Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex

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Both lesion and functional imaging studies in humans[1,2], as well as neurophysiological studies in nonhuman primates[3], demonstrate the importance of the prefrontal cortex in representing the emotional value of sensory stimuli. Here we investigated single-neuron responses to emotional stimuli in an awake person with normal intellect. Recording from neurons within healthy tissue in ventral sites of the right prefrontal cortex, we found short-latency (120–160 ms) responses selective for aversive visual stimuli.

The prefrontal cortex participates in linking perception of stimuli to the guidance of behavior[4], including the flexible execution of strategies for obtaining rewards and avoiding punishments as an organism interacts with its environment[5]. Regions in the medial and ventral aspects of the frontal lobe seem especially important in relating information about external sensory stimuli to interoceptive information that represents emotional significance. For instance, studies of this region in monkeys show responses that are modulated on the basis of the rewarding value of the stimulus, independent of its perceptual properties[3]. Studies in humans using the lesion method[1,5,6] and functional imaging[2] show that ventral and medial prefrontal cortex guide decision-making and social behavior on the basis

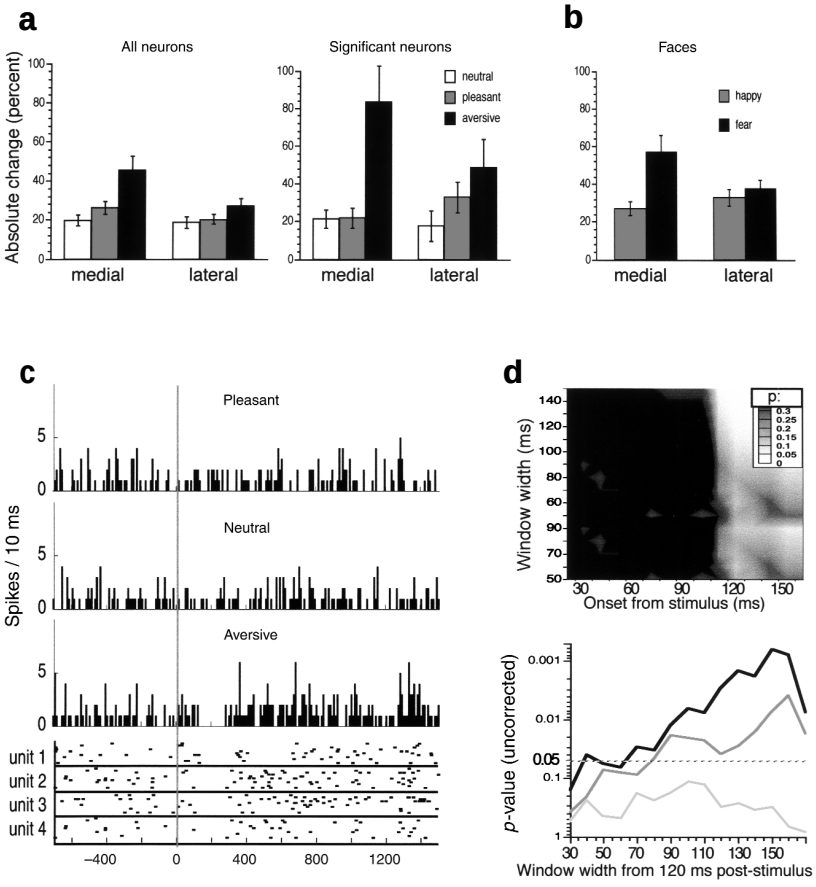

Fig. 1. Single-neuron responses to emotional stimuli. (**a**) Mean (± s.e.m.) responses to emotional scenes recorded at medial or lateral locations in right ventral prefrontal cortex, as a function of emotion category. For each neuron, we calculated the absolute change in firing rate before (–2000 to 0 ms) and after (0 to +1000 ms) the stimulus, normalized with respect to the mean rate before the stimulus across all neurons. Thus, a percent change shown on the figure could reflect either a decrease or an increase in firing rate. Left, responses for all neurons (46 medially, 47 laterally). Right, responses for neurons that showed a significantly different rate in at least one pairwise comparision of emotion categories (thresholded at $p < 0.05$). Mean absolute spike rate change recorded medially differed significantly only when comparing aversive pictures to pleasant ($p < 0.005$) or to neutral pictures ($p < 0.005$); at lateral sites, there were significant differences only between mean rates for aversive and neutral pictures ($p < 0.05$; Wilcoxon rank-sum tests). (**b**) Responses to emotional facial expressions (37 neurons medially, 35 laterally), using the same analysis as in (**a**). Whereas mean absolute spike rate change between happy and fearful faces differed significantly medially ($p < 0.05$), it did not differ at lateral sites ($p > 0.7$). (**c**) Composite peristimulus-time histograms (top) and raster plots (bottom) from four individual neurons recorded medially in response to emotional scenes (stimulus onset, vertical gray line). Raster plots are shown for presentations of each of 11 aversive stimuli at the bottom. (**d**) Speed of categorization reflected in response latency. Top, *p*-values (grayscale; Wilcoxon rank-sum test, uncorrected) showing that neuronal responses to aversive scenes differed from pre-stimulus baseline (–750 to 0 ms), for neurons recorded medially. *x*-axis, beginning of epochs after stimulus onset (10-ms steps); *y*-axis, width of epoch (10-ms steps). The sharp vertical 'edge' at 120 ms after the stimulus represents the time when the firing rate in time periods as small as 50 ms (that is, the window from 120–170 ms) differed at the $p < 0.05$ level from the rate during the pre-stimulus period. Bottom, *p*-values showing that neuronal responses to different emotion categories differed from one another, as a function of the width of a window beginning at 120 ms after the stimulus. Whereas aversive scenes differed from both pleasant scenes (top black line) and neutral scenes (middle gray line) at widths of 40 ms and 80 ms respectively, pleasant and neutral scenes did not differ from one another at any window (bottom light gray line).

