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Activity in ventromedial prefrontal cortex covaries with sympathetic skin conductance level: a physiological account of a "default mode" of brain function

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We examined neural activity related to modulation of skin conductance level (SCL), an index of sympathetic tone, using functional magnetic resonance imaging (fMRI) while subjects performed biofeedback arousal and relaxation tasks. Neural activity within the ventromedial prefrontal cortex (VMPFC) and the orbitofrontal cortex (OFC) covaried with skin conductance level (SCL), irrespective of task. Activity within striate and extrastriate cortices, anterior cingulate and insular cortices, thalamus, hypothalamus and lateral regions of prefrontal cortex reflected the rate of change in electrodermal activity, highlighting areas supporting transient skin conductance responses (SCRs). Successful performance of either biofeedback task (where SCL changed in the intended direction) was associated with enhanced activity in mid-OFC. The findings point to a dissociation between neural systems controlling basal sympathetic tone (SCL) and transient skin conductance responses (SCRs). The level of activity in VMPFC has been related to a default mode of brain function and our findings provide a physiological account of this state, indicating that activity within VMPFC and OFC reflects a dynamic between exteroceptive and interoceptive deployment of attention.

Keywords: Skin conductance; fMRI; Biofeedback

Introduction

Skin conductance indexes covert modulation of bodily states of arousal during emotional, cognitive and physical behaviour, expressed in the activity of sympathetic cholinergic neurons at the level of eccrine dermal sweat glands (Venables and Christie, 1980). Skin conductance level (SCL) and responses (SCRs) are sensitive measures of tonic and transient modulation of sympathetic arousal responses, respectively. The SCL, reflecting overall degree of arousal, decreases with physiological relaxation such as rest and sleep (Malmo, 1959). The SCR is widely used in experimental psychological studies as an objective measure of conscious and unconscious emotional processing and attention (Damasio, 1994; Frith and Allen, 1998; Ohman and Soares, 1994; Sores and Ohman, 1993). Indeed, the generation, representation and subjective awareness of autonomic change in bodily arousal are proposed to be fundamental components of emotion and feeling states (Damasio, 1994; Dolan, 2002; James, 1983; Schachter and Singer, 1962). Moreover, autonomic arousal is associated with enhanced memory consolidation and is proposed to influence decision-making and motivational behavior (Bechara et al., 1997; Cahill and McGaugh, 1998; Damasio, 1994).

Brain mechanisms controlling states of sympathetic arousal, particularly skin conductance, are relatively under-explored. Animal experiments indicate that thermoregulatory pathways originating in hypothalamus descend ipsilaterally via pons, medulla and mediolateral spinal cord to preganglionic sympathetic efferents that relay in paravertebral sympathetic ganglia. Unmyelinated postganglionic efferents innervate sweat glands and provide an anatomical substrate for sweat gland control reflected in changes in skin conductance (Boucsein, 1992; Wang, 1964). Animal and human experiments demonstrate descending cortical and subcortical influences on hypothalamic and brainstem mechanisms controlling sympathetic arousal. In particular, the amygdala exerts an influence on autonomic responses including skin conductance activity (Asahina et al., 2003; LeDoux, 1996; Phelps et al., 2001; Williams et al., 2001). Lesion and electrical stimulation studies also implicate specific brain regions, including orbitofrontal (OFC), cingulate and insular cortices in generating changes in peripheral autonomic measures (Cechetto and Saper, 1990).

Among cortical regions, OFC and ventromedial prefrontal cortex (VMPFC) are implicated in generation and feedback representation of sympathetic arousal, indexed by skin conductance, in the context of social, emotional and motivational behaviors (Damasio, 1994). Damage to these areas diminishes generation of SCRs (Bechara et al., 1999; Tranel and Damasio, 1994), but also impair behaviors influenced by feedback representation of states of bodily arousal (Bechara et al., 2000; Damasio, 1994). Such observations underpin a theory of emotion and motivation that assigns a crucial role to OFC and VMPFC in the generation of "somatic markers" that guide adaptive behavior (Damasio, 1994).

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Recently, the role of VMPFC has been discussed in the context of a default mode of brain function (Raichle et al., 2001). Activity in VMPFC is prominent when individuals are in a restful, but mentally alert, state (Raichle et al., 2001). Interestingly, neurons in this region have been described that become more active during low arousal states such as rest and sleep (Rolls et al., 2003). Deactivation in VMPFC is observed during cognitive tasks which demand focused attention (Gusnard et al., 2001; Raichle et al., 2001). Interestingly, the magnitude of deactivation is influenced by the degree of task engagement and is attenuated by emotional modulation, for example, induced anxiety (Simpson et al., 2001a,b).

Recent functional imaging data report neural activity associated with changes in sympathetic arousal, indexed by skin conductance responses (SCRs) and induced using psychological stimulation (Critchley et al., 2000; Fredrikson et al., 1998; Patterson et al., 2002; Williams et al., 2001). Regions including cingulate, insula, right inferior parietal cortex and VMPFC are associated with generation of transient SCRs during tasks inducing emotion-related arousal. Amygdala and medial prefrontal activation is also reported in association with SCRs evoked by processing fear and threat stimuli (Buchel et al., 1998; Phelps et al., 2001; Williams et al., 2001).

