Title: Regional brain responses associated with thermogenic and psychogenic sweating events in humans

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Abbreviated Title: Brain control of sweating

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Abstract
Sweating events occur in response to mental stress (psychogenic) or with increased body temperature (thermogenic). We previously found that both were linked to activation of common brainstem regions, suggesting that they share the same output pathways: a putative common premotor nucleus was identified in the rostral-lateral medulla. We therefore looked in higher brain regions for the neural basis that differentiates the two types of sweating event. Previous work has identified hemispheric activations linked to psychogenic sweating, but no corresponding data have been reported for thermogenic sweating. Galvanic skin responses were used to measure sweating events in two groups of subjects during either psychogenic sweating (n=11, 35.3±11.8 years) or thermogenic sweating (n=11, 34.4±10.2 years) while regional brain activation was measured by BOLD signals in a 3Tesla MRI scanner. Common regions activated with sweating events in both groups included the anterior and posterior cingulate cortex, insula, premotor cortex, thalamus, lentiform nuclei and cerebellum (P_{corrected}<0.05). Psychogenic sweating events were associated with significantly greater activation in the dorsal mid-cingulate cortex, parietal cortex, premotor cortex, occipital cortex and cerebellum. No hemispheric region was found to show statistically significantly greater activation with thermogenic than with psychogenic sweating events. However, a discrete cluster of activation in the anterior hypothalamic/preoptic area was seen only with thermogenic sweating events. These findings suggest that the expected association between sweating events and brain regions implicated in ‘arousal’ may apply selectively to psychogenic sweating; the neural basis for thermogenic sweating events may be subcortical.
Introduction

Sweating in humans at rest may occur in response to increased body temperature (thermogenic) or during mental or emotional stress (psychogenic). Although early views considered that unique neural pathways (Chalmers and Keele 1952; lwase et al. 1997; List and Peet 1938), different neurotransmitters (Nakazato et al. 2004; Noppen et al. 1997; Robertshaw 1977) and even sweat glands from separate skin regions (Darrow 1937; Kuno 1956; Ogawa 1975) were responsible for thermogenic and psychogenic sweating, recent studies indicate that these sweating events are all cholinergically driven phenomena (Machado-Moreira et al. 2012) that are expressed across the entire body surface (Machado-Moreira and Taylor 2012a; b). Bursts of the sudomotor nerve activity that drives sweating events are also highly correlated in time and amplitude between nerves innervating different skin regions (Bini et al. 1980a). In line with this evidence, we recently found that common brainstem pathways were activated in association with both thermogenic and psychogenic sweating events in humans (Farrell et al. 2013). The brain mechanisms generating the two categories of sweating event cannot be identical, however. To underline this point, volleys of cutaneous vasoconstrictor activity are co-activated with psychogenic sweating events, but not with thermogenic sweating events (Bini et al. 1980a; b; Delius et al. 1972; Macefield and Wallin 1996). So, if their brainstem pathways are indistinguishable, it makes sense to look for differences in higher brain regions.

Hemispheric brain regions driving psychogenic sweat events have been studied previously, and appear to be relatively stable, irrespective of the psychogenic stress that gives rise to sudomotor activity. For instance, studies of brain activity associated with skin conductance responses during different mental tasks (gambling and working memory), have demonstrated common neural activation across those tasks (Patterson et al. 2002). Brain regions showing sweating-related activation are widely distributed and include the anterior and posterior cingulate cortices, ventromedial prefrontal cortex, premotor and motor areas, visual cortex, thalamus and cerebellum (Craig et al. 2000; Fredrikson et al. 1998; James et al. 2013; Nagai et al. 2004; Patterson et al. 2002; Williams et al. 2000). Additionally, event-related EEG dipoles have implicated the inferior frontal
gyrus, amygdala and hippocampus in the generation of sweating events during mental arithmetic (Homma et al. 1998). However, the hemispheric regions associated with thermogenic sweating are essentially unknown.

The mental and emotional stimuli that are typically used to elicit psychogenic sweating also evoke a wide range of autonomic responses that collectively are part of the arousal response (Critchley et al. 2013). Cerebral regions associated with arousal have been extensively studied. In this context, the dorsal midcingulate cortex has been identified by Critchley and others as the common region associated with arousal-related activation of a wide range of sympathetic nerves (Critchley et al. 2013). By contrast, body heating is associated with drowsiness (Gilbert et al. 2004; Qian et al. 2014), which could have implications for regional brain activation during thermal sweating. However, the few studies investigating responses in the hemispheres to whole-body heating have failed to produce a consensus on the brain regions that are activated during periods of either increased thermoafferent or thermoefferent flow (Egan et al. 2005; Fechir et al. 2010; Nunneley et al. 2002).

