

COGNITIVE NEUROSCIENCE

From affective value to decision-making in the prefrontal cortex

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Abstract

Representing the affective value of a reward on a continuous scale may occur separately from making a binary, for example yes vs no, decision about whether to choose the reward. To investigate whether these are separable processes, we used functional magnetic resonance imaging to measure activations produced by pleasant warm, unpleasant cold, and affectively complex combinations of these stimuli applied to the hand. On some trials the affective value was rated on a continuous scale, and on different trials a yes–no decision was made about whether the stimulus should be repeated in future. Decision-making contrasted with just rating the affective stimuli revealed activations in the medial prefrontal cortex area 10, implicating this area in binary decision-making. Activations related to the pleasantness ratings and which were not influenced when a binary decision was made were found in the pregenual cingulate and parts of the orbitofrontal cortex, implicating these regions in the continuous representation of affective value. When a decision was yes vs. no, effects were found in the dorsal cingulate cortex, agranular (anterior) insula and ventral tegmental area, implicating these areas in initiating actions to obtain goals.

Introduction

Representations of the affective (reward and punishment) value of many stimuli and events are present in the orbitofrontal and anterior cingulate cortex, as shown by neurophysiological, functional neuroimaging and clinical neuropsychological investigations. These include the reward and punishment value, and correlations with the pleasantness/unpleasantness of olfactory (Rolls *et al.*, 1996, 2003a; Anderson *et al.*, 2003; Grabenhorst *et al.*, 2007), taste (Rolls *et al.*, 1989; Small *et al.*, 2003; Grabenhorst *et al.*, 2008), somatosensory (Rolls *et al.*, 2003b), temperature (Guest *et al.*, 2007; Rolls *et al.*, 2008), visual (O'Doherty *et al.*, 2003a), monetary (O'Doherty *et al.*, 2001a; Knutson *et al.*, 2007) and social stimuli (Hornak *et al.*, 2003; Kringelbach & Rolls, 2003; Moll *et al.*, 2006; Spitzer *et al.*, 2007). When taking a decision about a reward or punisher, however, a representation of the affective value may be formed, and that may be followed by a decision process about whether to accept or work for that amount of reward (Rolls, 2008; Rolls & Grabenhorst, 2008). It is not yet known to what extent the representations of affective value are also involved in the decision itself, or whether these are to some extent separable processes. To the extent that they may be at least partly separable, it is not clear whether when a decision is being taken this in turn feeds back to influence the affective representations. To investigate this, we performed a functional magnetic resonance imaging (fMRI) investigation in which four thermal stimuli with

different affective values were rated on some trials for pleasantness and intensity, but on other trials a binary 'yes'/'no' decision was made about whether the stimulus would be chosen in future, to test the hypothesis that activations in different brain regions were related to these different types of processing. Previous investigations of decision-making have not addressed this issue, though have investigated contributions of the parietal (Glimcher, 2003; Sugrue *et al.*, 2005), prefrontal (Kringelbach & Rolls, 2003; Heekeren *et al.*, 2004; Hampton & O'Doherty, 2007; Knutson *et al.*, 2007), cingulate (Behrens *et al.*, 2007; Marsh *et al.*, 2007) and ventral premotor (Romo *et al.*, 2004; Deco & Rolls, 2006) cortices to decision-making.

In this investigation, we used warm and cold stimuli that have affective components such as feeling pleasant or unpleasant. These components may have survival value, for approach to warmth and avoidance of cold may be reinforcers or goals for action built into us during evolution to direct our behaviour to stimuli that are important for survival (Rolls, 2005). Indeed, warm and cold stimuli may be important prototypical primary, that is unlearned, reinforcers, and investigation of the neural mechanisms that are related to these stimuli and the feelings they arouse may provide a direct approach to understanding the brain mechanisms of emotion and indeed of decision-making (Rolls, 2005, 2008).

Materials and methods

Design

Warm and cool thermal stimuli, and mixtures of them, were applied to the hand. Because the human participants made ratings of the

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pleasantness and intensity of the stimuli on half the trials during the fMRI investigation, we were able to analyse how their subjective feelings of pleasantness, unpleasantness and intensity were related to activations in different brain regions. The design allowed us not only to investigate where warm and cold stimuli are represented, but also how the brain systems that represent their affective value respond when binary decisions are made about the stimuli. We explicitly did not use in this study thermal stimuli that were painful, whether hot or cold, but restricted the temperatures applied for 5 s at a time to the hand to the range 12–41°C, with values selected individually for each subject to be rated as cold and unpleasant but not painful, or warm and pleasant. In this study, we found that the activations in some brain areas were correlated with the pleasantness ratings. Although the pleasantness ratings increased in this study with the warmth of the stimuli, we note that the pleasantness correlations with the brain activations found in this study were related to the pleasantness *per se* and not the absolute temperature, as can be seen by the fact that if we had increased the temperature to the noxious range with a ‘hot’ stimulus of perhaps 45°C, then such a stimulus would almost certainly break any correlation at a pleasantness brain site with the absolute value of the temperature, given that at these sites (e.g. the pregenual cingulate and orbitofrontal cortex) the activations are correlated with the pleasantness of stimuli in other modalities, including taste, flavour, touch and the sight of touch (Grabenhorst *et al.*, 2008; McCabe *et al.*, 2008). Further evidence that at these brain sites the activations were not related to the physical (as contrasted with the affective) attributes of the stimuli is that the activations in these brain regions to the same thermal stimuli during the same imaging sessions were not related to the intensity ratings of the stimuli (Rolls *et al.*, 2008). Further evidence that the activations did not reflect the absolute temperature of the stimuli is that when the tuning of thermosensitive neurons is investigated in regions such as the insular cortex, some neurons have increasing firing rates as a function of temperature, some have decreasing firing rates as a function of temperature, and some are tuned with a peak at a particular temperature (Verhagen *et al.*, 2004), making it unlikely that a blood oxygen level-dependent (BOLD) activation would reflect absolute temperature *per se*.

