

Task-Independent Functional Brain Activity Correlation with Skin Conductance Changes: An fMRI Study

James C. Patterson II,¹ Leslie G. Ungerleider, and Peter A. Bandettini

Laboratory of Brain and Cognition, National Institute of Mental Health, Bethesda, Maryland 20892

Received May 13, 2002

Lesions of the ventromedial prefrontal cortex cause a loss of skin conductance response (SCR) to stimuli with affective content and an inability to integrate information with social consequences into decisions. Previous behavioral studies using a gambling task were able to differentiate patients with lesions in this region from normal subjects. In the present imaging study, this region, among others, was shown to be “spontaneously” activated during three different cognitive states: a gambling task, a working memory task, and resting state. SCR data were simultaneously collected during the scanning process. Six subjects were scanned at 1.5 T during all three states, and one subject was scanned at 3 T during the resting state only. SCR data were used as a reference function for correlation analysis with the fMRI time series during each of the three tasks. SCR changes were evident during the gambling and two-back tasks as well as during rest. SCR activity was not observed to be specifically related to reward-based decisions in the gambling task. Correlation of the fMRI time series directly with the SCR data revealed a consistent set of activated regions. The activity of these regions showing correlation with the SCR appeared independent of the cognitive state. Further, the subject scanned only at rest (without the possible confound of task-related carryover activity) replicated the findings in the original six subjects. From these data, SCR appears to be a marker of a network that is active during, but independent of, the task being studied. © 2002 Elsevier Science (USA)

INTRODUCTION

In a typical functional magnetic resonance imaging (fMRI) experiment, using either a blocked or an event-related design, activations during two or more conditions are con-

trasted with each other and/or with a resting control state. In these instances, the reference function for correlation analysis is modeled *a priori* from the different conditions (e.g., finger tapping vs rest for a motor task) or from different components of a single condition (e.g., sample stimulus vs delay interval vs recognition test for a working memory task). Such an approach is constrained, however, by the exact conditions established in the design of the experiment, thereby limiting the type of hypothesis that can be made. In the present study, by contrast, the reference function for correlation analysis was modeled directly by a covert physiological response, namely, skin conductance. The specific hypothesis was that an increase in skin conductance would be temporally correlated with activation of a specific set of cortical and subcortical brain regions, independent of the particular task being performed. Accordingly, subjects were scanned during three different conditions, a gambling task, a working memory task, and a resting state, while skin conductance responses (SCRs) were continuously measured and then used in the subsequent correlation analysis. The SCR is derived from changes in resistance between two electrodes caused by changes in sweat production, driven by sympathetic nervous system activity (adapted from Bouscein, 1992). As illustrated in Fig. 1, the sympathetic system is controlled in large part by the hypothalamus as well as the brainstem. The hypothalamus receives its main cortical input from the ventromedial prefrontal cortex (PFC) (Ongur and Price, 2000) and its main subcortical input from the amygdala. The orbitofrontal cortex projects to both of these structures (Ongur and Price, 2000). The ventromedial PFC is a region that has been implicated in reward-based decision-making, as patients with lesions in this part of the brain are unable to choose advantageously, either on a gambling task or in real-life situations (Damasio *et al.*, 1990; Bechara *et al.*, 1994). Patients with these lesions also have severe deficits in producing SCRs in situations in which they are present in normal, control subjects (Bechara *et al.*, 1996).

Several previous imaging studies in normal subjects have examined the relationship between SCR and brain activity. In one recent fMRI study, brain activity associated with spontaneous fluctuations in SCR during performance of a reward-related gambling task (Critchley *et al.*, 2000) was found in right orbitofrontal and anterior insular cortices, left cerebellum, and visual cortices (left lingual and right fusi-

¹To whom correspondence and reprint requests should be addressed at the Biomedical Research Institute PET Imaging Center, Louisiana State University Health Sciences Center, 1505 Kings Highway, Shreveport, LA 71130. Fax: (318) 675-6148. E-mail: jpatte@lsuhsc.edu.

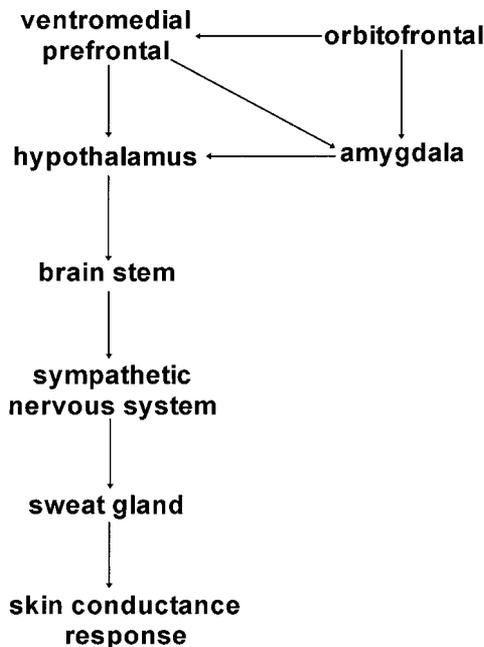


FIG. 1. Cerebral origins of the skin conductance response.

form gyri). At a less stringent level of significance, activity in ventromedial PFC and the right inferior parietal lobule also covaried with SCR. These findings thus suggest that areas associated with emotion and attention are also associated with expression of this peripheral autonomic response. Of note were the activations in ventromedial and orbitofrontal PFC, which are both part of the anatomical circuit thought to mediate generation of the SCR (Fig. 1). In another recent fMRI study, nonspecific SCR fluctuations were measured during the presentation of checkerboard patterns and trials were sorted depending on whether SCR greater than $0.05 \mu\text{S}$ were present (Williams *et al.*, 2000). It was hypothesized here that orienting to potentially significant events would produce increases in SCR and this would be reflected in greater cerebral activity in regions either causing the SCR change or being caused by the SCR change. Indeed, it was found that, on trials with significant SCRs, there was increased activity in ventromedial PFC, the subgenual anterior cingulate cortex, and the hippocampus. Activity also covaried with SCR in other areas, including, bilaterally, the visual cortices (lingual and fusiform gyri), the cerebellum, and the anterior temporal cortices. It therefore appears that even spontaneous fluctuations in the attentive state, which do or do not produce an orienting-associated SCR, covary with regionally specific brain activity. As in the first study described, activations in this study included the ventromedial PFC, the cerebellum, and the visual cortices.