This study was designed to compare regional activation during both psychogenic and thermogenic sweating events, focusing on regions above the midbrain. As in our previous study (Farrell et al. 2013), we sought brain regions that were selectively activated in association with sweating events rather than with mean ongoing sweating levels. Our aim was to look for similarities and differences in the cerebral mechanisms driving human sudomotor function under these different forms of external stress.
Materials and Methods

Participants
The study was undertaken according to procedures approved by the Melbourne Health Human Research Ethics Committee (#2008.147). Participants provided written, informed consent before enrolment. A total of 22 people contributed data for the study, of which there were two groups of eleven aged 34.4 (±10.2; Thermogenic Group) and 35.3 (±11.8; Psychogenic Group) years, and including the same proportions of men and women (91% male). Some of the data collected from these participants has been reported previously (Farrell et al. 2014; Farrell et al. 2013). The data presented herein from the Psychogenic Group have not previously been reported, and all outcomes reported from the current analyses of the Thermogenic Group data are also novel. The Thermogenic Group data were previously used in an analysis focused on the preoptic area, and investigated the sweating-related activation and functional connectivity of that region based on contrasts with a normothermic resting-state data set (Farrell et al. 2014)

Recording of Sweating Events and Skin Temperature
Sweating was monitored by recording galvanic skin responses with Ag-AgCl electrodes (TSD203 electrodes, Biopac Systems, CA, USA) fixed on the palmar surfaces of the right index and middle fingers. Cabling (MECMRI-3 MRI Cable, Biopac Systems, CA, USA) and filters (MRIRFIF interference filter set, Biopac Systems, CA, USA) connected the electrodes to a constant voltage amplifier (GSR100C Galvanic Skin Response Amplifier, Biopac Systems, CA, USA). The signal was digitized at 1 khz (Power 1401, Cambridge Electronic Design, England) and recorded to computer (Spike2 (ver.7), Cambridge Electronic Design, England). Gradient artefacts related to magnetic resonance image acquisition were excised from the GSR recording. The electrodermal signal was recorded as an AC signal (0.5 Hz high pass filter) to identify discrete electrodermal events independently of any shift in mean signal level (Kunimoto et al. 1991). Output signals from the scanner control panel were used to trigger recordings of electrodermal data so that it could be matched with synchronously acquired functional brain images.
Type T (copper – constantan) thermocouples were attached to three different sites on each participant’s trunk (left, right, midline) and recorded via an electronic thermometer (TH-5, Physitemp Instruments, NJ, USA). Signals from the thermocouples were filtered, digitised and recorded to computer using the same procedures and equipment as those described above for the recording of electrodermal events. Finally, those data were averaged to yield an unweighted, mean torso skin temperature.

Sweating-Related Stimulation

Thermogenic Sweating

Heating was induced by means of a water-perfused garment (LCG) (Med-Eng BCS4 Body Cooling System, Allen Vanguard, ON, Canada) as previously described (Farrell et al. 2014; Farrell et al. 2013). Temperature-controlled water (40 to 50°C) was circulated through a network of small diameter tubes sewn into the garment, which covered the torso, arms and legs, but excluded the head, hands and feet. Layers of insulating fabric were added to minimize heat loss to the environment. Passive heating was sustained until regular sweating events were detected electrodermally, at which time functional brain image acquisition commenced with heating maintained throughout. As previously described (Farrell et al. 2013), the water temperature was then adjusted to sustain a low mean rate of sweating events.

Psychogenic Sweating

Psychogenic sweating was achieved through the imposition of a mentally challenging colour/word Stroop task as previously reported (Farrell et al. 2013). Visual stimuli were projected onto a screen that was visible to participants lying in the magnetic resonance imaging (MRI) scanner via a mirror mounted on the head coil. A sequence of coloured words was presented in a random order. This contained both congruently (e.g., the word “red” written with red text) and incongruently coloured letters (e.g., the word “red” written with green text). These were presented for a 2 min block followed by a 30-s rest interval, and the cycle was repeated three times during functional brain scanning scans. The task
was to count the number of nominated events (e.g., count the words “red” written with yellow letters) that occurred in each 2-min block. The tasks (counting congruent or incongruent events) and stimuli (colour words and text colours) used during each blocks were varied within and across scanning runs. Participants used a button box to record their count by indicating their choice of answer from options displayed at the conclusion of the 2-min block. These responses were not recorded. However, the timing of the participants’ actions were taken into account in the analysis of functional brain images to prevent their potential confounding influence (elaborated below).