In the experiment, we compared brain responses when participants were taking decisions about whether they would select a thermal stimulus (yes vs. no), with activations to the same stimuli on different trials when only affective ratings were required and there was no decision about whether the participants would say yes or no to the stimuli if they were available in the future. Both the decision and rating trials were identical from the start of each trial at $t = 0$ until $t = 5$ s when a visual stimulus was shown for 1 s stating ‘decide’ or ‘rate’ the thermal stimulus being applied, and at $t = 6$ s a green cross appeared until $t = 10$ s. On decide trials from $t = 6$ until $t = 10$ s the participants had to decide whether yes or no was the decision on that trial. At $t = 10$ s a visual stimulus with yes above no or vice versa in random order was shown for 2 s, and the participant had to press the upper or lower button on the button box as appropriate to indicate the response. On rating trials from $t = 6$ until $t = 10$ s the participants had to encode the pleasantness and intensity of the thermal stimulus being applied, so that the ratings could be made later. On rating trials at $t = 10$ s the pleasantness rating could be made using the same button box, and then the intensity rating was made. Thus, a comparison of the activations at time $t = 6$ s on different trials reflected differences between taking a decision about whether to select yes for an affective thermal stimulus, and making an affective and intensity rating of the thermal stimulus, without a decision of yes or no. Because the responses were not made until $t = 10$ s on both types of trial,

the activations while the green cross was being shown with identical stimuli being applied reflected differences between making a decision or an affective/intensity rating. Further, the actions required at $t = 10$ s were to press one of two adjacent button box keys to indicate yes vs. no on decision trials, or to move the rating scale on rating trials, and the responses of pressing one or other of the two button box response keys were so similar that they could not be distinguished in any of the areas described in this study, as shown in the Results. However, we note that participants could between $t = 6$ and $t = 10$ s on rating trials prepare a movement in terms of which of the two buttons they would press later to make a rating, but could not determine at the same time on decision trials which of the two buttons they would press later. The plan of the design was to enable processes involved in the affective representation of sensory (thermal) stimuli to be compared with decision-making about the same affective stimuli. Brain mechanisms involved in decision-making might involve decoding an affective representation of a stimulus, and then taking a decision about the stimulus, and the design was to allow investigation of what extra processes might be involved in taking the decision as compared with only representing the affective value. The thermal stimuli were a warm pleasant stimulus (41°C) applied to the hand (‘warm2’), a cool unpleasant stimulus (12°C) applied to the hand (‘cold’), a combined warm and cold stimulus (‘warm2 + cold’), and a second combination designed to be less pleasant (39 + 12°C; ‘warm1 + cold’). The data were collected in the same experimental sessions as those in a different investigation (Rolls *et al.*, 2008), with all results about decision-making and decision-making trials reported only in this paper.

We investigated how decision-making and the affective value of the thermal stimuli were represented in brain areas identified by prior hypotheses, such as the orbitofrontal and anterior cingulate cortex where the pleasantness and unpleasantness of touch and oral temperature are represented (Rolls *et al.*, 2003b; Guest *et al.*, 2007; McCabe *et al.*, 2008), in the insula and somatosensory cortex where thermal stimuli are represented (Craig *et al.*, 1996, 2000; Tracey *et al.*, 2000; Brooks *et al.*, 2005; McCabe *et al.*, 2008), and in brain areas such as the prefrontal cortex (Heekeren *et al.*, 2005; Behrens *et al.*, 2007; Burgess *et al.*, 2007a) and ventral tegmental area (Morris *et al.*, 2006) implicated by previous studies in decision-making.

Participants

Twelve healthy volunteers (six male and six female, mean age 26 years) participated in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Central Oxford Research Ethics Committee, and written informed consent from all subjects was obtained before the experiment.

Stimuli

Controlled cool thermal stimuli were applied using an adapted commercially available Peltier thermode (MEDOC, Haifa, Israel; 3 × 3 cm thermo-conducting surface) strapped to the dorsum of the left hand. The thermode was switched on in time to produce the temperature of 12°C for the period $t = 6$ –10 s on each trial. The warm stimulus was applied using a thermal resistor 2 × 1.5 cm strapped to the palm of the left hand. The thermal resistor device was designed and built at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB; Bantick *et al.*, 2002), and was switched on in time to produce the temperature of 41°C (for warm2) or 39°C (for warm1) for the period $t = 6$ –10 s on each trial.

The placement of the stimuli on the dorsum and palm of the hand was designed to minimize thermal interaction between the stimuli in the short delivery period of 4 s, and was designed so that even with any topologically mapped representation of the body surface that might be present in the activated brain regions, the regions of activation would be close in the brain. The method of stimulus delivery ensured that the devices were continually in place during the experiment, and that only temperature changes were occurring in the stimulation periods. In preliminary testing, the exact temperatures used for each subject were tailored $\pm 2^\circ\text{C}$, so that warm2 was rated as very pleasant; cold as unpleasant but not painful or very unpleasant so that when it was combined with warm2 the combination sometimes at least was more pleasant than neutral; and warm1 was adjusted so that it was less pleasant than warm2 and more pleasant than neutral.

Experimental protocol

The overall protocol is described above under 'Design'. The experimental protocol consisted of an event-related interleaved design presenting in random permuted sequence the two experimental conditions and four thermal stimuli for each condition. There was a 4-s period from $t = 6$ to $t = 10$ s in which the temperature stimuli were held constant and a green cross was shown indicating to the subject that this was the relevant period for which ratings were required, or in which a decision about the stimulus being applied should be taken. Starting at $t = 10$ s on ratings trials subjective pleasantness ratings were then made resulting in ratings on a continuous scale between +2 (very pleasant) and -2 (very unpleasant). The next rating was for the intensity of the stimulus on a scale from 0 (very weak) to 4 (very intense). The ratings were made with a visual analogue rating scale in which the subject moved the bar to the appropriate point on the scale using a button box. On decision trials, at $t = 10$ s, the words 'yes' and 'no' appeared above or below each other on the screen for 2 s, and in this period that participant had to select which button key response to make (up button or down button) for the decision that had been taken in the green cross decision period. Each of the trial types was presented in random permuted sequence 15 times. For one of the main contrasts described in this paper, activations on decision vs. rating trials, there were thus 60 decision trials and 60 rating trials. This general protocol and design has been used successfully in previous studies to investigate activations and their relation to subjective ratings in cortical areas (Rolls *et al.*, 2003a,b; de Araujo *et al.*, 2005; Grabenhorst *et al.*, 2007, 2008), and correlations between subjective ratings and brain activations have been described in other studies (Craig *et al.*, 2000; Anderson *et al.*, 2003; Northoff *et al.*, 2007).