Inasmuch as activity in similar brain regions correlated with the SCR in two very different experimental paradigms, we sought to determine in the present study the degree to which such correlations are task-independent. We therefore examined correlations of fMRI time series and SCR from the same subjects during a gambling task, during a two-back

working memory task, and during rest. The two-back working memory task was chosen because it has many of the same components as the gambling task, but lacks the reward-based decision-making component. Our analysis revealed SCR-related brain activity in consistent regions independent of the task being performed, and these correlations were maintained in the resting state.

METHODS

Subjects

Seven normal volunteer subjects (age 27 ± 6 , two females, all right handed) were scanned, six under three cognitive states (performing a gambling task, performing a two-back working memory task, and at rest) and one subject during the resting state only. Subjects were screened for medical and psychiatric illness, underwent a physical examination, and had normal structural MRI brain scans. All subjects gave written informed consent prior to scanning. The study was conducted under a protocol approved by the National Institute of Mental Health Institutional Review Board. Subjects received a small, standard monetary compensation for their time.

Task Design

One week prior to scanning, SCR changes were measured in all subjects to familiarize them with the equipment and to ensure that a typical physiological response was present (i.e., spontaneous SCR $> 0.05 \mu\text{S}$). Also prior to scanning, subjects were trained on the two-back working memory task until performance reached approximately 70–80% correct, and they were familiarized with the gambling task by performing 7–10 trials. Behavioral responses and functional data related to the tasks per se will be presented in a separate paper.

Gambling Task

This task was based on one originally designed to discriminate patients with lesions in the ventromedial PFC from normal controls (Bechara *et al.*, 1994). The subjects were given the following instructions:

Make believe you are playing a game. You will see four game tokens displayed on the screen. Each of these game tokens has both payoffs and penalties associated with it. I want you to choose one token at a time, by pressing the corresponding key, from any of the four tokens. Each time you choose one you will either win or lose some money. The money is shown as two dollar amounts on the screen (for example):

\$ 100
 \$\$ 1250

The top amount is how much you made or lost on the token you just chose. The bottom amount is a running total of how much money you have made (or lost). You start the game with \$500.00. You are free to choose from any of the four tokens you wish, and you can switch from one token to another any time you wish. The goal is to make as much money as possible. It is important to know that this is not random, and you can win by choosing the right token(s). You must wait for the tokens to flicker to choose one, this happens 1 s after they appear. We will

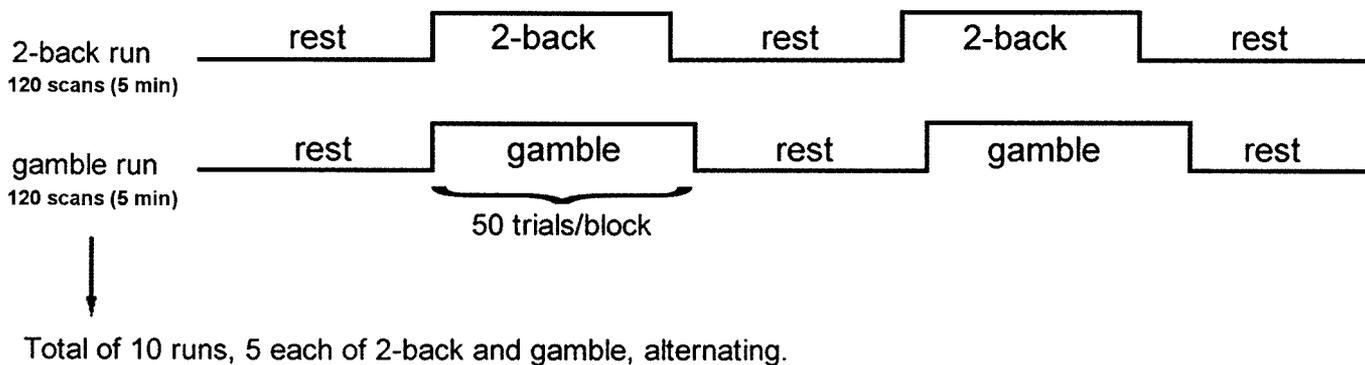


FIG. 2. Experiment design. The two-back runs were done in 1-min blocks, alternating with rest blocks of 1 min. The gambling runs were 50 trials per block and approximately 1 min. For each 5-min run, 120 scans were collected ($TR = 2.5$ s).

average the best two sessions, and if you win over \$1000.00 in play money, you get \$50.00 in real money as a bonus! Notify me when you are ready to begin, or if you have a question. Good luck!

On each trial, four game tokens were displayed on the screen for 1 s and then flickered, indicating that a choice should be made. The subject then picked one of the tokens by pressing a button on a button box. After the subject chose a token, feedback was given in the form of two numbers displayed on the screen. The top number was the amount won or lost on the just-chosen trial, and the bottom number was the payoff accumulated over time. The goal was to learn which two tokens make money in the long run to win the game. Unknown to the subjects, two tokens had large rewards but larger penalties, such that in the long run the subject would lose if chosen consistently. The other two game tokens had small rewards but even smaller penalties, such that in the long run the subject would win if these tokens were chosen consistently. The frequency of wins and losses in the four tokens varied and token valence changed from run to run in a pseudo-random fashion. Subjects had to make at least \$1000.00 on the average of the two best runs to win an additional \$50.00 in real money reward, in addition to the standard compensation. Subjects were not penalized for losing. Figure 2 illustrates the experimental design. There were 100 trials per 5-min run, with 50 trials per block in a rest-gamble-rest-gamble-rest design. As this paradigm required subject-determined timing of responses instead of a fixed response time, the gamble blocks varied slightly in length. The overall trial length was kept constant at 5 min by varying the length of the last rest period. There were five runs per experiment, and 120 scans were collected for each run ($TR = 2.5$ s). The first 5 scans were discarded to allow for longitudinal magnetization to reach steady state, leaving 115 scans for analysis.