The aforementioned studies focus on transient changes (SCRs) rather than basal tonic skin conductance level (SCL). One difficulty in interpreting SCR-related brain activity in the above studies is that, in many cases, the experimental paradigm does not permit secondarily induced SCR-related neural activity to be dissociated from activity related to psychological stimulus processing. Biofeedback paradigms using skin conductance provide one means of addressing these concerns by examining brain activity associated with directed volitional modulation of tonic sympathetic activity. Critchley et al. (2001, 2002) investigated brain activity related to biofeedback relaxation using PET and functional magnetic resonance imaging (fMRI), where anterior cingulate cortex was identified as crucial to integration of feedback regarding tonic states of arousal, indicating a role in cognitive and perceptual aspects of biofeedback task performance.

In the current study, we examined neural activity associated with performance of biofeedback relaxation (where the intention is to decrease tonic SCL) and biofeedback arousal (where the intention is to increase tonic SCL) tasks. We used the continuous measure of each subject's own skin conductance activity to investigate if the same or different brain regions mediate decreases and increases in overall sympathetic tone during volitional modulation of peripheral arousal. Importantly, we examined changes in tonic SCL independently of transient changes in skin conductance (typically SCRs), by modeling skin conductance activity and the temporal derivative of skin conductance activity together within the same design matrix. The temporal derivative is the rate of change in skin conductance, and captures rapid phasic changes in activity (i.e. skin conductance responses, or SCRs) while minimally reflecting low frequency drifts in signal (SCL). Thus, this within-subject approach allowed us to distinguish the functional neuroanatomy underlying changes in SCL and SCR in a manner that is unbiased by between subject differences in overall electrodermal activity or task performance. Clarifying brain mechanisms responsible for tonic and phasic changes in sympathetic bodily arousal is of great importance to psychophysiological science and for interpretation of neuroimaging studies reporting differences in regional brain activity that may be associated with changes in bodily arousal state.

Methods

Subjects

Eight healthy volunteers (five males, three females; mean age in years ± SD, 32 ± 4) gave fully informed consent to take part in the study which was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

Task and experimental design

Subjects were scanned using fMRI on two occasions while performing biofeedback tasks. In one session, they performed a biofeedback relaxation task and in the other session they performed a biofeedback arousal task. Both sessions were 6 min in duration and were undertaken in a counterbalanced order across subjects. No other control tasks were performed since all our analyses examined within-subject and within-session covariation of regional brain activity with skin conductance changes in the contexts of the two task types. Biofeedback, that is, receiving feedback of one's own physiological responses, enables one to influence and control covert bodily processes such as states of autonomic arousal. This skill can be learned in principle after only few minutes of practice, although overall performance ability may vary markedly across subjects. All eight subjects, who were initially naïve to biofeedback techniques, were familiarized with the tasks, but not overtrained, so that task performance achieved the intended direction of sympathetic SCL modulation but nevertheless embodied periods of success and failure. Skin conductance activity (i.e. both SCL and SCR) was continuously recorded (using SCL200 apparatus, Biofeedback Systems, Manchester) via silver electrodes from the palmar surface of the left hand and contact facilitated with KCl electrolyte gel. Subject safety during physiological monitoring was ensured by optical isolation intrinsic to the battery powered SCL200 apparatus, which was in the scanner room. The analogue

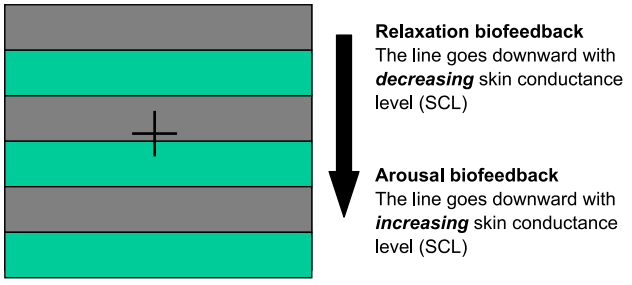

Fig. 1. Experimental task paradigm. Subjects were scanned when performing biofeedback arousal and biofeedback relaxation tasks. Skin conductance activity (SCL and SCR) was measured from the palmar surface of the left hand. Biofeedback of electrodermal activity was achieved using a visual display of horizontal lines, updated at 8 Hz. These lines moved downwards to reflect changes in skin conductance in the direction intended by the task. Thus, during periods of successful biofeedback relaxation performance, the horizontal lines would move downward, driven by decreasing skin conductance. Similarly, during periods of successful biofeedback arousal, the lines would move downward at the rate of skin conductance increases. The lines remained static if there was no change in skin conductance, or if skin conductance increased during the relaxation task or decreased during arousal task performance.

output was relayed from the scanner room via radiofrequency (RF) filters to prevent contamination of acquired fMRI data by extrinsic RF interference. The skin conductance voltage signal (linearly proportional to true skin conductance value in microsiemens) was then relayed via an analogue-to-digital converter (CED 1401, CED, Cambridge) to a computer which controlled the biofeedback program. Low-pass filtering of the skin conductance signal (sympathetic neural activity operates at frequencies below 0.15 Hz) was used to remove high-frequency scanner RF noise. The visual biofeedback presented to the subject was derived directly from this filtered trace.