fMRI data acquisition

Images were acquired with a 3.0-T VARIAN/SIEMENS whole-body scanner at the FMRI, where 27 T2*-weighted EPI coronal slices with in-plane resolution of 3×3 mm and between plane spacing of 4 mm were acquired every 2 s (TR = 2). We used the techniques that we have developed over a number of years (O'Doherty *et al.*, 2001b; de Araujo *et al.*, 2003), and as described in detail by Wilson *et al.* (2002) we carefully selected the imaging parameters in order to minimize susceptibility and distortion artefact in the orbitofrontal cortex. The relevant factors include imaging in the coronal plane, minimizing voxel size in the plane of the imaging, as high a gradient switching frequency as possible (960 Hz), a short echo time of 28 ms, and local

shimming for the inferior frontal area. The matrix size was 64×64 mm and the field of view was 192×192 mm. Continuous coverage was obtained from +62 (A/P) to -46 (A/P). A whole brain T2*-weighted EPI volume of the above dimensions, and an anatomical T1 volume with coronal plane slice thickness 3 mm and in-plane resolution of 1×1 mm was also acquired.

fMRI data analysis

The imaging data were analysed using SPM5 (Statistical Parametric Mapping, Wellcome Institute of Cognitive Neurology, London). Pre-processing of the data used SPM5 realignment, reslicing with sinc interpolation, normalization to the MNI coordinate system (Montreal Neurological Institute; Collins *et al.*, 1994), and spatial smoothing with a 6-mm full-width-at-half-maximum isotropic Gaussian kernel. The time series at each voxel were low-pass filtered with a haemodynamic response kernel. Time series non-sphericity at each voxel was estimated and corrected for (Friston *et al.*, 2002), and a high-pass filter with a cut-off period of 128 s was applied. In the single event design, a general linear model (GLM) was then applied to the time course of activation where the decision or rating period onset ($t = 6$ s in each trial) were modelled as single impulse response functions and then convolved with the canonical haemodynamic response function (Friston *et al.*, 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation (Kiebel *et al.*, 1999), in the first stage of analysis condition-specific experimental effects (parameter estimates or regression coefficients, pertaining to the height of the canonical HRF) were obtained via the GLM in a voxel-wise manner for each subject. The results were obtained in the following GLM models: (a) regressors of decide trials and rate trials during the stimulus period, and of button box responses made in the response period (used for the main analysis of decide vs. rate); (b) regressors of yes trials, and no trials, and rating trials during the stimulus period; (c) separate regressors for each stimulus for the decide and rate trials used for the analyses shown in Figs 1b, 2b, 3b and 4b; (d) separate regressors for the pleasantness and intensity ratings on rating trials. In the second (group random effects) stage, subject-specific linear contrasts of these parameter estimates were entered into a series of one-sample *t*-tests, each constituting a group-level statistical parametric map. The correlation analyses of the fMRI BOLD signal with given parameters of interest (e.g. the pleasantness ratings) were performed at the second-level through applying one-sample *t*-tests to the first-level subject-specific statistical parametric maps resulting from performing linear parametric modulation as implemented in SPM5. We report results for brain regions where there were prior hypotheses as described in the Materials and methods, Design, section and applied small volume (false discovery rate) corrections for multiple comparisons (Genovese *et al.*, 2002) with a radius corresponding to the full-width-at-half-maximum of the spatial smoothing filter used. These brain regions with prior hypotheses identified in this way were, for example, as follows: medial prefrontal cortex area 10 [-6 54 -14] (Heekeren *et al.*, 2005); ventral insula [40 -2 -12] (McCabe *et al.*, 2008); pregenual cingulate cortex [-4 38 -4] (McCabe *et al.*, 2008); orbitofrontal cortex [24 38 0] (Craig *et al.*, 2000); and dorsal anterior cingulate cortex [-6 26 34] (Behrens *et al.*, 2007). Peaks within 10 mm of these to allow for variations due to the exact site of stimulation on the body surface and type of stimulation are reported for which $P < 0.05$, though the exact corrected probability values are given in the text. In addition to the statistical criterion just described for a

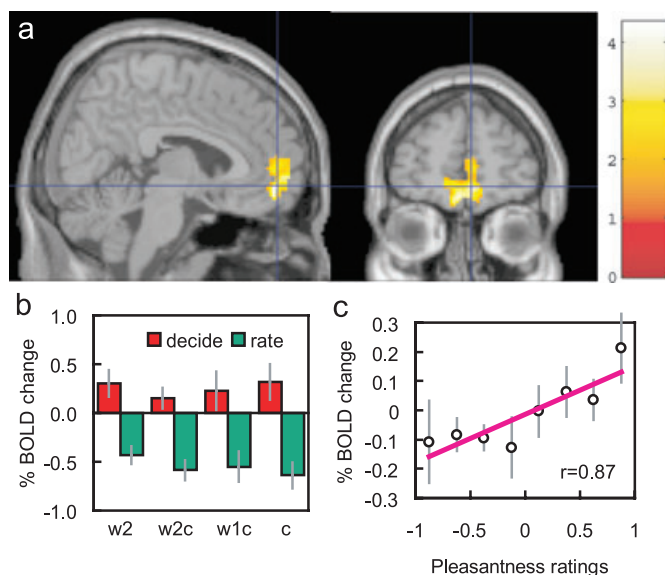


FIG. 1. Decisions – ratings: medial area 10. (a) A contrast of all trials on which decisions were made vs. all trials on which ratings were made. An extensive region of activation was found in medial area 10 with a peak at [6 54 -8], $z = 3.24$, $P = 0.022$ (at cursor). (b) The peaks of the percent blood oxygen level-dependent (BOLD) signal averaged across subjects (mean \pm SEM) show activation on decision trials, compared with deactivation on rating trials. w2: 41°C; w2c: 41°C and 12°C; w1c: 39°C and 12°C; c: 12°C. (c) The % BOLD signal was correlated with the pleasantness ratings on the trials on which ratings were made ($r = 0.87$, $df = 7$, $P = 0.005$). [The % BOLD values in (c) were calculated by obtaining the average (\pm SEM) BOLD signal for pleasantness ratings binned at increments of 0.25 for each subject, and then averaging across subjects.]