Two-Back Working Memory Task

This task had many features in common with the gambling task, but lacked the reward-based decision-making component. The same four game tokens were used as in the gam-

bling task. The subjects were given the following instructions:

You will see four game tokens displayed on the screen. You will notice that the tokens begin blinking one at a time every couple of seconds. Your task is to keep track of the order that they blink in. When a token blinks, press the button that corresponds to the token that blinked two times back. The task keeps going automatically, so you have 2 s to respond. This will run for 60 s, and then you will have 60 s of rest. This entire session lasts 5 min.

The tokens were displayed for 2 s, and then one token, chosen at random, blinked off for 200 ms. The subject's task was to remember the order in which the tokens blinked and choose by button-press the token that blinked two times back. Like the gambling task, the two-back working memory task was run in the following order: rest-working memory-rest-working memory-rest. The two-back runs were interleaved with gambling runs for a total of 10 runs, 5 of each task.

Resting State

For both tasks, interleaving rest periods lasted for 1 min, and there were three such periods per run. Data from the rest periods during the gambling task were analyzed separately from data during the two-back working memory task, which enabled us to determine whether any differences existed between the resting states of the two cognitive tasks. During rest, subjects were shown a fixation cross on the screen and instructed to relax but remain still. To further focus on activity during rest, uncontaminated by possible task-related residual activity, one of the subjects was scanned only in the resting state; data were collected for a total of 30 min.

MRI Data Acquisition

Functional and structural MRI scans for the six subjects performing cognitive tasks were collected using a GE Signa 1.5-T scanner (GE Medical Systems, Milwaukee, WI). The seventh subject (rest only) was scanned at rest using a GE 3-T scanner. The subject's head and neck were stabilized

with foam padding within a brain-specific RF head coil (Medical Advances, Milwaukee, WI). An EPI pulse sequence was used to collect functional data with the following parameters: TR = 2.5 s, TE = 30 ms, FOV 24 cm, matrix 64×64 . The entire brain was covered in 20 or 21 slices collected in the sagittal plane, resulting in voxel dimensions of $3.75 \times 3.75 \times 7$ mm. In addition, a high-resolution fast 3D-SPGR structural T1-weighted image (TE = 6 ms, FOV 24 cm, $256 \times 256 \times 124$ voxels of $1.9 \times 1.9 \times 2$ mm) was collected as an anatomical reference image. Data collected from the 3-T MRI used parameters identical to those of the 1.5-T machine. Image data were reconstructed and ported to AFNI (Analysis of Functional Neuroimages) software format for processing and analysis (Cox, 1996).

Skin Conductance Data Acquisition

The skin conductance signal was recorded simultaneously with functional imaging. Standard fingertip AgCl leads were placed on the index and middle fingers of the left hand of each subject. The electrode leads were connected to a UFI Bioderm Model 2701 SC Recorder (UFI, Morro Bay, CA) outside the magnet room. Analog signals were recorded at 10 Hz, passed to an A-to-D converter, and collected via Slic-8000 software (UFI, Morro Bay, CA).

Data Processing and Analysis

fMRI Data

The processing and analysis of fMRI data were carried out in AFNI. Individual images were concatenated into a 3D+time image, and a linear detrending algorithm was applied to correct for linear drifts in the data. All images were realigned to the first image, and noncerebral voxels were removed from further analysis. A three-point linear temporal smoothing filter was then applied to the functional time series. After global image intensity correction, correlation analysis using AFNI was then carried out, as described below. The resulting functional data were spatially normalized to standardized stereotactic space (Talairach and Tournoux, 1980) and resampled to a $2 \times 2 \times 2$ -mm isotropic voxel size to facilitate across-subject comparison in the group analysis.

SCR Data

The SCR data were processed using a five-point moving average filter to remove high-frequency scanner-induced artifact. This was an alternating current SCR measurement device, obtaining the first derivative of the SCR. Actual skin conductance data were obtained by taking the integral of these data. A standard high-pass filter was used to take out low-frequency drift, to remove baseline changes in skin conductance level for evaluation of the SCR per se. This subtraction of baseline drift removed information regarding slow changes over time possibly related to alertness, but also removed artifactual signal drift changes related to temperature and possible changes in sweatiness due to temperature fluctuations. The SCR waveform was then resampled by interpolation to match the TR (2.5 s) used in the functional imaging data analysis. The waveform was also time-

shifted ± 1 TR (2.5 s) to account for hemodynamic variability across the brain. As the SCR "impulse response" is nearly identical in shape and latency to that of the hemodynamic impulse response (see Fig. 3), no convolution with a standard hemodynamic response waveform was necessary. Actual SCR time courses varied across subject and also depended on environmental conditions, such as room temperature. The temperature in the magnet room was controlled and set to 72°F. Lower temperatures are known to increase SC response time (Boucsein, 1992). The numbers of peaks above $0.05 \mu\text{S}$ (mean \pm SD), two-back, 25 ± 8 ; gamble, 25 ± 8 ; two-back rest, 20 ± 6 ; and gamble rest, 20 ± 8 . There was no significant difference between the numbers of peaks in the different task conditions.