In both biofeedback relaxation and biofeedback arousal tasks, the visual appearance of the feedback was identical, consisting of horizontal lines and a central fixation cross projected onto a screen visible by the subject in the scanner. The horizontal lines moved downwards across the screen if skin conductance followed the intended direction of the biofeedback task session (i.e. decreasing skin conductance in the relaxation task and increasing for the arousal task) (Fig. 1). The visual presentation remained static if skin conductance did not change in the intended direction (e.g. increased during the relaxation task). Visual feedback was continuously updated at 8 Hz and measures of both visual feedback and skin conductance activity were recorded (logged) at 8 Hz, simultaneously with fMRI scan timings. Because our analyses addressed brain activity covarying with skin conductance within subject, there was no formal baseline period before scanning. In the biofeedback relaxation task, subjects were instructed to attempt to move the visual display (horizontal lines) in a downward direction by relaxing their mind and body. A brief practice session allowed all subjects to become familiar with the relationship between their level of mental and physical tension and relaxation feedback. In the biofeedback arousal session, similar instructions were given. Subjects were instructed to attempt to move the visual display (horizontal lines) in a downward direction, but this time by maintaining mental alertness with the intention of blocking their relaxation. They were explicitly discouraged from using muscle tension as a means of performing the arousal task, as we were concerned about movement as a possible confound. Again, a brief practice session allowed subjects to become familiar with the relationship between their level of mental tension and relaxation feedback. In both cases, we intended that cognitive, rather than respiratory or skeletomuscular, processes to govern how the tasks were performed. However, we did not explicitly train subjects or offer them further practical guidance, other than that described above. We debriefed each subject to establish what processes were used in performing each biofeedback task.

fMRI data acquisition

Data was acquired with a 2-T Siemens Magnetom VISION scanner using T2* echoplanar imaging weighted for blood oxygenation level-dependent (BOLD) contrast (32 slices, flip angle 90°, echo time (TE) 40 ms, TR, 2.4 s, 106 acquisitions/session), and fMRI data were reconstructed using trajectory-based reconstruction (Josephs et al., 2000). During data acquisition subjects were placed in the scanner with their head fixed to avoid head movement. The first six scans were discarded to allow for T1 equilibration effects. Following acquisition of functional scans, a T1-weighted MPRAGE structural sequence (TR/TE = 11 ms/4 ms, TI/TD = 1 s/0.5 s, flip angle 12°, 176 sagittal slices) (Deichmann et al., 2000) was acquired for each subject to screen for significant anatomical variation and enable co-registration with individual functional data sets.

fMRI data analysis

Data preprocessing and subsequent analyses were conducted using SPM99(02a) on Matlab 6.1 platform (Mathworks Inc., Natick, MA). Standard methodology was applied for realignment, normalization and smoothing (12-mm full-width half maximum Gaussian kernel) of functional data sets for each session. Continuous regressors of skin conductance (SCL) and the derivative of skin conductance (dSC, reflecting acute changes in skin conductance, capturing SCR-related activity) were constructed per session and resampled (interpolated from 8 to 0.4 Hz) at the midpoint of each scan time, modeling synchronous time courses for skin conductance change and blood oxygenation level-dependent hemodynamic responses (Patterson et al., 2002). Absolute values for physiological regressors did not affect the analysis of brain activity, which related only to within-session correlations with changes in

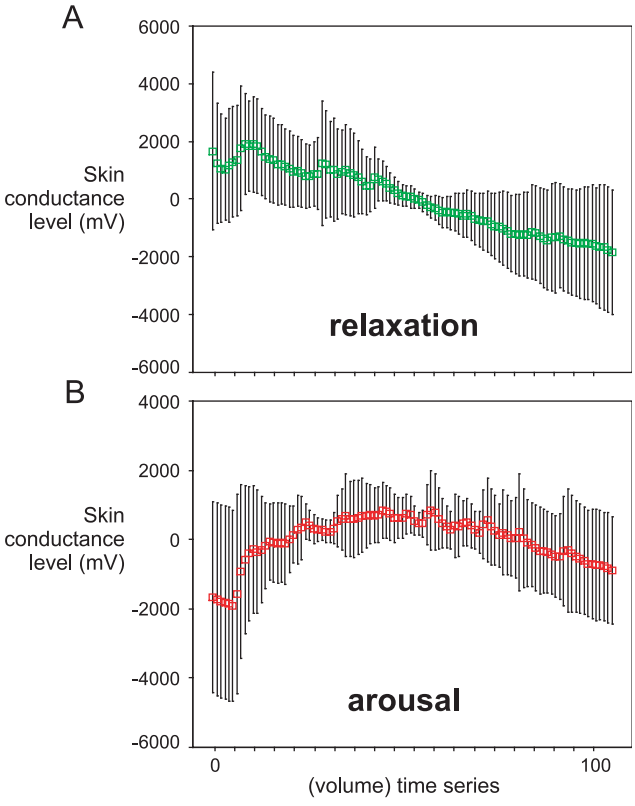

Fig. 2. Averaged task performance data. The figure plots group data showing the average changes in skin conductance (±SD) over the course of the relaxation and arousal biofeedback tasks. The *x*-axis represents the number of scans acquired in the experimental session (i.e. time) and the *y*-axis shows mean-corrected skin conductance level (mV). Different starting points of each graph reflect only our mean correction of each subject's data. Across subjects, the overall intention of the tasks was met, with a net increase in skin conductance over the arousal task and a decrease in skin conductance over the relaxation task. Individual variability was marked both in terms of initial tonic arousal level and the variability in skin conductance over the time course of each task.