Image Acquisition
Images were acquired with a Siemens 3Tesla magnetic resonance imaging scanner (Trio system) with a 32-channel head coil at the Murdoch Children’s Research Institute (Melbourne, Australia). High resolution structural images of participants’ brains were collected using a T1 weighted image sequence (192 x 0.9mm sagittal slices, 256x256 matrix, in-slice resolution 0.8mm x 0.8mm, TR=1900ms, TE=2.59ms, flip angle=9o). Functional brain images sensitive to blood oxygen level-dependent (BOLD) contrast were also acquired for all participants (TR=1900ms, TE=35ms, flip angle=90o). The field of view of the functional images encompassed the brain hemispheres, cerebellum and brainstem (30 slices of 4mm thickness, in-slice resolution=3.6x3.6mm). Each functional scan lasted for 7 min and 55 s and included 250 sequential brain volumes (1.9 s per brain volume). Two of these functional scans were collected from each participant.

Analysis
Preprocessing
Preparation and statistical analysis of functional brainstem images was performed with the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FMRIB, Oxford, UK, FSL version 4.1 (http://www.fmrib.ox.ac.uk/fsl/)). Sequential functional brainstem images from single scanning runs were realigned to the middle image of the time-series to correct for any head movement during the scanning run using MCFLIRT
Images were spatially smoothed using a Gaussian kernel of 5mm full width at half maximum. The time-series of each scanning run was mean-based intensity normalised and high-pass filtered. Functional brain images from each participant were co-registered with a standard brain to facilitate amalgamation of statistical outcomes across participants. Transformations were performed with FMRIB's Linear Image Registration Tool (FLIRT) (Greve and Fischl 2009; Jenkinson et al. 2002; Jenkinson and Smith 2001).

**Statistical Analysis**

The first level of functional brain imaging analysis was performed on individual scanning runs using general linear modelling including local autocorrelation correction as instituted in the FMRI Expert Analysis Tool (FEAT, FMRIB's Improved Linear Model (FILM) (Smith et al. 2004; Woolrich et al. 2009). The regressor of interest for each scanning run analysis was derived from the recording of electrodermal events obtained contemporaneously with the functional brainstem images. The signals from the electrodermal recordings were initially down-sampled to correspond with the acquisition time of functional brainstem images (one observation every 1.9 seconds). Timing adjustments were then made to the electrodermal regressor to take account of delays between activation of brain regions involved in sweating control and the occurrence of electrodermal events. Homma and colleagues (1998) recorded EEG, median sympathetic nerve activity and sweating at the finger tip during performance of mental arithmetic and using dipole source localisation, concluded that activity in cortical regions occurred 5 to 5.5 seconds before sweating events (Homma et al. 1998). Consequently, the electrodermal regressors were translated backward in time by an interval corresponding to the acquisition of three brain volumes (5.7sec). The mental task involved instructions, blocks of visual stimuli and button presses to indicate participants’ responses. Regressors representing the mental task components were included in the modelling of BOLD signal changes in order to take account of these known sources of variance. Specifically, a regressor was used to indicate the onsets, durations and offsets of periods during which participants were viewing images for the Stroop task, and another regressor was included in the analysis to
indicate the timing of response cues and resulting button presses. The
hemodynamic response measured with BOLD contrast occurs at a delay of 4 to 6
seconds after neural activation and so the electrodermal and task regressors
were convolved with a model of the hemodynamic response function (Gamma
function) and included temporal derivatives of the regressor to account for
variations in the timing of events (Henson and Friston 2006).