Correlation Analysis and Conjunction Map

The correlation between the fMRI time series data and the simultaneously collected SCR time series data was calculated on a voxel-wise basis. We evaluated the data using signals segmented to represent only a given component of the task (e.g., SCR during two-back), as well as continuous SCR throughout the experiment (e.g., SCR during two-back and during rest). As the fMRI time series consisted of alternating blocks of task and rest, the correlation analysis for a given cognitive state was carried out on only those blocks of the image and SCR time series collected during that state. In addition, the first 15 s of data from each block was ignored to prevent confounding the analysis with transitional changes in activity from state to state, as well as to exclude possible orienting SCR changes due to the transition. The resulting r statistic from the correlation was converted to a Z score and a 3-mm spatial filter was applied to account for differences across subjects in anatomical variability prior to across-subject averaging. Data from the six subjects performing the cognitive tasks were averaged to produce a group image. These group Z maps were thresholded at a Z of 3 ($P = 0.0027$) and cluster size equivalent to three (original, nonresampled) voxels. This threshold was determined by Monte Carlo simulation (AlphaSim component of AFNI) of possible significance thresholds based on both intensity and the spatial extent of any given region with the smoothing level used. Group Z score maps were created that evaluated brain regions with activity that correlated with SCR for each of four conditions: gambling task, rest periods during the gambling task, two-back working memory task, and rest periods during the two-back working memory task.

In order to evaluate which regions from the maps generated for the four conditions (described above) had similar areas of activation conjunction analysis was carried out. To perform this, a binary mask was made of each processed map created with the aforementioned threshold ($Z = 3$, $P = 0.0027$). The four masked images were then summed. Prior to mask creation and summation, each map was further spatially smoothed with a 3-mm isotropic kernel to produce more homogeneous regions of activity within the individual binary masks. Regions with a score of 3 or 4 represent those regions in which three or four of the individual maps had overlapping activations.

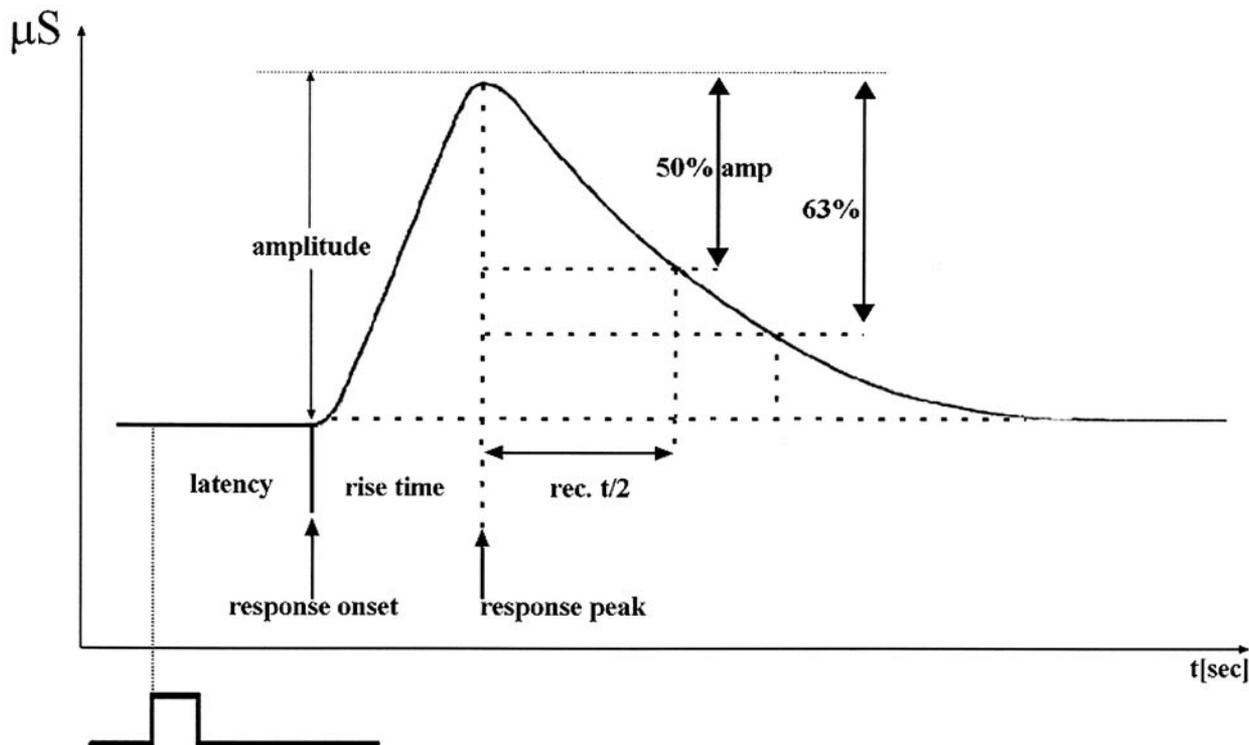


FIG. 3. Standardized SCR curve. This curve displays the various components of the SCR curve. Both latency and rise time are approximately 1 to 3 s in length. The hemodynamic response function is virtually identical to this curve (from Boucsein, 1992, reproduced with permission).