skin conductance activity. By modeling both SCL and dSC within the same analyses, shared variance in tonic and phasic sympathetic changes in arousal is controlled for implicitly, removing contributions from ambiguous "slow" SCRs and very rapid changes in SCL. Moreover, this technique overcomes theoretical differences and technical difficulty in gauging occurrences of discrete SCRs within a continuous biofeedback task, since the bidirectional metric of dSC preferentially weights phasic changes in skin conductance by their rate, emphasizing the most rapid, discrete events. Design matrices modeling covariates (SCL and dSC) for each session were constructed initially at two levels of analysis; first, at individual subject level and next using a fixed-effect group analysis. Infer-

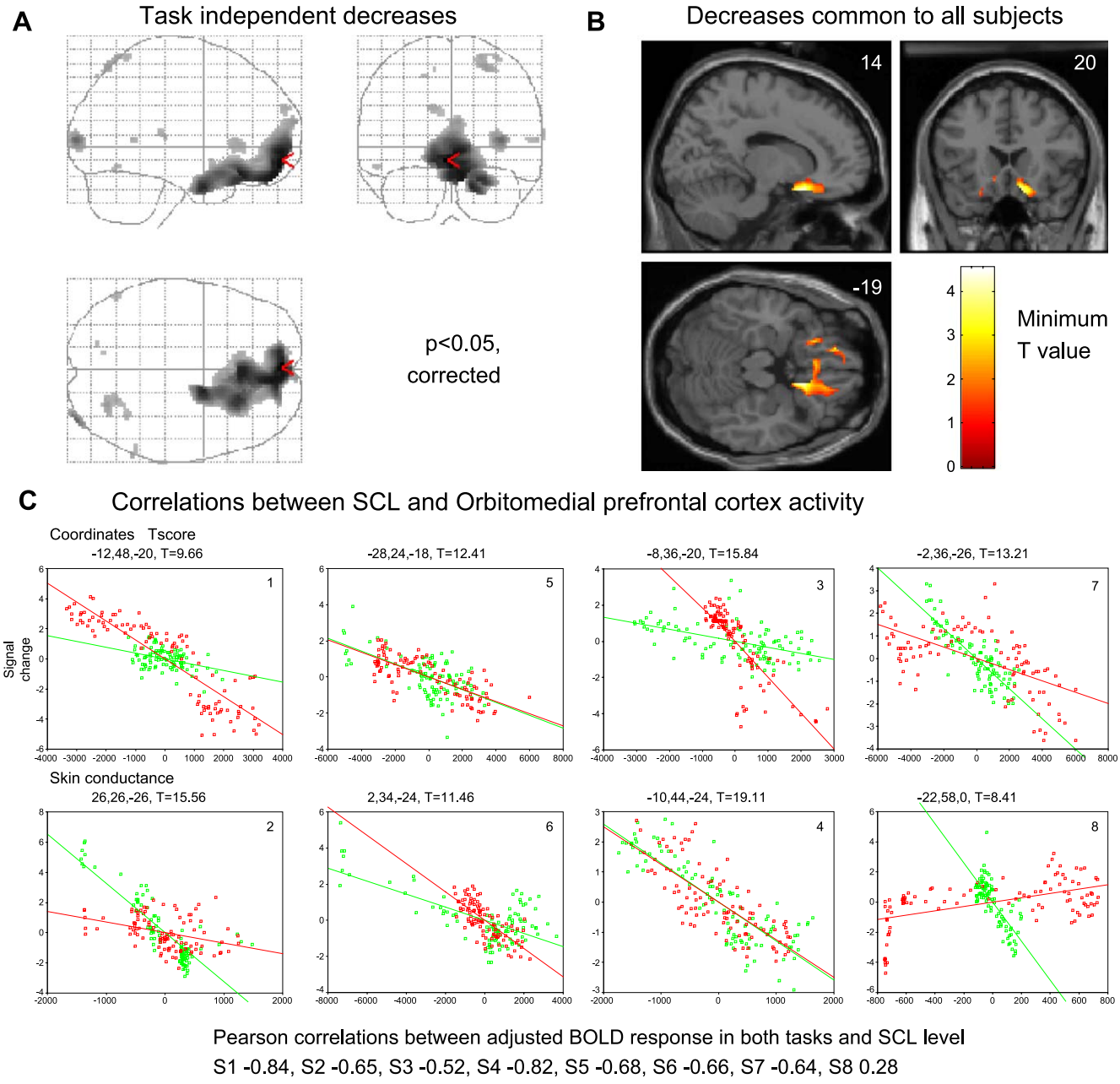

Fig. 3. Regional brain activity associated with decreases in skin conductance level. (A) Regional brain activity related to task-independent decreases in skin conductance level (SCL). Decreases in SCL were associated with increased activity in VMPFC and OFC. A conjunction analysis was used to identify regional activity negatively correlating with across both biofeedback relaxation and arousal tasks ($P < 0.05$, corrected). (B) Regional brain activity associated with decreases in tonic skin conductance level common across all subjects (conjunction analysis associated with decreases in skin conductance), presented on a normalized template brain scan ($P < 0.05$, corrected). The color scale represents the minimum t value shared by all eight subjects contributing to the conjunction analysis. Common brain activity was found in VMPFC and OFC. (C) Plots of individual subjects' data showing correlations between skin conductance and ventromedial and orbitofrontal BOLD activity during biofeedback relaxation (green dots) and arousal tasks (red dots). Data are plotted for the peak voxels of activity identified in first-level individual subject analyses. Pearson correlations showed significant negative correlation between adjusted VMPFC and OFC BOLD responses and task-independent SCL activity in the eight subjects.

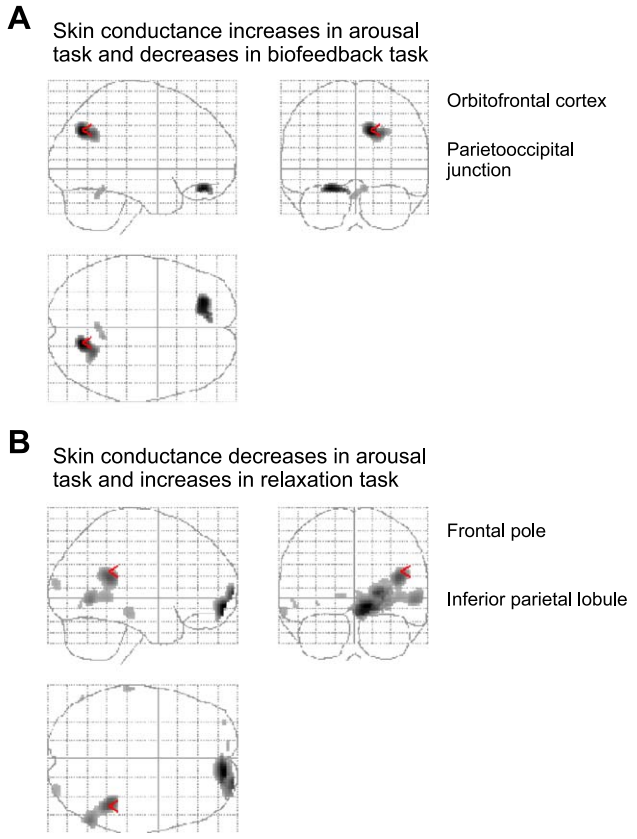

Fig. 4. Group data of brain regions related to intentional and unintentional biofeedback performance. (A) Brain regions related to intentional biofeedback performance. Enhanced activity in mid-OFC and parieto-occipital cortex was associated with increases in SCL during arousal biofeedback and decreases in SCL during relaxation biofeedback. One explanatory account is that this activity represents internal monitoring of task performance success and associated hedonic representation. (B) Brain regions related to unintentional biofeedback performance. Enhanced activity in frontal pole and inferior parietal lobule was associated with SCL decreases in arousal task and increases during the relaxation task. Failure to perform the task successfully and associated error monitoring may account for this observed pattern of activity.