Additional regressors were included in the general linear modelling of BOLD
signal changes during scanning runs to take account of non-neural related
variability. Physiological processes contribute to BOLD signal noise including
respiratory effects on local magnetic field properties and changes in the blood
and cerebrospinal fluid associated with the cardiac cycle. This physiological
noise does not usually confound fMRI analysis because it varies independently of
many stimuli and tasks employed in functional brain imaging paradigms.
However, sweating events are likely to correlate with other physiological
processes, especially in the case of mental stress (Fechir et al. 2008). In order to
reduce any confounding effects of physiological noise, regressors from three
regions of interest were used in the model to account for variance associated
with the cardiac and respiratory cycles. The regions of interest were identified in
the white matter, ventricles and circulation for each scanning run, according to
procedures previously described (Farrell et al. 2012), and signals from those
regions were extracted and included as the physiological noise regressors. The
influence of head movement on BOLD signal intensity was also taken into
account by including the six motion parameters (three translations and three
rotations) into the modelling of signal changes.

A parameter estimate was calculated for the fit of each regressor to the observed
BOLD signal for each voxel in the space of functional brain images resulting in a
series of statistical parametric maps for each scanning run. Parameter estimates
for the fits of regressors of interest (electrodermal responses) were carried
forward to higher levels of analysis that firstly averaged responses across
scanning runs for individual participants using fixed effects, and then
subsequently calculated average responses among group participants.
(Thermogenic Group, Psychogenic Group) and between groups (Thermogenic
greater than or lesser than Psychogenic) using mixed effects (FMRIB's Local
Analysis of Mixed Effects (FLAME) (Beckmann et al. 2003). Regions of activation
were considered statistically significant when the constituent voxels had values
exceeding $z=2.3$, and a cluster-corrected threshold of $P<0.05$ to take account of
the spatial smoothness of the images and the effects of multiple comparisons on
inferences of significance (Worsley et al. 1992).

Brainstem hemodynamic responses associated with sweating were
characterised with region of interest (ROI) analyses. This was done to confirm
that the timing of events were compatible with the expected response profiles, to
compare outcomes with previous reports from the study cohort, and to
characterise the nature of any between-group differences. ROIs were selected
from the midbrain and medulla according to previously described procedures
(Farrell et al. 2013). Clusters of between-group activation were also defined as
ROI. BOLD signals extracted from ROI were compiled in one of two ways. The
first method was used to assess the temporal profile of sweating-related signal
change. BOLD signals were averaged across the voxels within ROI for each time
point in individual scanning runs after motion correction, high-pass filtering and
spatial smoothing. Sections of time corresponding with sweating events were
identified for scanning runs by calculating the mean and standard deviation of
electrodermal signals and choosing peaks with values greater than the sum of
the mean and one standard deviation. Time points 28.5 s before and after each
peak were extracted from ROI time-series and averaged. The average BOLD
signals during sweating events of individual scanning runs were expressed as a
percentage of the average of the first three time points (28.5 to 24.7 s before the
peak). Percentage signal changes of all scanning runs were averaged to produce
the grand mean of BOLD signal changes during sweating events. The second
method was used to visualise the relative size of sweating-related signal changes
between the groups. The Featquery tool was used to estimate percentage signal
changes across sweating events for each scanning run and the outcomes were
averaged across groups.
Results

Skin Temperature and Sweating Event Frequency
Passive heating for thermogenic sweating was associated with an increased skin temperature (36.2±S.D. 1.3°C) compared with the non-heated state during psychogenic sweating (33.2±1.2°C, t(20)=5.7, P<0.001). Sweating events occurred with similar frequency during functional brain scans for the two experimental procedures (Thermogenic = 7.7±1.7 per scan, Psychogenic = 7.5±S.D. 2.0 per scan, t(20)=0.2, n.s.). Sweating activity patterns were similar to those reported previously (Farrell et al. 2013).

Sweating Event-Related Activation
Sweating events were associated with activation in widely distributed regions of the brain for both thermogenic and psychogenic stimuli (Fig. 1, Tables 1&2). Extensive cingulate activations were principally in the dorsal mid-cingulate cortex with psychogenic sweating events, whereas thermogenic sweating was notable for clusters of event-related activation in the posterior and pregenual cingulate cortices. Mesial activation was also seen in the precuneus for both stimulus types, while only thermogenic sweating was associated with activation in the anterior hypothalamus/preoptic area (AH/PO). Sweating-related activation was seen in the insula with both stimuli, being predominantly anterior in both hemispheres with psychogenic sweating events, and mid (right) and posterior (left) for thermogenic sweating events. Right prefrontal cortex activation was noted with both types of sweating event (Middle Frontal Gyrus, BA10). Other regions activated with both types of sweating event were the bilateral thalami, lentiform nuclei and cerebellum.