RESULTS

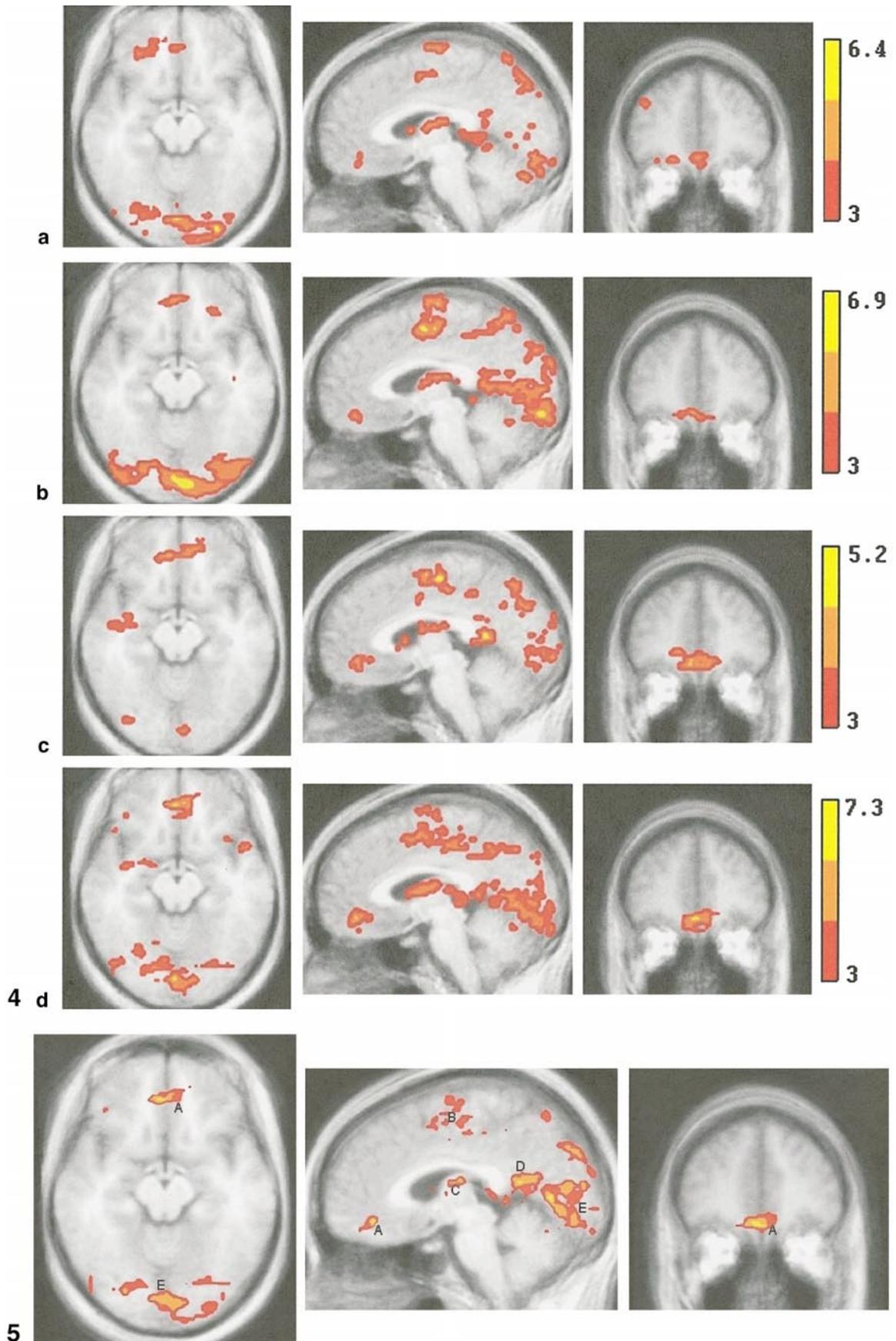
Brain activity correlated with the SCR response is shown for the four conditions analyzed (during the gambling task, rest during gambling, during the two-back working memory task, and rest during working memory) in Fig. 4. Activations are displayed for the six subjects scanned at 1.5 T on three representative orthogonal slices from a structural group map. The results show, first, that changes in SCR were present during all three cognitive states. Second, activity in a specific group of regions was consistently correlated with changes in SCR during all three states. This network included the ventromedial PFC, posterior cingulate cortex, right anterior superior temporal cortex, bilateral inferior parietal cortex, supplementary motor cortex, cingulate cortex adjacent to the supplementary motor area, bilateral cerebellum, and thalamus. In addition, several bilateral visual cortical areas as well as left primary motor cortex had activations that correlated with SCR across cognitive states. The conjunction map, illustrated in Fig. 5, gives a better appreciation of the degree of overlap in SCR-correlated activity among the different cognitive states. The regions that were found to be consistently present in three or four of the cognitive states (including the two resting states) are presented in Table 1, along with their coordinates.

To further focus on a rest condition uncontaminated by possible task-related activity, a single subject was scanned at rest for a total of only 30 min. This subject did not perform either the working memory task or the gambling task. The

results of the correlation analysis of brain activity with simultaneously collected spontaneous SCR changes are shown in Fig. 6. The pattern of activity is nearly identical to those seen during cognitive activations.

In addition to the regions listed above, there were others that had activation correlated with SCR. However, these regions did not pass the threshold for group significance due to the small magnitude of the signal or inconsistent locations of activation. Striatal activity was commonly seen ($n = 5$), mainly in ventral parts of the caudate nucleus and/or putamen. The midbrain was also active ($n = 4$) (see single-subject data in Fig. 6). A region or regions bordering the extreme lateral orbitofrontal cortex and the anterior insula was consistently present in all subjects either unilaterally or bilaterally, but was stronger on the right. This activation was often found in conjunction with an anterior superior temporal polar region of activity.

Finally, there were also several regions in which the activity correlated with SCR appeared to be specific for a given task or specific during rest. For example, during the working memory task, we found bilateral temporal polar activation [left, ($x = -27, y = 0, z = -35$), $Z = 5.16, P = 2.4 \times 10^{-7}$; right, ($x = +29, y = +6, z = -32$), $Z = 4.30, P = 1.7 \times 10^{-5}$] that was also significantly present during rest periods of the two-back working memory task. These areas were not active during the gambling task, during the rest period of the gambling task, or in the single subject scanned only at rest. Additionally, there were changes in orbitofrontal activity