ences relating to consistency and generalizability of findings are reported using across-task and across-subject conjunctions of effects to identify common regional activity in each individual, after initial exploration at the fixed-effects group level (Friston et al., 1999). The fixed-effects group approach is a standard sensitive method for identifying effects within a group of subjects in this case relating to psychophysiological mechanisms. Moreover, by using conjunction analyses to illustrate identical effects in eight case replications, this approach represents an extremely robust yet sensitive method of validating group effects that can be generalized to a wider population (Friston et al., 1999). The stringent threshold used in these comparisons for statistical significance is reported at $P < 0.05$, corrected for multiple comparisons across whole brain using family-wise error correction (FWE, akin to a Bonferroni correction). In addition, a random-effects analysis was conducted to underscore the generalizability of specific regional findings, reported at $P < 0.001$ uncorrected). In the tables, we report Z scores where conjunction analysis were used to determine significance, otherwise T or F scores are given as appropriate to the test.

Results

Behavioral performance

Individual task performance was variable across subjects. The majority of subjects showed fluctuation (both increases and decreases) in SCL over the course of both tasks. All but one subject showed an overall decrease in SCL during biofeedback relaxation, indicating successful overall achievement of the task objective. Consistent with a greater subjective difficulty in sustaining an increasing or high level of arousal in the scanning environment, performance of the biofeedback arousal task was less successful, with three subjects showing an overall drop in SCL over the arousal feedback session. Nevertheless, all subjects demonstrated substantial periods of ramping of SCL arousal over the course of the biofeedback arousal experiment. The mean changes in SCL during biofeedback task performance are illustrated in Fig. 2. Both experimental tasks achieved the aim of providing increases and decreases in SCL, respectively, for each subject during the different intentional states, relaxation and arousal.