Thermogenic and psychogenic sweating event-related activation was seen in the midbrain, pons and medulla. In agreement with previous findings (Farrell et al. 2013), the location of midbrain activations was similar for the two types of sweating and was mainly seen in the dorsal part of the region (Fig. 2). Overlaps of sweating activations for thermogenic and psychogenic stimuli were also apparent in the rostral medulla, being located symmetrically lateral (Fig. 2). This again agrees with previous findings (Farrell et al. 2013).
Differential Activation by Psychogenic and Thermogenic Sweating Events

Contrasts between the two types of sweating event-related activation revealed sites of significantly greater activation with psychogenic than with thermogenic sweating events, but not the reverse (Fig. 3, Table 3). Regions showing increased psychogenic versus thermogenic sweating activation included the dorsal midcingulate cortex, premotor regions, parietal associative cortex, occipital cortex and cerebellum. Examinations of time series of BOLD signal changes and mean levels of sweating activations suggested that these regions were exclusively activated with psychogenic sweating events, with little or no activation related to thermogenic sweating events (Fig. 3).

Several brain regions showed substantial clusters of activation that were prominent only with thermogenic sweating, but statistical comparison fell short of proving that this was greater than with psychogenic sweating events. Such regions included the lentiform nuclei (P = 0.1), amygdalae (P = 0.1) and AH/PO (P = 0.09).
Discussion

This study has provided the first direct description of the network of forebrain regions associated with thermogenic sweating events. It also confirmed the findings of previous studies on the cerebral activations associated with psychogenic sweating events (Craig et al. 2000; Fredrikson et al. 1998; Nagai et al. 2004; Patterson et al. 2002; Williams et al. 2000) and skin sympathetic nerve activity (SSNA), which includes both sweating and vasomotor events (James et al. 2013). Besides confirming our previous finding of common brainstem regions activated with both thermogenic and psychogenic sweating events (Farrell et al. 2013), we now find such common regions in the cerebral hemispheres. Those regions include parts of the cingulate, insular and premotor cortices, thalamus, lentiform nuclei and cerebellum. But the current study also revealed important differences. Psychogenic sweating events were associated with significantly greater activation than thermogenic sweating events in the supplementary motor area, premotor cortex, parietal cortex, parts of the cerebellum and dorsal mid-cingulate cortex. Thus, as would be predicted, the two types of sweating event were linked to distinct patterns of brain activation.

Both these types of sweating event occur episodically and synchronously across the entire body surface (Hagbarth et al. 1972; van Beaumont et al. 1966) following sweat gland priming (Machado-Moreira and Taylor 2012a; b). The phasic sweating events that informed the analysis used in this study are driven by bursts of sympathetic sudomotor activity (Bini et al. 1980b; Hagbarth et al. 1972; Ogawa and Bullard 1972). The measure used in this study, episodic increases in skin conductance, measures the timing and amplitude of sweating events. Although measured here at the fingers, the timing and amplitude of these conductance changes accurately and linearly reflect bursts of sudomotor nerve activity, which are highly correlated across skin regions (Bini et al. 1980a). We are therefore confident that the brain activation patterns we have identified here apply not only to finger sweating but to sweating events across the body. The sudomotor bursts driving the sweating events are likely to be driven by the output of rostral-lateral medullary nuclei, whose event-related activation was identified in this and an earlier study (Farrell et al. 2013), and whose location is
homologous with the sympathetic premotor nuclei for sweating identified in the
cat medulla (Shafton and McAllen 2013).

Resistance of the skin is principally due to the stratum corneum (Lawler et al.
1960), and skin conductance increases only when fluid-filled sweat ducts pierce
that resistive layer. This makes skin conductance measurements insensitive to
any change skin in blood flow. In line with this, atropine abolishes sweating
events but leaves skin vasomotor responses intact, while bretylium does the
reverse (Lader and Montagu 1962). Even though vasomotor nerve volleys may
be activated at the same time as sudomotor nerve volleys (Bini et al. 1980a), they
should have had no influence on the electrodermal measurements that we used
to identify activated brain regions.

As have others, we found widespread forebrain regions activated in association
with psychogenic sweating events (Craig et al. 2000; Fredrikson et al. 1998;
Nagai et al. 2004; Patterson et al. 2002; Williams et al. 2000). It is likely that
many of these represent other arousal-related cerebral events that co-activate
with sweating, (e.g., cognitive, premotor and other autonomic processes).