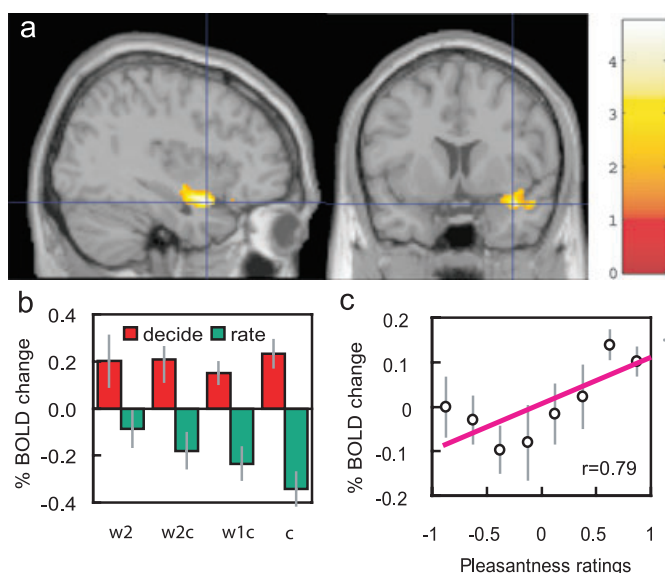


FIG. 2. Decisions – ratings: ventral insular cortex. (a) A contrast of all trials on which decisions were made vs. all trials on which ratings were made showed an extensive region of activation at [38 8 -20], $z = 3.43$, $P = 0.008$. (b) The peaks of the percent blood oxygen level-dependent (BOLD) signal averaged across subjects (mean \pm SEM) show some activation on decision trials, compared with deactivation on rating trials. (c) The relation between the % change in the BOLD signal and the pleasantness ratings on the trials on which ratings were made ($r = 0.79$, $df = 7$, $P = 0.011$).

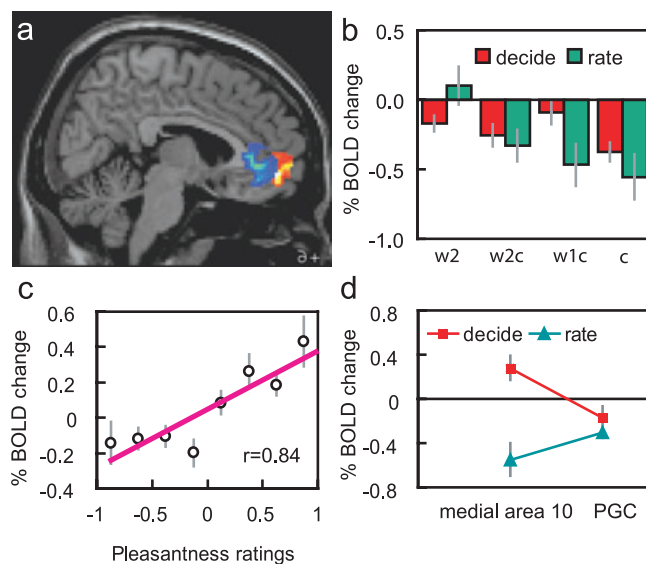


FIG. 3. Pregenual cingulate cortex. (a) A contrast of all trials on which decisions were made vs. all trials on which ratings were made showed no significant difference in the pregenual cingulate cortex, but we did find, in the blue activation, a strong and significant correlation with the pleasantness ratings ([4 38 -2], $z = 4.24$, $P = 0.001$). The area 10 region where there was a decide–rate difference is shown in red ([6 54 -8], $z = 3.24$, $P = 0.022$), and is clearly anterior to the pregenual cingulate cortex region where the activations were correlated with pleasantness. (b) The peaks of the percent blood oxygen level-dependent (BOLD) signal for the pregenual cingulate cortex averaged across subjects (mean \pm SEM) show that there were no consistent and large differences between the activations on decision trials and rating trials (consistent with the lack of significant effect in the contrast analysis). There was, however, as shown in (b) a clearly graded signal in the pregenual cingulate cortex for the different thermal stimuli, with warm2 producing activation and cold deactivation, consistent with the very significant correlation between the activations in the pregenual cingulate cortex and the pleasantness ratings. (c) The % BOLD signal was correlated with the pleasantness ratings on the trials on which ratings were made ($r = 0.84$, $df = 7$, $P = 0.005$). (d) Compares the activations (mean \pm SEM) in medial area 10 with those in the pregenual cingulate cortex (PGC) for decision and rating trials.

significant effect calculated for the peak voxel of a region of activation in an *a priori* defined region based on earlier findings, we used the additional statistical test (see Gottfried *et al.*, 2002; O’Doherty *et al.*, 2003b, 2006) that the results reported were in global contrast and correlation analyses significant using the criterion of $P < 0.001$ uncorrected for multiple comparisons and a cluster threshold of $k = 3$, and these additional statistics confirmed the same effects in the *a priori* regions in all cases in this paper except where otherwise stated.

To show the change in the % BOLD signal, we located activations within the *a priori* regions of interest and extracted from the fitted time course the event-related responses from the peak voxel for each subject. These peaks of the single-subject time courses were then averaged across subjects.

For voxels where significant correlations were found between the % BOLD signal and the ratings, we produced graphs to show how the ratings were related to the % BOLD signal. These were produced for each subject by taking the average of the BOLD response in the three time bins at 4, 6 and 8 s post-stimulus, on each trial, and the corresponding rating. For each subject the means were calculated in discretized ranges of the rating function (e.g. -2 to -1.75, -1.75 to -1.5, etc), and then these values were averaged across subjects to produce the graphs shown in Figs 1c, 2c and 3c.

