Brain stem representation of thermal and psychogenic sweating in humans

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Farrell MJ, Trevaks D, Taylor NAS, McAllen RM. Brain stem representation of thermal and psychogenic sweating in humans. Am J Physiol Regul Integr Comp Physiol 304: R810–R817, 2013.—Functional MRI was used to identify regions in the human brain stem activated during thermal and psychogenic sweating. Two groups of healthy participants aged 34.4 ± 10.2 and 35.3 ± 11.8 years (both groups comprising 1 woman and 10 men) were either heated by a water-perfused tube suit or subjected to a Stroop test, while they lay supine with their head in a 3-T MRI scanner. Sweating records were encoded as electrodermal responses (increases in AC conductance) from the palmar surfaces of fingers. Each experimental session consisted of two 7.9-min runs, during which a mean of 7.3 ± 2.1 and 10.2 ± 2.5 irregular sweating events occurred during psychogenic (Stroop test) and thermal sweating, respectively. The electrodermal waveform was used as the regressor in each subject and run to identify brain stem clusters with significantly correlated blood oxygen level-dependent signals in the group mean data. Clusters of significant activation were found with both psychogenic and thermal sweating, but a voxelwise comparison revealed no brain stem cluster whose signal differed significantly between the two conditions. Bilaterally symmetric regions that were activated by both psychogenic and thermal sweating were identified in the rostral lateral midbrain and in the rostral lateral medulla. The latter site, between the facial nuclei and pyramidal tracts, corresponds to a neuron group found to drive sweating in animals. These studies have identified the brain stem regions that are activated with sweating in humans and indicate that common descending pathways may mediate both thermal and psychogenic sweating.

HUMAN ECCRINE SWEAT GLANDS respond to both thermal and nonthermal drives (26, 27), and their secretions serve a wide range of secondary functions, such as facilitating tactile and thermal sensitivity, increasing contact friction (grip), and reducing the risk of tissue damage (55). The main nonthermal drive to sweating in resting individuals is mental stress or arousal, referred to here as psychogenic sweating (32). Despite earlier doubts (39, 48), it now seems clear that cholinergic sympathetic nerves are the final motor pathways for both thermal and psychogenic sweating (31) and that both types of sweating occur over the whole body rather than being restricted to certain skin areas (32, 33). It is probable (though not yet formally proven) that the same individual sympathetic neurons mediate these responses via common sudomotor units during both thermal and nonthermal sudomotor drives.

The central neural pathways that control sweating remain poorly delineated. One can assume that the central neurons controlling thermal and psychogenic sweating are not identical, although they might share common output pathways to the sympathetic sudomotor nerves. The prevailing view, based on animal studies, is that thermal sweating depends ultimately on the anterior hypothalamus/preoptic area (18, 34, 50, 51), while psychogenic sweating is believed to be driven from the forebrain (21, 44).

Clues to the regions of the human brain involved in psychogenic sweating can be found in imaging studies that have related regional brain activity to sweating, usually measured as electrodermal responses. Two elegant brain imaging studies on psychogenic sweating by Critchley and colleagues showed, for example, that the intensity of sweating responses to both mental arithmetic and physical work (handgrip) was associated most clearly with activation of a region in the dorsal midcingulate cortex (5, 7). Other measures of autonomic arousal were also associated with activations in this region, consistent with the view that cortical neurons in that region may ultimately drive psychogenic sweating, perhaps as part of a more general autonomic activation (7). A separate functional magnetic resonance imaging (fMRI) study by the same group showed that regions in the prefrontal and orbitofrontal cortex, as well as extrastriate visual cortex and cerebellum, were activated just before discrete sweating events, implicating neurons in those regions as potential drivers of psychogenic sweating (6).

Fechir and colleagues also used fMRI to identify brain regions activated proportionally with sweating in response to a graded mental task (12). Interestingly, while this study showed proportional activation in “task-related” regions, such as the visual, motor, and premotor cortices, as well as part of the cerebellum, it failed to show proportional activation of the mid-cingulate cortex (12).

A different approach—EEG dipole analysis—was used by Homma and colleagues to localize cerebral activation associated with sweating events during cognitive processing (21). These experiments indicated involvement of the inferior frontal gyrus, hippocampus, and amygdala (20, 21).

The cerebral regions with activity associated with thermal sweating were investigated as part of a separate study by Fechir and colleagues (13), who mapped brain regional metabolic responses with fluorodeoxyglucose positron emission tomography during whole body warming and cooling. These workers identified a small midline region of the posterior cingulate cortex whose metabolic activity was inversely related to sweat rate, but found no cerebral areas with a positive correlation. That posterior cingulate area could represent a locus of inhibitory control of thermal sweating. Alternatively, it might reflect this region’s known role as part of the “default mode circuit” that is inactivated during arousal (47).

For the brain stem, limited data from human pathophysiological studies indicate that the descending fiber tracts that supply drive to the spinal preganglionic sudomotor neurons
follow a course through the lateral parts of the medulla oblongata. This is based on the finding that those areas are damaged, sweating of any cause is abolished on the ipsilateral side of the head and neck (40). The finding that the deficit does not extend below the neck is attributed to spinal sudomotor pathways crossing the midline sufficiently to compensate lower levels of the sympathetic outflow (41). Where those descending fiber tracts originate and the locations of their cell bodies are unknown, however.

The present paper is focused on the brain stem, which has not yet received detailed attention in human imaging studies on sweating. We wanted to know the answers to three principal questions: 1) Where are the brain stem neurons that control sweating? 2) Do they differ between thermal and psychogenic sweating? and 3) Can we identify the human homolog of the rostral medullary cell group that drives sweating in cats (49)?