Prevailing views on the interaction between autonomic responses and cognition
posit a link between arousal state and the behavioural significance of stimuli
(Critchley et al. 2013). Research using similar mental stresses, (i.e., Stroop task),
and additional measures of autonomic responses would suggest that
performance errors trigger a change in bodily state, especially when there is a
conscious awareness of the error (Critchley et al. 2005; Hajcak et al. 2003;
Nieuwenhuis et al. 2001). This shift in autonomic responses is conceptualised as
a somatic marker that provides cognitive feedback to decrease the probability of
future errors.

The dorsal mid-cingulate cortex has been identified as the common cortical area
associated with autonomic activation, including sweating, in response to both
physical and mental effort (Critchley et al. 2000). In line with that view, the
present study confirmed the expectation that this region would be strongly
activated with psychogenic sweating events. Strikingly, however, this was a site
of strong functional contrast: it was not activated by thermogenic sweating. If the
dorsal mid-cingulate represents a key cortical site controlling several 'stress-
arousal-related' sympathetic outflows (Craig 2009; Critchley et al. 2000;
Critchley et al. 2003), the source of thermogenic sweating events needs to be
sought elsewhere.

Methodologically, finding such a contrast is reassuring, because it tells us clearly
that different brain mechanisms drive the two types of sweating event.
Therefore, the thermogenic sweating events were not simply mini-arousals that
happened to occur during whole body heating. On the other hand, we cannot
exclude the possibility that some such arousals did occur, even though the
heated condition was generally relaxing and subjects were left undisturbed. If so,
that might explain some of the forebrain sites that were activated with sweating
events from both protocols.

While no site was identified that showed significantly greater activation with
thermogenic than psychogenic sweating events, this could be a false-negative
conclusion due to noisy data. In this context, the AH/PO area merits mention.
This brain region is known from animal studies to play a key role in
thermoregulatory processes (Nakamura 2011) and, when locally heated, it can
drive sweating (Beaton et al. 1941). A discrete cluster there was activated with
thermogenic sweating events, but not psychogenic sweating events (Fig. 1). We
have reported elsewhere that this region showed enhanced functional
connectivity with other brain regions in humans during whole-body heating
compared with during the normothermic state (Farrell et al. 2014). Whether the
AH/PO area in humans is truly a source of thermogenic but not psychogenic
sweating events must await determination by more detailed study.

We still do not know exactly where either type of sweating event originates.
Presumably in each case there is a network of neurons whose synchronous
activity acts as the source of the burst. These in turn may be influenced by such
factors as brain temperature, or state of arousal. Other attempts to localise the
source of psychogenic sweating events have included the following. Event-
related fMRI studies have identified activation in prefrontal, cingulate, parietal, motor, insular and occipital cortex, and hippocampus, thalamus and cerebellum to psychogenic sweating events (Craig et al. 2000; Fredrikson et al. 1998; Nagai et al. 2004; Patterson et al. 2002; Williams et al. 2000), and additionally activation in the cingulate, superior frontal, precentral and occipital cortices to the mean sweating level by skin resistance (Fan et al. 2012; Nagai et al. 2004; Zhang et al. 2014). James and colleagues sought cerebral signals to variations in skin sympathetic nerve activity (SSNA) (James et al. 2013). The SNAA signal includes vasomotor as well as sudomotor nerve activity (Bini et al. 1980b; Macefield and Wallin 1996), although burst activity associated with these two autonomic responses can be synchronised (Bini et al. 1980a), in which case the associated regional brain activation would be the same. In the case of psychogenic sweating events a related EEG signal has been studied, and its sources located in two subjects to the inferior frontal gyrus, amygdala and hippocampus (Homma et al. 1998). No one has previously attempted to localise the origins of thermogenic sweating events.

**Limitations**

As with all fMRI studies, the results obtained here are correlative only. This means that the brain regions we identified as activated with sweating events could be due to other processes that may occur consistently at the same time. This may apply, for example, to cutaneous vasoconstrictor traffic that is co-activated with sudomotor bursts during psychogenic stimuli. It should not apply to thermogenic sweating events. This distinction may explain some of the differences we observe between the brain regions activated with psychogenic versus thermogenic sweating events.

Second, the study involved two groups of participants. A within-subject design would have been ideal, but a lag between study times prevented us recruiting all the same participants twice. Our experiment was designed to give a clear distinction between thermogenic and psychogenic stimuli, but we cannot eliminate the possibility that some psychogenic sweating events also occurred during the thermal stimulus runs and...
contributed to the fMRI findings. Against this, the heating protocol we used was mild, and likely to have been relaxing. Moreover, vasoconstrictor sympathetic nerve bursts were not found to occur in resting heated subjects (Bini et al. 1980b; Macefield and Wallin 1996).