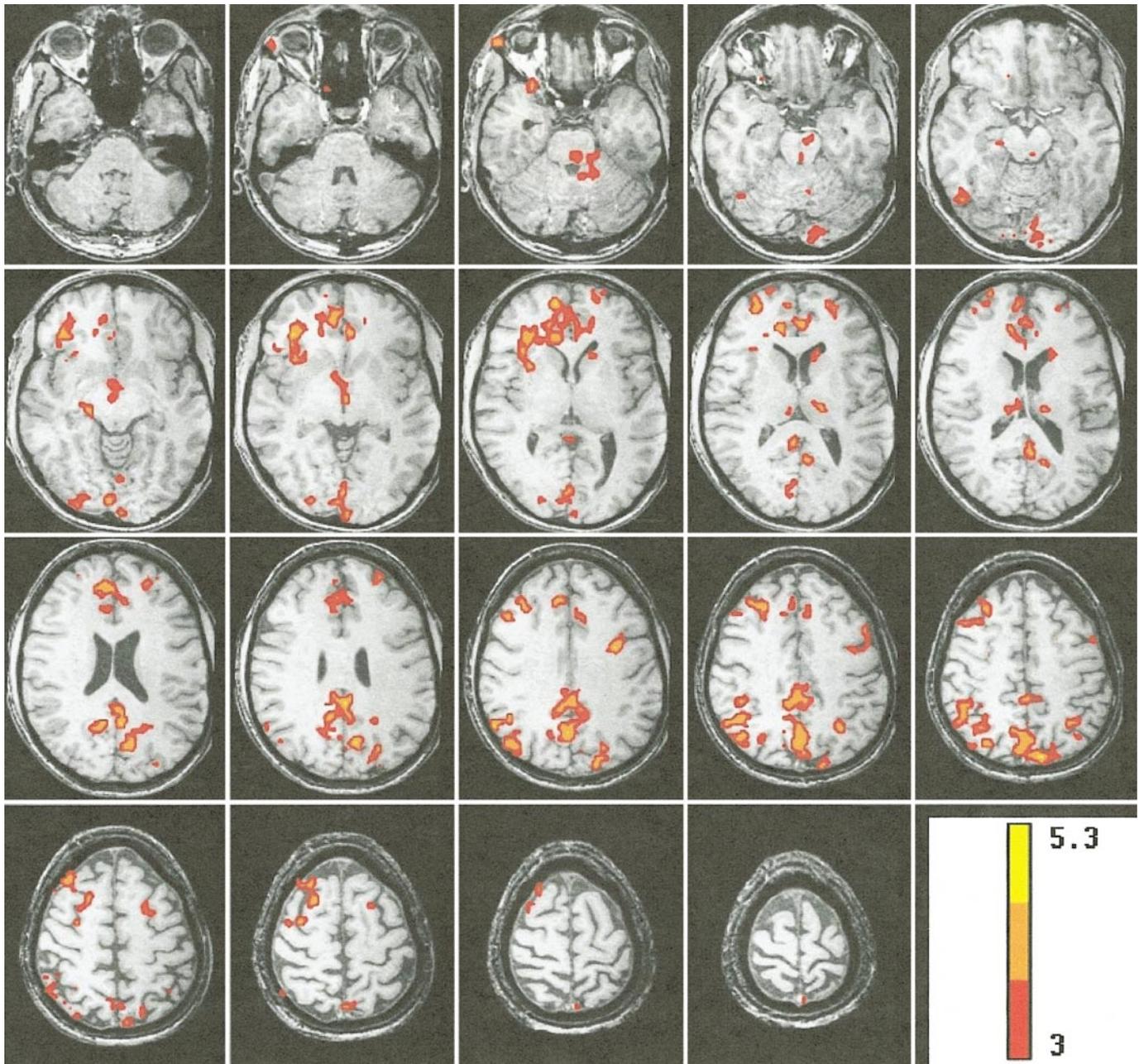


FIG. 6. Single subject at rest. Regions of activity that correlated with SCR in a single subject during the resting state. From top to bottom is shown a series of axial images from the cerebellum to the apex. The Z scores are represented by the color scale to the right.

that were task-specific. In both cognitive activation tasks, only the right orbitofrontal cortex was significantly activated. During the resting state of both tasks, however, either the

left orbitofrontal cortex [rest during gambling task: ($x = -24$, $y = +33$, $z = -9$), $Z = 4.62$, $P = 3.7 \times 10^{-6}$] or bilateral orbitofrontal cortex [rest during working memory task: left,

FIG. 4. Regions of activity induced by the SC response. (a) Gambling task, (b) rest during gambling, (c) working memory, (d) rest during working memory. From left to right are shown axial, sagittal, and coronal sections from an averaged anatomical image at slices $z = -10$ mm, $x = -4$ mm, and $y = 40$ mm, respectively. The Z scores of the activated regions are given in the color scales shown to the right.

FIG. 5. SCR conjunction map. Regions of activity that overlap from at least two of the four conditions shown in Fig. 3 are depicted. Slice orientation and location are the same as in Fig. 3. Red, orange, and yellow represent two, three, and four conditions overlapping, respectively. Regions with at least three conditions overlapping are shown in Table 1. A, ventromedial prefrontal cortex; B, cingulomotor region; C, thalamus; D, posterior cingulate; E, occipital cortex.

TABLE 1

Regions with Three or Four Conditions That Overlapped from the Conjunction Analysis

Location		Coordinates			Z score			
Region	BA	x	y	z	Gamb	G-rest	2-back	2bk-rest
VMPFC	10/32	3	39	-10	4.06	4.48	4.66	6.37
R sup temp	22	55	3	5	—	5.12	4.36	6.05
L parietal	40	-56	-20	14	3.88	5.27	3.99	5.65
R parietal	40	61	-26	25	—	5.43	3.74	5.38
Supp motor	6	-2	-7	66	4.36	4.87	—	4.89
Cingulomotor	6/24	-3	-8	48	4	6.63	5.12	5.95
L motor	4	-37	-21	58	—	5.11	4.25	6.21
Postcingulate	23/30	3	-49	13	4.88	5.08	5.02	3.99
Visual	17	1	-68	4	5.15	5.45	4.53	7.29
Visual	18	-5	-85	-10	5.25	6.89	5.06	6.31
Thalamus	—	-3	-7	9	5.18	3.82	3.47	6.16
R cerebellum	—	28	-58	-21	4.93	6.11	3.76	4.28
L cerebellum	—	-45	-58	-22	5.27	5.96	—	5.02

Note. Z scores and locations of regions of activity that were significantly correlated with the SCR from each cognitive state are presented. Regions within 5 mm of midline were bilateral and are thus not given a side designation; however, the coordinates of the most significant voxel in the cluster are shown. BA, Brodmann's area; Gamb, gambling task; G-rest, resting state during the gambling task; 2-back, working memory task; 2bk-rest, resting state during the working memory task; VMPFC, ventromedial prefrontal cortex; R sup temp, right superior temporal; Supp motor, supplementary motor.