Task-independent skin conductance level activity

We tested for significant regional brain activity related to increases and decreases in SCL independent of whether the subject performed a biofeedback arousal or relaxation task. A conjunction analysis between SCL-related activity during biofeedback relaxation and arousal conditions ensured that activity was not biased by one or other of these two tasks, but only related to decreases and increases in SCL. To show that no subject independently biased our findings, we performed a further conjunction analysis to test for commonalities across individual subjects. The raw data reflecting

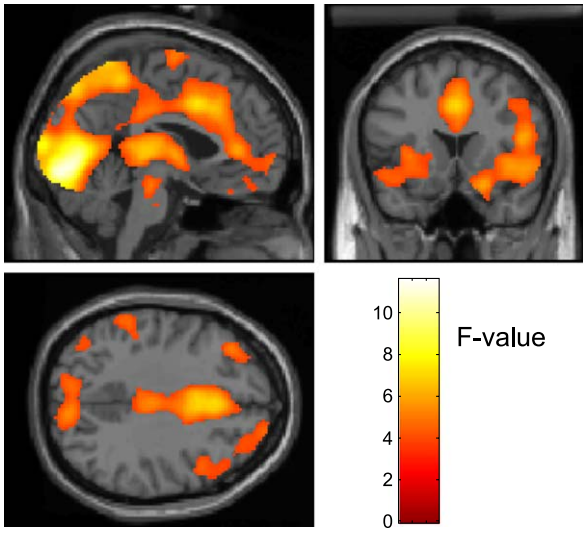

Fig. 5. Brain activity reflecting transient skin conductance responses. Enhanced activity associated with rapid transient changes in skin conductance highlighting regions associated with generation and representation of SCRs. This activity was identified using an F test of the derivative of measured skin conductance, identifying SCR-related activity within striate and extrastriate cortices, anterior cingulate, thalamus, insula and lateral regions of prefrontal cortex. Activity is thresholded at $P < 0.01$, corrected to permit discrimination of different regions.

subject-specific responses were also explored at the individual level.

Across tasks, decreases in SCL were associated with increased activity in VMPFC and OFC, extending to right medial temporal lobe and right temporal pole (Fig. 3A, Table 1A). This activity was observed across all subjects with common peaks in VMPFC and OFC, right ventral frontotemporal junction and medial temporal pole ($P < 0.05$, corrected) (Fig. 3B). Individual subject analyses were conducted to examine variation in location of this SCL-related activity. For each subject, we selected the peak voxel reflecting activity negatively correlating with SCL and plotted the raw adjusted data against SCL. Regions of VMPFC and OFC were highly correlated with decreasing SCL in both arousal and relaxation sessions, with individual anatomical variation noted in the location of the peak voxel in lateral and in rostro-caudal locations (Fig. 3C). Despite some variation in the location of peak VMPFC activity across subjects, the random-effects analysis of these data from all eight subjects nevertheless also showed significant ($P < 0.001$, uncorrected) activity in medial VMPFC (coordinates in mm, −4, 32, −22; $T = 5.15$).

Increasing SCL was associated with a distributed pattern of enhanced BOLD activity, involving left medial occipitotemporal junction, premotor cortex and anterior cingulate cortex. This pattern appeared more variable, with only a dorsomedial frontal/premotor region showing a significant common effect across all subjects (Table 1B).

We next tested for brain areas showing differential SCL-related activity between the biofeedback relaxation and arousal tasks. First, using a *t* test of contrast images at the second level, we tested for brain regions that showed activity corresponding to the direction of the intended SCL change, that is, enhanced BOLD activity with SCL increases during the arousal task and with decreases in SCL during relaxation task performance. Regions identified with such "successful performance" included left mid-OFC, medial occipitoparietal junction and cerebellar vermis (Table 2A, Fig. 4A). The converse *t* contrast, testing for brain regions where activity reflected failure to maintain the intended change in SCL (i.e. enhanced BOLD activity with increases in SCL arousal during the relaxation task and decreasing SCL arousal during the arousal task), identified right frontal pole and right superior temporal gyrus as regions showing a significant effect of mismatch between intended and true direction of skin conductance level (Table 2B, Fig. 4B).

Activity related to rate of change in skin conductance, (dSC, in effect highlighting activity associated with SCRs) was examined using bidirectional *F* tests to identify modulation of regional BOLD activity by transient arousal responses across the two experimental conditions. Changes in activity related to SCRs were seen in striate and extrastriate visual cortices (including V5), dorsal anterior cingulate and insular cortices, thalamus, hypothalamus and lateral prefrontal cortex (Table 3, Fig. 5).

Table 1

Region	Side	Coordinates of peak activity	*Z* score
(A) Regional brain activity associated with decreases in skin conductance level independent of task			
Ventromedial prefrontal cortex	L	−2, 58, −10	9+
Superior frontal gyrus	L	−12, 60, 28	5.36
Intra parietal sulcus	R	26, −72, 58	5.89
Middle temporal gyrus	R	64, −52, 6	5.31
Middle occipital gyrus	R	36, −94, 4	7.43
Genu of corpus callosum	L	−6, 26, 2	5.41
(B) Regional brain activity associated with increase in skin conductance level independent of task			
Medial occipitotemporal junction	R	36, −62, 4	5.76
Superior frontal gyrus	R	4, 2, 66	4.92
Superior frontal gyrus	L	−8, 2, 72	5.36
Precentral gyrus	L	−16, −32, 60	5.36
Parahippocampal gyrus	L	−24, −48, 0	5.51
Middle occipital gyrus	R	42, −72, 16	5.76
Lateral occipitotemporal sulcus	R	48, −42, −24	5.70
Anterior cingulate cortex	L	−12, 32, 36	4.80