Finally, to measure responses through the whole brain we traded spatial for temporal resolution. The size of voxels used could have prevented us from resolving small distinct clusters from a larger mass of activation, and could have made it more difficult to detect local differences between psychogenic and thermogenic sweating-related activations.

Perspectives

This study has been the first successful foray into the functional imaging of thermogenic sweating activation in the hemispheres of the human brain. The network of brain regions activated during thermogenic sweating events shares some common regions that are activated also during psychogenic sweating events, but regional differences are also apparent. Notably, neural activation in the dorsal mid-cingulate cortex was linked to psychogenic more than thermogenic sweating events. This difference is likely to reflect greater levels of arousal during psychogenic sweating. Previous studies have linked this region with sympathetic activation (including sweating) during stress and arousal. Our findings support that view. But the sources of thermogenic sweating events are clearly different, and may ultimately be found in subcortical structures such as the AH/PO area. Taken together with previous findings, this study suggests that distinct supratentorial mechanisms generate psychogenic and thermogenic sweating events, but these converge on common brainstem pathways en route to the sweat glands.

Acknowledgments

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### Table 1

**Clusters of significant activation during psychogenic sweating**

<table>
<thead>
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<th>Region</th>
<th>BA</th>
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<th>x</th>
<th>y</th>
<th>z</th>
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The table gives the coordinates of the voxel with the highest Z-score in each cluster of activation, and records the value of that Z-score. The Brodmann Areas (BA) of peak voxels are listed for clusters located in cortical regions. The coordinates correspond to the Montreal Neuroscience Institute standard brain template: x values are mm left (-) or right (+) of the anterior commissure; y values denote mm anterior (+) or posterior (-) to the anterior commissure, z gives mm above (+) or below (-) the anterior commissure.

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Clusters of significant activation during thermogenic sweating

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See notes for Table 1 for explanations of table contents.
Table 3

Psychogenic Greater Than Thermogenic Sweating Activation

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See notes for Table 1 for explanations of table contents.
A. Thermogenic sweating event-related activation occurred bilaterally in the cerebellum (CB) (lobule Crus II) and pons. B. Pontine and cerebellar activation was apparent in association with psychogenic sweating events, the later occurring bilaterally in the declive (lobule VI). C. Bilateral thalamic (Thal) and lentiform (LN) activation occurred during thermogenic sweating events, as well activation in the right prefrontal cortex (PFC). D. Right prefrontal activation was also a feature of psychogenic sweating events, along with bilateral insula (Ins), temporal (TC) and occipital (OC) cortices. E. Cingulate cortex (CC) activation occurred during thermogenic sweating events. F. In addition to activation in the cingulate cortex, psychogenic sweating events were associated with activation in the premotor (PMC) and parietal cortices (PC). G. Thermogenic sweating event-related activation was seen bilaterally in the amygdalae (AM). H. Amygdala activation was not seen in association with psychogenic sweating events, but did occur bilaterally in lentiform nuclei (LN). I. Mesial activation during thermogenic sweating events occurred in clusters incorporating the posterior cingulate cortex (PoCC), dorsal mid-cingulate cortex (dMCC) and pregenual cingulate cortex (PreCC). Activation was also seen in the anterior hypothalamus/preoptic area (AH/PO). J. The dorsal mid-cingulate cortex was activated during psychogenic sweating events, as was the precuneus (PCn).
commonly activated voxels in the rostral medulla showed BOLD signal increases during both types of sweating event.

Figure 3.

Brain regions showing differential activation when thermogenic and psychogenic sweating event-related activations were contrasted. No region was more strongly activated with thermogenic sweating events: sites more strongly activated with psychogenic sweating events are shown here by shades of blue in A and D. B shows the BOLD signal time courses extracted from the dorsal mid-cingulate cortex (dMCC) region shown in A. Bar graphs in C-G show the mean ±SEM BOLD signal changes with thermogenic and psychogenic sweating events in the regional clusters indicated: C, left Premotor Cortex (PMC_L); E, right Posterior Parietal Cortex (PPC_R); F, left Superior Parietal Cortex (SPC_L); G, right Superior Parietal Cortex (SPC_R).