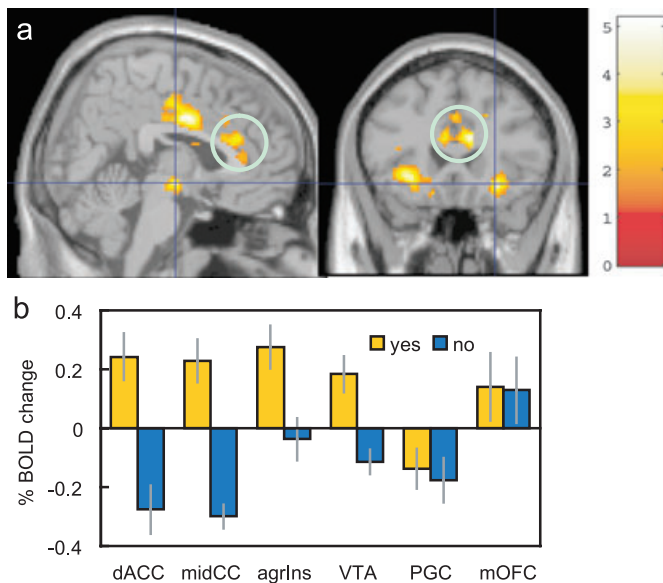


FIG. 4. Contrast of trials with yes vs. no decisions. (a) Significant effects were found in the ventral tegmental area (sagittal slice, at cursor; [4 -12 -8], $z = 3.38$, $P = 0.036$); dorsal anterior cingulate (sagittal and coronal slices, circled; [6 30 22], $z = 3.28$, $P = 0.013$); mid cingulate cortex (sagittal slice; [4 -4 36], $z = 3.51$, $P = 0.003$); and agranular insula (coronal slice, at cursor; [28 24 -14], $z = 3.61$, $P = 0.015$). (b) The peaks of the percent blood oxygen level-dependent (BOLD) signal averaged across subjects (mean \pm SEM) for the dorsal anterior cingulate cortex (dACC); the mid cingulate cortex (midCC); the agranular insula (agrIns); the ventral tegmental area (VTA); the pregenual cingulate cortex (PGC); and the medial orbitofrontal cortex (mOFC).

Results

Behavioural results for the ratings and the decisions

The affective (pleasantness) ratings of the thermal stimuli across subjects were (on a scale of +2 = very pleasant to -2 = very unpleasant) for warm2: 0.62 ± 0.17 ; for warm2cold: -0.14 ± 0.16 ; for warm1cold: -0.32 ± 0.15 ; and for cold: -0.36 ± 0.16 ($F_{3,66} = 88.5$, $P \ll 0.001$). Consistent with these pleasantness ratings, the subjects chose the warm2 stimulus on $96 \pm 1.1\%$ (SEM) of choices, the warm2cold stimulus on $36 \pm 8.5\%$ of choices, the warm1cold on $24 \pm 6.9\%$ of choices, and the cold on $18 \pm 6.1\%$ of choices. The intensity ratings of the thermal stimuli across subjects were (on a scale of +4 = very intense to 0 = very weak) for warm2: 2.04 ± 0.22 ; for warm2cold: 2.3 ± 0.19 ; for warm1cold: 2.12 ± 0.21 ; and for cold: 2.09 ± 0.24 (with no significant difference in the ANOVA).

Activations related to decisions vs. ratings

Medial prefrontal cortex area 10

A contrast of all trials on which decisions were made vs. all trials on which ratings were made revealed an extensive region of differential activation in medial prefrontal cortex area 10 with a peak at [6 54 -8], $z = 3.24$, $P = 0.022$, as shown in Fig. 1a. The region was anterior to the pregenual cingulate cortex. The region continued ventrally towards a part of the medial orbitofrontal cortex with a local peak at [-4 52 -14], $z = 2.94$, $P = 0.025$ (not significant in the global analysis), which is evident extending below the cursor in Fig. 1a. The effect found in medial area 10 was an increase in the BOLD signal on decision trials, compared with a deactivation on trials on which only

ratings were made, as shown in Fig. 1b. These signals were measured at identical times in the two trial types, at $t = 6$ s, which is the time at which the temperature stimulus was being applied and had reached its plateau, and starting immediately after the 1 s instruction appeared that a decision or a rating had to be made on that trial. The activations thus occur in a period when the subject is either making a decision about whether the stimulus would be chosen (yes vs. no), or is required to rate the pleasantness and intensity of the stimulus on that trial. The SPM rating regression analysis showed that there was some indication for a parametric modulation of the BOLD signal related to the pleasantness ratings in this region ([10 50 -6], $z = 2.76$, $P = 0.032$), though this did not reach the criterion in the global analysis (see Materials and methods). Figure 1c shows how the % change in the BOLD signal was related to the pleasantness ratings obtained on the rating trials ($r = 0.87$, $df = 7$, $P = 0.005$). The SPM analysis showed no correlation with the intensity ratings in this region.

The activations in this region were not related to movements in the response period of the task, based on the following evidence. First, the activations were found at $t = 6$ s in the trial, immediately after the 1-s instruction to decide was displayed, and the cue to indicate which button key to press to indicate yes or no was not shown until $t = 10$ s. Second, the contrast shown in Fig. 1 was exclusively masked by the activations occurring when the response was made at $t = 10$ s. (This mask was made for $t = 10$ s by a conjunction of the activations on both the decision and rating trials with the conservative criterion of $P = 0.05$ for the exclusive mask. These movement-related activations are shown in Fig. 5, and were in different brain regions, such as the supplementary motor area and primary motor cortex area 4.) Third, a response was required at the identical time of $t = 10$ s on decision and rating trials, made with the same button box, to indicate yes or no, or

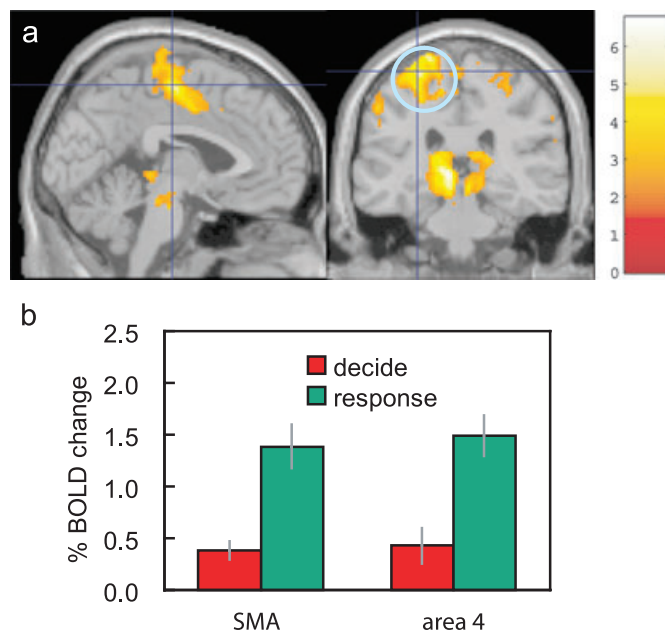


FIG. 5. Response-related activation: a conjunction across decision and rating trials of the activations at $t = 10$ s when a button box response was made to indicate a decision or to make a rating (obtained in a separate SPM analysis to ensure orthogonality). (a) Significant effects were found in the supplementary motor area (SMA, sagittal slice, at cursor; [-2 18 58], $z = 4.45$, $P < 0.001$); motor cortex, area 4 (coronal slice, circled; [-28 -30 68], $z = 4.46$, $P < 0.001$). (b) The peaks of the percent blood oxygen level-dependent (BOLD) signal averaged across subjects (mean \pm SEM) for decision period and the response period for the SMA and motor cortex area 4.

to move the rating bar. The same control showed that the effects described next for the ventral insula were not due to responses made.