Table 2

Region	Side	Coordinates of peak activity	*T* score
(A) Regional brain activity related to successful biofeedback			
Orbitofrontal cortex	L	−22, 42, −18	6.06
Orbitofrontal cortex	L	−10, 46, −20	5.59
Occipitoparietal junction	R	14, −68, 36	6.14
Cerebellar vermis	–	0, −54 −24	4.88
(B) Regional brain activity related to unsuccessful biofeedback			
Ventromedial prefrontal cortex	R	12, 60, −8	10.44
Superior temporal gyrus	R	42, −44, 18	7.81
Middle temporal gyrus	L	−64, −26, −14	5.30
Middle occipital gyrus	R	28, −94, 14	5.13

Table 3
Regional brain activity related to change in skin conductance

Region	Side	Coordinates of peak activity	*F* score
Extrastriate cortex	L	−6, −86, −10	11.58
Dorsal anterior cingulate	–	0, 10, 40	7.40
Dorsal anterior cingulate	–	2, 22, 36	7.04
Genu of anterior cingulate	–	−2, 38, 6	5.81
Medial posterior thalamus (pulvinar)	–	6, −26, 2	6.99
Geniculate/posterior hippocampus	L	−14, −26, −10	7.12
Geniculate/posterior hippocampus	R	20, −28, −4	6.79
Superior temporal gyrus	L	−46, −30, 20	6.95
Middle temporal gyrus	L	−62, −40, −14	4.16
Inferior frontal gyrus	R	50, 24, 14	6.36
Anterior insula	R	36, 24, −8	5.96
Precentral gyrus	L	−46, 4, 52	5.42
Medial premotor cortex	L	−8, −2, 76	5.24
Middle frontal gyrus	L	−36, 34, 36	5.07
Middle frontal gyrus	R	28, 2, 66	4.28
Lateral frontopolar cortex	R	50, 50, −4	4.82
Anterior hippocampus	R	36, −6, −16	4.58
Post central gyrus	R	38, −50, 60	4.23
Ventral striatum	R	20, 12, −16	5.96
Ventral striatum	L	−12, 6, −14	5.54
Medial orbitofrontal cortex	L	−2, 32, −24	3.95
Orbitofrontal cortex	L	−14, 26, −18	3.76
Cerebellum	L	−32, −42, −28	3.89
Lateral frontal polar cortex	L	−28, 56, −6	3.76

Discussion

In this study, we examined neural activity related to changes in skin conductance (SCL and SCRs) using biofeedback relaxation and arousal tasks. A significant negative correlation was seen between SCL and BOLD signal in VMPFC and OFC in all subjects, during both arousal and relaxation tasks, suggesting that activity in these cortical regions support a task-independent representation of autonomic state. This is in contrast to a distributed pattern of activity associated with transient SCR responses. In the current study, tonic and phasic changes in skin conductance activity (both SCL and SCR) were induced in the context of biofeedback, with the intention of minimizing extraneous physical and emotional effects on skin conductance change. Moreover, the biofeedback relaxation and arousal techniques that were employed preferentially influence tonic sympathetic arousal, a process only indirectly influenced and often ignored in studies of brain correlates of stimulus-induced autonomic responses.

Previous imaging studies have reported modulation of skin conductance activity (with particular reference to SCR's) by physical stimulation, emotional processing and mental burden (e.g. aversive tones, emotional slides or performance of gambling tasks (Buchel et al., 1998; Critchley et al., 2000; Fredrikson et al., 1998; Patterson et al., 2002; Phelps et al., 2001; Williams et al., 2001). There is evidence suggesting that, above the brainstem, skin conductance activity may be modulated by separate amygdala-dependent and cortical pathways. Emotional stimuli may provide the critical context for amygdalar modulation of SCR (Patterson et al., 2002; Williams et al., 2001). Electrical stimulation of the amygdala enhances SCR in animals (Yokota et al., 1963) and during emotional processing in humans, SCR has been observed to correlate significantly with activity in left amygdala (Phelps et al., 2001). However, activity in other regions, including cingulate, insula, right parietal lobule, motor cortex and VMPFC, is associated with changes in skin conductance activity (principally SCRs) during cognitive and motor behaviors, suggesting that the amygdala is one among a set of modulatory regions influencing but not uniquely generating SCRs (Critchley et al., 2001, 2002; Fredrikson et al., 1998).

Modulation of activity within VMPFC and OFC was found to be independent of task demands (i.e. whether the subject was actually trying to increase or decrease skin conductance level), yet directly related to decreases in tonic SCL. Patterson et al. (2002) have previously described task-independent VMPFC activity in relation to transient SCR *arousal* responses, suggesting this region maps tonic and phasic changes in autonomic state in different ways. Neuroanatomically, VMPFC and OFC, in contrast to lateral prefrontal regions, are closely connected to homeostatic control centers within hypothalamus and brain stem (Onger and Price, 2000). Interestingly, the VMPFC and OFC regions that show the greatest negative correlation with SCL in our study overlap with areas having high metabolism in an awake *resting* state (Raichle et al., 2001). These regions also deactivate with cognitive demands, especially attention-demanding cognitive tasks (Binder et al., 1999; Gusnard et al., 2001; Raichle et al., 2001; Simpson et al., 2001a,b). Indeed, from these observations, VMPFC, together with medial parietal cortex, has been proposed to support a default mode of the awake brain (Raichle et al., 2001).