of emotional value. However, the participation of this brain region in the processing of human emotion has not been investigated directly at the single-cell level.

We recorded from 93 neurons at four sites on 2 depth electrodes (1 lateral, 1 medial), in the right ventral prefrontal cortex of a 48-year old man with a history of medically refractory epilepsy. The subject had a normal neuropsychological and psychiatric profile, and was oriented and attentive. He performed normally on tests of frontal lobe function, including the Iowa Gambling Task[6], which has been directly linked to the operation of ventromedial prefrontal cortex[1,6]. With the subject's informed consent, hybrid clinical-research depth electrodes[7] were implanted stereotactically in the prefrontal cortex. The electrodes permitted isolation of neurons from high-impedance tetrode contacts using the DataWave system. (For detailed methods and neuroanatomy of the recording sites, see supplementary information.) Subsequent clinical evaluations using electroencephalographic (EEG) recording, as well as the outcome of the neurosurgical resection, confirmed a seizure focus in right motor/premotor cortex, distal to the sites from which we report recordings.

We showed the subject pictures of visual scenes and facial expressions, selected from standardized databases (the International Affective Picture System and Pictures of Facial Affect, respectively). In right ventromedial prefrontal cortex, single-neuron responses to aversive visual scenes differed significantly from responses to pleasant or neutral scenes (**Fig. 1a**); likewise, responses to facial expressions of fear differed significantly from responses to facial expressions of happiness (**Fig. 1b**). These differential responses could not be explained by differences in the physical properties of our stimulus images, which were of equivalent luminance, size and color composition.

Examination of raster plots and of the peristimulus-time histogram showed that aversive stimuli triggered a short-latency, transient inhibition followed by a prolonged excitation; no such responses were seen to neutral or to pleasant stimuli (**Fig. 1c**). Only for aversive scenes were there differences between response rates before and after the stimulus, and these differences became significant at 120 ms after stimulus onset, for time periods as short as 50 ms (that is, for the interval 120–170 ms; **Fig. 1d**, top). Furthermore, the response to aversive stimuli during this inhibitory period (from 120 ms after stimulus) differed significantly from responses to pleasant or to neutral stimuli during the same period, for windows as small as 40 or 80 ms, respectively (**Fig. 1d**, bottom). Thus, these data provide evidence that neuronal responses in human ventromedial frontal cortex are influenced selectively by the emotional content of visual stimuli within 120–160 ms, a form of rapid and coarse stimulus categorization. Whereas the speed of such emotion categorization is surprising, it is consistent with evoked potential studies in humans, which find visual responses in frontal cortex with latencies of 150 ms (ref. 8). Our findings are also consistent with functional imaging studies reporting responses to aversive visual stimuli in medial sectors of the prefrontal cortex[9].

Our data indicate categorization that seems to be specific to an ecologically salient category: stimuli related to fear, threat or danger. The responses we observed may be related to increased emotional arousal or increased allocation of attention to such stimuli; in all likelihood, arousal, attention and other cognitive processes would be affected together to prepare an organism for rapid behavioral response to stimuli that signal potential danger. Furthermore, our data showed visually different neuronal responses to aversive stimuli as early as 120 ms after the stimulus (**Fig. 1c**), but these differences were not statistically significant for windows smaller than 40 ms due to sparse firing rates (**Fig. 1d**).

Only during neurosurgical intervention is there an opportunity to record single-neuron data from the human brain, and this constraint dictates the neuroanatomical locations from which recordings can be obtained. Whereas responses related to visual processing have been studied in a variety of brain structures in a neurosurgical setting[10,11], we investigated emotion processing at the single-neuron level in human ventral prefrontal cortex. Our findings indicated that neurons in right ventromedial prefrontal cortex participate in encoding the emotional value of aversive visual stimuli. Surprisingly, we found responses with latencies as short as 120–170 ms to aversive stimuli, suggesting that prefrontal neurons can provide a rapid and coarse categorization of the emotion. Prefrontal responses may modulate visual information processing in other brain regions, for instance, by feedback to temporal cortices[12], a function consistent with top-down influences on visual responses in that region[13]. In addition, we also found a longer-latency response to aversive stimuli, consisting of a prolonged increase in firing rate. Rapid and delayed response components may thus reflect an iterative function, whereby the prefrontal cortex guides the processing of emotional stimuli at multiple temporal scales. Possibly, such scales could encompass both covert processes as well as processing that contributes to conscious awareness of the emotion.

Note: detailed methods information is available on the Nature Neuroscience web site (http://neurosci.nature.com/web_specials/).

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