Ventral insula

A contrast of all trials on which decisions were made vs. all trials on which ratings were made revealed an extensive region of differential activation in the ventral insula (bilaterally) with a peak at [38 8 -20], $z = 3.43$, $P = 0.008$, as shown in Fig. 2a. (The activation extended from $y = 10$ to $y = -8$.) The effect found in the ventral insula was an increase in the BOLD signal on decision trials, compared with a deactivation on trials on which only ratings were made, as shown in Fig. 2b. The signal shown in Fig. 2b on the rating trials is graded according to the pleasantness of the four stimuli and, consistent with this, the SPM rating regression analysis provided an indication that there was a parametric modulation of the BOLD signal by the pleasantness ratings in this region ([38 -2 -22], $z = 3.06$, $P = 0.027$, though this did not reach the criterion in the global analysis (see Materials and methods)). Figure 2c shows how the % change in the BOLD signal was related to the pleasantness ratings obtained on the rating trials ($r = 0.79$, $df = 7$, $P = 0.011$). There was no correlation with the intensity ratings in this region. The signal in this region was graded for the four stimuli on the rating trials, but not on the decision trials, as shown in Fig. 2b. The activation was found bilaterally in the insula ([-38 2 -18], $z = 3.49$, $P = 0.011$).

Premotor cortex

One of the areas active in the decide–rate contrast, the insula, projects to the premotor cortex (Cipolloni & Pandya, 1999) and, consistently, activations in the decide–rate contrast were found in the premotor cortex at [-22 10 50], $z = 3.78$, $P = 0.001$; [-24 10 54], $z = 4.29$, $P < 0.001$; and [-12 24 52], $z = 3.33$, $P = 0.012$.

The opposite contrast, of rate–decide, masked identically to that used above, showed no significant activations.

Activations related continuously to affective value and not influenced by a binary decision

Pregenual cingulate and orbitofrontal cortex

A contrast of all trials on which decisions were made vs. all trials on which ratings were made showed no significant difference in the pregenual cingulate cortex. However, Fig. 3a shows in the blue region, a strong and significant correlation with the pleasantness ratings ([4 38 -2], $z = 4.24$, $P = 0.001$). The medial prefrontal cortex area 10 region where there was a decide–rate difference is shown in red in Fig. 3a ([6 54 -8], $z = 3.24$, $P = 0.022$), and is clearly anterior to the pregenual cingulate cortex region where the activations were correlated with the pleasantness ratings. Consistent with the contrast just described, Fig. 3b shows that the peaks of the percent BOLD signal for the pregenual cingulate cortex averaged across subjects (mean \pm SEM) had no consistent and large differences between the activations on decision trials and rating trials. However, as shown in Fig. 3b, there was a clearly graded signal in the pregenual cingulate cortex for the different thermal stimuli, with warm2 producing activation and cold deactivation, consistent with the very significant correlation between the activations in the pregenual cingulate cortex and the pleasantness ratings just described. Figure 3c shows how the % change in the BOLD signal was related to the pleasantness ratings obtained on the rating trials ($r = 0.84$, $df = 7$, $P = 0.005$). The activations in this pregenual cingulate cortex region had no correlation in the SPM analysis with the intensity ratings.

Figure 3d compares the activations in the medial area 10 and pregenual cingulate cortex in the decision and rating conditions. An ANOVA showed a significant difference in what is represented in these regions [the interaction was significant in a within-subjects ANOVA ($F_{1,10} = 8.6$, $P = 0.015$)]. The pregenual cingulate cortex is thus by these activation analyses especially related to the affective value of the thermal stimuli, and is not strongly related to deciding vs. only rating the stimuli. This is in contrast to the more anterior region, area 10, where the effects were much larger when deciding than when rating.

In addition to the pregenual cingulate cortex, activations with strong correlations with the pleasantness ratings of the same thermal stimuli were found in parts of the orbitofrontal cortex (e.g. [-26 38 -10], $z = 3.25$, $P < 0.04$; Rolls *et al.*, 2008) and, in the present investigation, this part of the orbitofrontal cortex did not show effects in the decide–rate contrast. Thus, parts of both the pregenual cingulate and orbitofrontal cortex are implicated more in affective value than in decision-making.

Activations related to decisions of ‘yes’ vs. ‘no’

On the decision trials, the subjects were asked to choose whether they would wish to select the stimulus being applied. The pre-experiment instructions stated that the participants might have such an opportunity for selection of the stimuli later on, after the imaging experiment. It was found that some brain areas had more activation on trials when the subject decided ‘yes’ than ‘no’. The activations were not related to particular responses, in that the subjects were not informed until $t = 10$ s which response key to press if their decision was yes or no. We note that a response was required on every decision trial, so the activations in this analysis were not related to whether a response was made or not, but to whether the decision was yes or no.

One area in which more activation was found for ‘yes’ vs. ‘no’ decisions (in a SPM contrast analysis) was the ventral tegmental area, as shown in Fig. 4a left ([4 -12 -8], $z = 3.38$, $P = 0.036$). The activations were higher for the warm2 and warm2cold stimuli than for the other two stimuli, and this is consistent, in that the subjects chose the warm2 stimulus on 96% of choices, the warm2cold stimulus on 36% of choices, the warm1cold on 24% of choices and the cold on 18% of choices.

A second area in which more activation was found for ‘yes’ vs. ‘no’ decisions was the dorsal anterior cingulate cortex, as indicated in Fig. 4a ([6 30 22], $z = 3.28$, $P = 0.013$). There was a positive correlation with the pleasantness (but not intensity) ratings in the SPM analysis in the same brain area ([6 22 20], $z = 4.04$, $P = 0.002$). Similar activations were also found in a third area, in the mid cingulate cortex, as indicated in Fig. 4a left ([4 -4 36], $z = 3.51$, $P = 0.003$).

