorter (v4): neuronal data preparation |
|-----------------|------------------------------------------------------|
| Data analysis   | MATLAB (2015b) custom routines: statistical analysis |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

- [x] Life sciences
- [ ] Behavioural & social sciences
- [ ] Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf
Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size
A total of 39 participants were involved in the study. Of these, 11 underwent single-neuronal recordings, 4 had previously undergone focal dlPFC lesion resection and 3 underwent anterior temporal resection. For further comparison using separate control tasks, an additional 4 participants underwent neuronal recordings, 5 had focal dlPFC lesion resections and 12 served as healthy controls. Our main neuronal analysis is based on data from 31 task-responsive neurons out of 119 neurons in total. An additional 71 neurons were recorded for control in subjects performing a sensory perceptual task. The sample size is large enough for the statistical analyses we have performed in our study consistent with previously published data.

Data exclusions
No subjects were excluded from analysis. For neuronal analysis, any units that did not demonstrate waveform stability over the course of the experiment were excluded from the analysis per pre-established standard criteria for off-line single unit sorting. Units that displayed significant overlap in their PCA distributions by MANOVA (p < 0.01) or overlapped with the baseline signal/noise were considered multi-units and excluded from further analyses.

Replication
For neuronal analyses (tests for task modulation and model fitting of behavior with single unit activity), similar results were observed across study participants. Other core analyses were performed on the population level, across individuals, in which case the variation in subject responses was incorporated into statistical testing/modeling. This variability in response is also shown through the plotting of individual raw data or data ranges in the figures as applicable.

Randomization
There was no randomization procedure for subject selection/enrollment since all participants performed the same task. Nonetheless, we assessed for possible correlation with participant diagnosis but found no significant difference in results when looking within these subgroups. Finally within a given experimental session trial stimuli order was randomly generated to avoid effects potentially attributable to trial order.

Blinding
Blinding of enrollment was not possible since the neuronal recordings were performed by the principal investigator in a surgical setting. Other control studies were performed by the research team in a direct clinical setting. Blinding of analysis was not relevant since all subjects underwent similar task design.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

| Materials & experimental systems | Methods |
|----------------------------------|---------|
| n/a Involved in the study        | n/a Involved in the study |
| ☑ Antibodies                    | ☑ ChIP-seq |
| ☑ Eukaryotic cell lines         | ☑ Flow cytometry |
| ☑ Palaeontology                  | ☑ MRI-based neuroimaging |
| ☑ Animals and other organisms   |         |
| ☑ Human research participants   |         |
| ☑ Clinical data                  |         |

Human research participants

Policy information about studies involving human research participants

Population characteristics
The primary population level covariate that was considered was patient diagnosis. In the neuronal recordings, 7 patients had essential tremor and 2 patients at primary dystonia, and 2 had Parkinson’s disease. No significant differences in performance or neuronal activity was observed across the different diagnostic categories. Among post-lesion patients who underwent behavioral testing varied diagnosis (glioma, metastasis, arteriovenous malformation). Behavior, viz. psychometric curves, did not significantly covary across diagnostic labels.

Recruitment
For neuronal recordings, participants underwent intraoperative neurophysiology as part of their planned deep brain stimulator (DBS) placement. Prior to consideration, candidates for the study were evaluated by a multidisciplinary team of neurologists, neurosurgeons, and neuropsychologists and decisions for surgery were unrelated to study participation. All patients meeting inclusion criteria for intraoperative recordings were approached regarding study enrollment solely based on these criteria and not based on other features (e.g. study team’s anticipated likelihood of patient choosing to enroll) in order to prevent selection bias as best possible. After surgical consent was obtained and the participants were scheduled for surgery, an independent member of the research team approached the patient for study participation. They then filled a separate research consent if they wished to participate in the study. At any point in the study, including during the intraoperative phase, patients were freely able to withdraw from the study without any consequence to their clinical care. Lesion patients, who were contacted retrospectively, were identified based upon a sequential review of the electronic medical system in order provide a systematic approach to contacting participants that independent of disease course or other clinical or demographic factors. A large majority of patients who were contacted chose to enroll in the study, making self-selection biases less likely.
Ethics oversight

Massachusetts General Hospital Institutional Review Board

Note that full information on the approval of the study protocol must also be provided in the manuscript.