($x = -40$, $y = +25$, $z = -6$), $Z = 4.90$, $P = 9.4 \times 10^{-7}$; right, ($x = +28$, $y = +30$, $z = -6$), $Z = 4.08$, $P = 4.5 \times 10^{-5}$] was activated.

DISCUSSION

In the present study, we found that brain activity correlated with changes in the skin conductance response. In this analysis, we found a consistent group of regions activated independent of cognitive state, most consistently the ventromedial PFC (BA 10/32), left inferior parietal cortex (supramarginal gyrus, BA 40), cingulomotor cortex (BA 6/24), posterior cingulate cortex (BA 23/30), early visual areas (right calcarine sulcus and left lingual gyrus, BA 17, 18), right cerebellum, and thalamus. Although other imaging studies have also recently reported regionally specific activations that correlate with SCR (see below), our findings demonstrate that the effect is a robust one which transcends the specific task requirements and is present even during the resting state.

The correlation of ventromedial PFC activity with SCR has been found previously in imaging studies and is consistent with the anatomical connections of this area with the hypothalamus, the main nexus of control of the sympathetic nervous system (Bouscein, 1992). Moreover, it was predicted from the results of patients with lesions of the ventromedial PFC, who fail to show a normal SCR (Bechara *et al.*, 1994, 1996). Damasio's somatic marker hypothesis postulates that the ventromedial PFC is involved in evaluating current or contingent activity based on previous accounts (Damasio, 1996). The somatic state elicited by memories of the previous behavior is recalled and used to weigh current decision-making processes. According to Damasio, the somatic state is related to both skeletomotor and visceromotor (autonomic) responses; SCR changes would fall under the latter category.

We had expected that other regions anatomically implicated in generation of the SCR would also show correlations between their activity and SCR changes. In particular, significant correlations were anticipated in orbitofrontal cortex and the amygdala, based on both their anatomical connections with the ventromedial PFC (Fig. 1) and previous reports of their involvement with positive and/or negative reward processing (Breiter and Rosen, 1999; O'Doherty *et al.*, 2000). Although activity in the orbitofrontal cortex did correlate with SCR, the pattern seemed to differ depending on the specific task; whereas the right orbitofrontal cortex was active during both the gambling and the working memory tasks, during the resting state only left or bilateral activations were found. On the other hand, amygdala activity was totally absent in all but one subject. There are several explanations for this finding. First, many studies that have found amygdala activation have used aversive tasks. Thus, because there was no real penalty for losing (in either the gambling or working memory task), our experiment may not have engaged the amygdala. Another explanation is that, because activity in the amygdala to repeated visual stimuli habituates rapidly, our continuous SCR measurements may not have been the optimal way to pull out signal in this structure (Breiter *et al.*, 1996). In addition, lesion data have shown that SCRs generated directly following reward or punishment during a gambling task are susceptible to damage to the amygdala (Bechara *et al.*, 1999). However, it has also been found that SCRs produced in anticipation of reward or punishment are equally vulnerable to damage of the ventromedial prefrontal and medial orbitofrontal cortex. It therefore seems likely that there are at least two types of SCRs: anticipatory and reactive. As our design looked at a block of activity during the gambling task that combines both types of SCRs, we were unable to discriminate between the two types. By combining both reactive and anticipatory SCRs, we may

have weakened the expected effect in the amygdala and thus failed to detect strong correlated activity in this region. Finally, it is possible that the failure to detect correlated activity in the amygdala is due to signal dropout as a result of susceptibility artifact. A recent report found a high level of variability in signal in this area, and results from a cognitive task shown to activate the amygdala correlated with this variance (LaBar *et al.*, 2001).

One of the largest correlations between activity and SCR was found in the visual cortex, specifically in early visual areas (likely, V1 and V2). A probable explanation for this result is modulation of arousal, both during task performance and spontaneously during rest. Two prior imaging studies (Lane *et al.*, 1997; Lang *et al.*, 1996), one PET and one fMRI, reported increased visual activity with viewing affect-laden pictures, compared to neutral images, and this activity correlated with arousal as measured by SCR. Moreover, in imaging studies in which correlations between SCR and brain activity were measured directly, significant correlations were found in visual cortex; one used a gambling task (Critchley *et al.*, 2000), but the other simply had subjects passively view checkerboard patterns (Williams *et al.*, 2000). The latter study concluded that spontaneous fluctuations in orienting lead to increased neural signals, and we think that fluctuations in orienting or alertness could equally apply to our findings. Indeed, one study has previously demonstrated that enhanced signals in visual cortex as early as V1 are likely due to spontaneous increases in attention (Ress *et al.*, 2000).

Other consistent correlations between activity and SCR were found in the mid- and posterior cingulate regions. Both of these areas have been reported to coactivate with the ventromedial PFC and orbitofrontal cortex, especially in other reports of SCR activity (Fredrickson *et al.*, 1998; Critchley *et al.*, 2000). Increased activity in the posterior cingulate area (Binder *et al.*, 1999; Shulman *et al.*, 1997) has also been found in studies examining the resting state. The thalamus activity is best understood as being associated with a network of regions active during the generation of the SCR (Ongur and Price, 2000).

In addition to task-independent correlations, we had anticipated that some structures would show correlated activity with the SCR that was task-specific. In particular, because of the reward-based decision-making processes in our gambling task, we expected such correlated activity in the nucleus accumbens. Although this structure is thought to be central to reward processing, especially for pleasurable rewards and for addictive craving (Knutson *et al.*, 2001; Drevets *et al.*, 2001), we failed to observe activity here.