A fourth area in which more activation was found for ‘yes’ vs. ‘no’ decisions was the agranular insula cortex, as indicated in Fig. 4a right at the cursor ([28 24 -14], $z = 3.61$, $P = 0.015$; and the activation was bilateral, as shown in Fig. 4a).

Figure 4b also shows for comparison two areas in which there were no differences in the activations on ‘Yes’ vs. ‘No’ trials, the pregenual cingulate and medial orbitofrontal cortex, with the activations measured at the coordinates given above.

Areas with activations related to responses

In a control analysis, activations related to the button box responses were analysed, to investigate whether the decision-related activations described above were separate from the activations related to motor responses. The motor responses were initiated at $t = 10$ s, and

consisted of pressing a button box key on decision trials to indicate which decision had been made earlier in the trial, and of pressing a button box key on rating trials to make a rating. Figure 5 shows the conjunction across decision and rating trials of these activations at the response time. Figure 5a shows that significant effects were found in the supplementary motor area (SMA; sagittal slice, at the cursor; $[-218\ 58]$, $z = 4.45$, $P < 0.001$). Figure 5b (left) shows the peaks of the percent BOLD signal averaged across subjects (mean \pm SEM) for the decision period and the response period for this SMA region. The BOLD signal was large in this region at the time of the response but not at the time of the decision, and this difference was significant ($t = 5.44$, $df = 11$, $P < 0.001$). Figure 5a (circled) shows that significant effects were also found in the motor cortex area 4 (coronal slice, circled; $[-28\ -30\ 68]$, $z = 4.46$, $P < 0.001$). Figure 5b (right) shows the peaks of the percent BOLD signal averaged across subjects (mean \pm SEM) for the decision period and the response period for this motor cortex region. The BOLD signal was large in this region at the time of the response but not at the time of the decision, and this difference was significant ($t = 4.98$, $df = 11$, $P < 0.001$). There were no significant activations in the supplementary motor cortex and motor cortex area 4 in the decision–rating contrast.

The findings of activations in the motor cortex and SMA during the response period as shown in Fig. 5a and b, but no significant activations in the decision–rating contrast, and little activation during decisions as shown in Fig. 5b; together with the finding that the areas described above (medial area 10, medial orbitofrontal cortex and ventral insula) had activations related to the decisions (Figs 1 and 2) but not to the responses, provides evidence that we were able to separate in this investigation areas related to taking decisions from areas involved in making motor responses. A further analysis showed that which of the two adjacent button box keys was touched to make one of the two responses or to move the rating scale in one of two directions did not result in different signals in any of the regions investigated and described above, providing further evidence that response-related factors did not influence the difference in the signals described in regions such as the medial prefrontal cortex area 10 and the insula that were related to processing involved in choice decision-making vs. making ratings of continuous affective value. (The only regions in which activations in this study did reflect which of the two button box keys was pressed were the SMA ($[0\ -14\ 54]$, $z = 3.76$) and the mid/posterior cingulate cortex ($[12\ -12\ 42]$, $z = 3.69$.) These points of evidence suggest that there was not a confound of motor preparation being required during the decision as compared with the rating trials and accounting for the decision–rating effects, in that very similar button box responses were required at the same elapsed time during a trial in the decision and rating conditions; in that activations in brain areas where the response did produce effects later on in a trial were not differentially activated at the decision/rating time of $t = 6$ s on each trial; and in that the brain areas that were differentially activated by decisions at the decision/rating time ($t = 6$ s) on each trial were not differentially activated in relation to the motor response of which of the two button box keys was pressed.

Discussion

In this study, activations were found in the medial prefrontal cortex area 10 that were large when a decision had to be made, relative to the activations when the same affective thermal stimulus had to be rated for affective value and intensity (Fig. 1). The implication is that this part of medial area 10 contributes in some way beyond representing

affective value to the decision-making process. Consistent with this, the pregenual cingulate cortex (just posterior to area 10) was not activated in the same contrast, and was therefore similarly activated on the rating and decision trials (Fig. 3). Moreover, the pregenual cingulate cortex activations were highly significantly correlated with the pleasantness ($z = 4.24$, $P = 0.001$), whereas the area 10 activations were less correlated with the pleasantness ratings ($z = 2.76$, $P = 0.032$). The implication is that the pregenual cingulate cortex is closely involved in representing the (continuous) affective value of the thermal stimuli, whereas area 10 is relatively less involved in representing the pleasantness, but is more involved in the (binary) decision-making process itself. Part of the interest of this finding is that the stimuli being delivered on the rating and decision trials are identical, so that what has been revealed by the activation of medial prefrontal cortex area 10 is processing especially related to binary decision-making compared with only rating the stimuli for which they need to be represented on a continuous scale. The different processing in these areas, which was one of the hypotheses described in the Introduction to be tested, was confirmed by the significant statistical interaction between the brain areas and conditions illustrated in Fig. 3d.

The segregation of function found into brain areas that reflect the continuous affective value of the stimuli but do not have activations that are influenced by whether a choice is being made (orbitofrontal and pregenual cingulate cortex), and other brain areas with activations that are different when choices are made (medial area 10 and ventral insula) compared with when only ratings are made, is consistent with the fact that these seem to be separately implemented functions in humans, who can report separately on exactly how pleasant a stimulus is on a continuous scale even at a time when they are deciding that on this trial they would accept it or not. Although there was an indication that at least when choices were being made the activations of the choice-related regions in the medial prefrontal cortex and insula were not graded according to the pleasantness of the four stimuli (see Figs 1b and 2b, red bars, and the fact that on decision trials there was no correlation found between the mean pleasantness of each stimulus and the activations in these two regions in the SPM regression analyses between subjective ratings and BOLD activations), this is not a key point that we wish to make, for it could be that at least early on in the decision-making process on each trial the activity in the system might reflect in a more continuous way the values of the inputs, that is at a time before the neurons have fallen into the attractor states that appear to reflect choice decision-making (Wang, 2002; Deco & Rolls, 2006).

Consistent with the findings of this investigation, patients with medial prefrontal cortex lesions are impaired in a decision-making shopping task, as reflected for example by visits to previously visited locations (Shallice & Burgess, 1991; Burgess, 2000; Burgess *et al.*, 2007a). In one imaging study, area 10 activation has been related to moral decision-making (Heekeren *et al.*, 2005), though activations in other studies have been suggested to be related for different parts of medial area 10 to attending to external stimuli vs. imagining internally (Gilbert *et al.*, 2005; Burgess *et al.*, 2007b). The present investigation goes beyond the concept of attending to external stimuli vs. internal processing, and suggests that area 10 activations occur in relation to a (binary) decision-making process itself, when compared with rating the same stimuli for affective value and intensity on continuous scales.