The awake resting state embodies processes related to awareness of the inner state of the organism (interoceptive awareness) as well as awareness of a continuous sequence of semantic- and image-based thought processing. SCL reduces in such a resting state, as long as thoughts and images are not emotionally provocative, and as we have shown, there is enhanced VMPFC activity. By contrast, VMPFC deactivation, associated with increases in SCL, is associated with processes that include orienting to external cues and engagement in attentionally demanding tasks (Simpson et al., 2001a). At our a priori threshold of significance, we did not observe negative correlations between arousal state and activity in the medial parietal regions also implicated in a 'default mode' of brain activity. However, a feature of default brain states, in addition to low physiological arousal, is a reduction in goal-directed attention. Both our tasks engaged visual attention and cognitive strategies (including visualization) in contrast to the self-referential flow of thoughts occurring in a default state. Studies such as that of Gusnard et al. (2001) emphasize particularly the role of VMPFC (in contrast to the medial parietal region) in supporting default brain states. While our study provides a psychophysiological account for VMPFC, it is possible that the role of medial parietal lobe in default brain states may embody a cognitive account.

Previous neuroimaging studies of skin conductance biofeedback observed increased activity in dorsolateral prefrontal, anterior cingulate and parietal cortices, amygdala and basal ganglia associated with biofeedback relaxation (Critchley et al., 2001, 2002). Moreover, in the PET study, activity in anterior medial temporal cortex, an area that is closely and reciprocally connected to VMPFC/OFC, correlated with the rate of SCL decrease (Critchley et al., 2001). However, a relationship between medial temporal and VMPFC/OFC activity and SCL was not demonstrated in a fMRI study of biofeedback relaxation, perhaps reflecting methodological differences, including signal dropout from these regions (Critchley et al., 2002). The present study was optimized to examine SCL-related changes. The biofeedback tasks preferentially targeted tonic levels of skin conductance where rapid transient changes in skin conductance (reflecting SCRs), modeled by the temporal derivative of skin conductance, was treated as a confounding covariate. Task-independent SCL decreases were strongly and consistently (across both tasks in each subject) associated with VMPFC activity. In contrast, activity relating to increases in SCL was observed in distributed cortical and subcortical areas. We suggest that this activity profile, especially during the arousal task, reflects recruitment of volitional motor circuitry that directly influences peripheral sympathetic arousal via central command (Vissing et al., 1991). However, other factors, for example, the greater difficulty in sustained performance in arousal biofeedback compared to the relaxation biofeedback, may also account for this wider distribution of activity. Also, evidence for a shared substrate between high SCL states and generation of SCRs (that occur more readily in high arousal states) may have been compromised, in part, in our analyses as result of modeling both regressors together. Nevertheless, it is likely that multiple mechanisms underlie tonic enhancement of peripheral sympathetic neural activity, contrasting with the default VMPFC and OFC activity associated with tonic reduction in autonomic arousal.

Our experimental design also enabled us to investigate transient arousal responses, SCRs, modeled specifically by the regressor of the temporal derivative of skin conductance changes. Rapid transient changes in skin conductance (implicitly orthogonalized with tonic changes within the multiple regression analyses) were observed in anterior cingulate and insular cortices, thalamus, hypothalamus and lateral regions of prefrontal cortex and anterior striate and extrastriate visual cortices. Enhanced activity in many of these

brain regions have previously been reported in earlier studies investigating SCR (Critchley et al., 2001, 2002; Fredrikson et al., 1998) and include regions implicated in both the generation and representation of changes in internal bodily state.

Brain regions that demonstrated enhanced activity during successful performance of either biofeedback task (i.e. reduced SCL during relaxation task and increased SCL during arousal task) included left mid-OFC and right parieto-occipital junction. Regions of OFC are known to be activated by rewarding stimuli (with both primary and acquired salience) (Critchley and Rolls, 1996; O'Doherty et al., 2001, 2003). Our observation of OFC activity associated with task success suggests that this region may mediate self-generated reward, serving to reinforce behavior in the context of matching external information of biofeedback, representation of internal autonomic arousal state and cognitive representation of intent. Furthermore, it is notable that this mid-OFC region lies adjacent to regions that reflect task-independent decreases in sympathetic tone, suggesting an OFC mechanism for positive affect associated with attenuation of autonomic arousal.

Our findings provide insight into mechanisms involved in representation and volitional modulation of peripheral autonomic arousal states, indexed by skin conductance. In particular, activity within VMPFC and OFC covaries with tonic level of peripheral sympathetic arousal reflected in SCL. This finding implicates ventromedial prefrontal regions in a task-independent representation of background states of relaxation consistent with a proposed role in mediating a default baseline homeostatic state of brain activity. Moreover, the relationship between this activity and activity reported in association with rewarding stimuli suggests an OFC mechanism mediating background hedonic aspects of feeling states linked to levels of corresponding bodily arousal and relaxation.

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