The primary intent of our study was to identify the network of brain areas showing activity that was temporally correlated with simultaneously measured SCR and to determine whether these correlations are task independent. We feel that it is difficult to conclusively extract causality from these correlations (i.e., regions generating the SCR vs regions being activated by feedback from the periphery), given the 4-s spread in hemodynamic latencies and the uncertain time scale during which the feedback response occurs. Interestingly, Critchley *et al.* (2000) reported that, for a gambling

task, event-related activity that preceded SCR peaks by about 4 s occurred in the cerebellum, extrastriate visual cortex, and left medial PRC, which was interpreted to be associated with generation of the SCR; by contrast, event-related activity about 4 s after SCR peaks occurred in right medial prefrontal cortex, which was interpreted to be caused by feedback from the periphery (SCR-induced brain activity). These conclusions were based on time-shifting the reference waveform by approximately 4 s. By comparison, our results demonstrated those regions showing the best correlation on a voxel-wise basis in the range of ± 2 s. Importantly, our study shows regions of activation similar to those identified by Critchley *et al.* in their combined "nonlagged" and "lagged" analyses.

CONCLUSION AND IMPLICATIONS

The present results provide evidence that there are specific regions of the brain whose activity correlates with changes in the SCR. Furthermore it appears that this activity is not specific to the task being examined and even occurs spontaneously during "rest." Thus, SCR-related activity appears to be independent of the cognitive state, but dependent upon a consistent underlying process that is active even during the resting state. From an fMRI methodology development perspective, this analysis represents a new class of method for information extraction from fMRI time series. The use of simultaneously obtained behavioral/physiologic information, indicative of moment-to-moment changes of mental state, as regressors for time series analysis offers greater flexibility and power in paradigm design and perhaps an avenue to enhanced interpretation of fMRI data.

ACKNOWLEDGMENTS

This work was supported by NIMH-IRP. Data from this publication were published in abstract form at the Organization for Human Brain Mapping 2000 Meeting (Patterson *et al.*, 2000). We thank Drs. Michael Beauchamp, John Van Horn, Rasmus Birn, and Patrick Bellgowan for their valuable assistance in this study.

REFERENCES

- Bechara, A., Damasio, A. R., Damasio, H., and Anderson, S. W. 1994. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50**: 7-15.
- Bechara, A., Tranel, D., Damasio, H., and Damasio, A. R. 1996. Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cereb. Cortex* **6**: 215-225.
- Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Rao, S. M., and Cox, R. W. 1999. Conceptual processing during the conscious resting state: A functional MRI study. *J. Cognit. Neurosci.* **11**: 80-93.
- Boucsein, W. 1992. *Electrodermal Activity*. Kluwer Academic, Dordrecht/Norwell, MA.
- Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., Strauss, M. M., Hyman, S. E., and Rosen, B. R. 1996. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* **17**: 875-877.

- Breiter, H. C., and Rosen, B. R. 1999. Functional magnetic resonance imaging of brain reward circuitry in the human. *Ann. N. Y. Acad. Sci.* **877**: 523–547.
- Cox, R. W. 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* **29**: 162–173.
- Critchley, H. D., Elliott, R., Mathias, C. J., and Dolan R. J. 2000. Neural activity relating to generation and representation of galvanic skin conductance responses: A functional magnetic resonance imaging study. *J. Neurosci.* **20**: 3033–3040.
- Damasio, A. R. 1996. The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos. Trans. R. Soc. London B* **351**: 1413–1420.
- Damasio, A. R., Tranel, D., and Damasio, H. 1990. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav. Brain Res.* **41**: 81–94.
- Drevets, W. C., Gautier, C., Price, J. C., Kupfer, D. J., Kinahan, P. E., Grace, A. A., Price, J. A., and Mathis, C. A. 2001. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol. Psychiatry* **49**: 81–96.
- Fredrikson, M., Furmark, T., Olsson, M. T., Fischer, H., Andersson, J., and Langstrom, B. 1998. Functional neuroanatomical correlates of electrodermal activity: A positron emission tomographic study. *Psychophysiology* **35**: 179–185.
- Knutson, B., Adams, C. M., Fong, G. W., and Hommer, D. 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J. Neurosci.* **21**: 1–5.
- LaBar, K. S., Gitelman, D. R., Mesulam, M. M., and Parrish, T. B. 2001. Impact of signal-to-noise on functional MRI of the amygdala during emotional picture encoding. *NeuroReport* **12**: 3461–3464.
- Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., and Schwartz, G. E. 1997. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* **35**: 1437–1444.
- Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., and Nangia, V. 1998. Emotional arousal and activation of the visual cortex: An fMRI analysis. *Psychophysiology* **35**: 199–210.
- O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., and Andrews, C. 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat. Neurosci.* **4**: 95–102.
- Ongur, D., and Price, J. L. 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys, and humans. *Cereb. Cortex* **10**: 206–219.
- Patterson, J., Bandettini, P., and Ungerleider, L. 2000. Simultaneous skin conductance measurement and fMRI during cognitive tasks: Correlations of skin conductance activity with ventromedial prefrontal cortex (PFC) and orbitofrontal cortex (OFC) activity. *NeuroImage* **11**: S235.
- Ress, D., Backus, B. T., and Heeger, D. J. 2000. Activity in primary visual cortex predicts performance in a visual detection task. *Nat. Neurosci.* **3**: 940–945.
- Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., and Petersen, S. E. 1997. Common blood flow changes across visual tasks. II. Decreases in cerebral cortex. *J. Cognit. Neurosci.* **9**: 648–663.
- Talairach, J., and Tournoux, P. 1980. *Co-planar Stereotactic Atlas of the Human Brain*. Thieme, Stuttgart.
- Williams, L. M., et al. 2000. The neural correlates of orienting: An integration of fMRI and skin conductance orienting. *NeuroReport* **11**: 3011–3015.