We found that the medial area 10 activation related to decision-making vs. rating extended down into a part of the anterior medial orbitofrontal cortex. The interesting implication of this particular new finding is that at least a part of the medial orbitofrontal cortex may be

involved in decision-making beyond representing the affective value of the stimuli, or may receive feedback connections from brain regions such as medial area 10 implicated in the decision-making (Petrides & Pandya, 2007). However, in contrast to this, much of the orbitofrontal cortex had activations that were correlated with the pleasantness ratings, and did not respond differently on decision vs. rating trials, so that much of the orbitofrontal cortex was involved in representing the (continuous) affective value of the stimuli (Rolls *et al.*, 2008), and not in the decision-making.

Another part of the decision system identified in this investigation, or that could reflect backprojections from decision systems, is the ventral insula, which shows effects in the contrast decide–rate (Fig. 2). The region extends from $y = -8$ mm posteriorly, which is a region known to be activated by touch to the arm (McCabe *et al.*, 2008), to $y = 10$ anteriorly. This ventral part of the anterior insula is generally in front of the more posterior thermally activated region described by Craig *et al.* (2000) and the region in which we found correlations with the intensity of these thermal stimuli (Rolls *et al.*, 2008), and the more anterior part of the ventral insula described in the present study (but not the more posterior insula) had activations related to the decision-making, as well as a correlation with the pleasantness of the thermal stimuli. Interestingly, there are projections from area 10 to the ventral insula (Petrides & Pandya, 2007), and these are a possible source of the decision-related activations found.

Some brain areas had activations that were related to the decision outcome, that is to yes vs. no for whether the stimulus being applied should be repeated later on. For example, the ventral tegmental area, the agranular insula and parts of the dorsal anterior cingulate cortex had greater activations on yes vs. no trials (Fig. 4). These activations were related to a yes decision, and not to the particular response made to indicate yes vs. no. However, these areas in general did not reflect the pleasantness of the stimuli when ratings were being made, so we suggest that their activations are especially related to a ‘Go’ decision, compared with a decision not to Go or not to choose a stimulus. The activations of the ventral tegmental area and these related systems might reflect activation of dopamine neurons, which it has been suggested may be related to the initiation of actions (Rolls, 2005, 2008). Consistently, dopamine neuron firing in macaques appears to reflect the value of an upcoming action (Morris *et al.*, 2006). The anterior cingulate cortex has been implicated in action–outcome learning (Rushworth *et al.*, 2007a,b), and its activation described here on yes trials (implying the initiation of an action to do something) is consistent with an important role of the cingulate cortex in decision-making. In this investigation, we show that the contribution of the anterior cingulate cortex is in the decision-making itself, and does not occur just in relation to the pleasantness of the stimuli, or in relation to the particular response that must be made, but instead to whether the action should be chosen.

The implication of the findings described here is that whereas areas such as the pregenual cingulate cortex and parts of the orbitofrontal cortex (Rolls *et al.*, 2008) provide a representation of the value of affective stimuli on a continuous scale, the medial prefrontal cortex area 10 is involved beyond the evaluation of affective stimuli in the decision-making process itself. For the evaluation, the neural activity needs to represent a stimulus in a way that continuously and faithfully represents the affective value of the stimulus, and this could be present independently of whether a binary decision is being made or not. On the other hand, when a binary decision must be reached, the neural activity needs no longer to continuously represent the affective value of the stimulus, but needs to fall into a state in which the high firing of some neurons represents one decision, or the high firing of other neurons a different decision. Processes such as this transition to a

binary state of firing of neurons (fast vs. slow) are known to occur in some premotor and related areas such as the macaque ventral premotor cortex (Romo *et al.*, 2004; de Lafuente & Romo, 2006). The evidence described here indicates that the human medial prefrontal cortex may be particularly involved in this special transition that is thought to occur as the binary decision is being reached (Deco & Rolls, 2006; Rolls, 2008).

The circuitry that may underlie this may be as follows, based on the connective anatomy and the activations found in the different areas. Areas such as the orbitofrontal cortex project to the pregenual cingulate cortex (Carmichael & Price, 1996; Price, 2006), in both of which affective value is represented (Rolls *et al.*, 2003b; de Araujo & Rolls, 2004; Rolls, 2005; Grabenhorst *et al.*, 2008). The pregenual cingulate cortex in turn projects forward to the medial prefrontal cortex, area 10 (Carmichael & Price, 1996; Price, 2006), where processes related to the binary (choice) decision-making appear to occur as shown here. Other studies have related medial area 10 to decision-making (Paulus & Frank, 2003; Greene *et al.*, 2004; Daw *et al.*, 2006; Hampton *et al.*, 2006; Soon *et al.*, 2008), though not explicitly to choice decision-making in which a categorical state must be reached as in the present study. Medial area 10 in turn has connections to the ventral insular cortex (Petrides & Pandya, 2007), where the decision-related activations could reflect an effect on somatosensory processing from the hand (which projects to an overlapping part of the ventral insula; McCabe *et al.*, 2008), or on autonomic effects resulting from the decision (Critchley *et al.*, 2004). Medial area 10 also projects to the orbitofrontal cortex (Petrides & Pandya, 2007), and this is a possible route for some parts of the orbitofrontal cortex to have activations that reflect the decision-making, though other parts of the orbitofrontal cortex were related to the affective value and not the decision-making. Medial area 10 also projects to the anterior cingulate cortex (Petrides & Pandya, 2007), and this area (together with the ventral tegmental area) had activations in the present study that were related to the particular action, yes vs. no, implying that the anterior cingulate cortex is involved in the more detailed specification of the action (cf. Walton *et al.*, 2007; Rushworth & Behrens, 2008). Having described this overall circuitry, we note that no one cortical area takes a decision on its own, for each of the areas involved in decision-making are connected by reciprocal forward and backward connections, so that neuronal activity in a number of areas can contribute to a final binary decision (Deco & Rolls, 2006; de Lafuente & Romo, 2006).

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Abbreviations

BOLD, blood oxygen level-dependent; fMRI, functional magnetic resonance imaging; GLM, general linear model; SMA, supplementary motor area.

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