**METHODS**

**Participants.** Approval for the study was obtained from the Melbourne Health Human Research Ethics Committee (approval no. 2008.147). Two groups of 11 healthy participants were recruited for the two parts of the study: thermal stimulation and mental task. The thermal stimulation group had a mean age of 34.4 (± SD 10.2) years, and the mental task group had 35.3 (± SD 11.8) years old. Both groups consisted of 10 males and 1 female, with four males participating in both trials.

**Physiological recordings.** Galvanic skin responses (GSR) were used to record sweating events, and these were measured using a pair of Ag-AgCl electrodes (TSD203 electrodes; Biopac Systems, CA, USA) that were positioned on the palmar surfaces of the participants’ right index and middle fingers. The electrodes were connected via a cable (MECMRI-3 MRI cable; Biopac Systems, Goleta, CA, USA) and filter (MRIRFIF interference filter set; Biopac Systems) to a constant voltage amplifier (GSR100C Galvanic Skin Response Amplifier; Biopac Systems). The signal was digitized at 1 kHz (Power 1401; Cambridge Electronic Design, Cambridge, UK) and recorded to computer (Spike2, ver. 7; Cambridge Electronic Design). Artifacts incurred from magnetic field switching during scanning runs 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 (28). Signals from the scanner control panel were recorded to computer and used to match the timing of electrodermal events to functional brain stem images.

**Thermal stimulation.** Participants wore a body suit (Med-Eng BCS4 Body Cooling System; Allen Vanguard, Ottawa, ON, Canada), incorporating a network of small-diameter (4 mm) plastic tubes through which temperature-controlled water was circulated. Lower and upper garments extended from ankles to the neck, covering both arms to the wrists. Additionally, a woolen blanket was placed over the suited participants, while they were warmed and scanned. The suit was connected to a water reservoir and a pump located in the scanner operating room via 10 m of 15-mm diameter plastic tubing. The water in the reservoir was adjusted to between 40°C and 50°C and was adjusted once sweating commenced (usually after 20–30 min) to maintain a low mean rate of sweating events.

**Mental task.** Participants performed a color, word Stroop task during scanning. Visual stimuli were projected onto a screen that was visible to participants via a mirror mounted on the head coil. Two different color words written with congruent or incongruent colored letters were presented sequentially in random order for 2-min blocks, interspersed with 30-s rest intervals, during the 7.9-min functional brain-scanning runs. The task was to count the number of nominated events (e.g., count the words “RED” written with yellow letters) in a 2-min block, but the subjects’ responses to the task were not analyzed and did not form part of the experiment. The sequence of events in thermal and psychogenic scanning runs is illustrated in Fig. 1.

**Functional brain images.** The magnetic resonance images used for the study were acquired with a Siemens 3-T Trio system and 32-channel head coil located at the Murdoch Children’s Research Institute (Melbourne, Australia). Functional brain stem images were acquired with blood oxygen level-dependent (BOLD) contrast that measures hemodynamic responses subsequent to neural activity (43). The slices of functional brain stem images (echo planar images) were positioned in an oblique, coronal orientation aligned with the dorsal surface of the medulla. Functional brain stem images had 21 slices of 2.5-mm thickness, and covered the entire brain stem upward from the cervical cord. Slices were divided into a 128 × 128 matrix with a spatial resolution of 1.88 mm × 1.88 mm. Functional images were acquired every 1.79 s [time to repetition (TR) = 1790 ms] with a time to echo (TE) of 30 ms and a flip angle of 70°. Scanning runs lasted 7.9 min and incorporated 265 sequential functional brain stem images. Two scanning runs were acquired from all participants during the thermal stimuli and mental tasks. A third scanning run was acquired from three participants during thermal stimulation to ensure that two runs contained sufficient instances of sweating events.

**Anatomical images acquired for registration.** To allow data from different participants to be grouped, each participant’s brain images were warped to the Montreal Neurological Institute (MNI) standard template at a spatial resolution of 1 × 1 × 1 mm (4, 11). Two types of anatomical image were acquired to control the warping. First, an echo planar image (EPI) of the whole brain (whole brain EPI) was obtained with similar parameters to the functional brain stem images (2.5-mm oblique coronal slices aligned with the dorsal surface of medulla, 128 × 128 matrix, in slice resolution 1.88 mm × 1.88 mm, TE 1100 ms, TR 1100 ms). Two functional brain stem images, one thermal and one psychogenic, were acquired for each participant. The thermal-stimulation images were acquired first, followed by the psychogenic images. The brain images were then warped to the Montreal Neurological Institute (MNI) standard template at a spatial resolution of 1 mm × 1 mm × 1 mm to allow the data from different participants to be grouped. This was achieved using SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK).

**Fig. 1.** Experimental timelines for thermal (A) and psychogenic (B) scanning runs.
= 30 ms, flip angle = 70°), but incorporating 59 additional slices (80 in total) and taking 5.5 s to acquire (TR = 5,500 ms). Secondly, a high-resolution, T1-weighted anatomical image of the whole brain was acquired from each participant (192 × 0.9 mm sagittal slices, 256 × 256 matrix, in-slice resolution 0.8 mm × 0.8 mm, TR = 1900 ms, TE = 2.59 ms, flip angle = 9°).

Image registration. The transformation of functional brain stem images from each participant to the MNI standard brain was done in three steps using the Functional Magnetic Resonance Imaging of the Brain’s (FMRI B’s) linear image registration tool (FLIRT) (16, 23, 24). In the first step, the middle image of a scanning run (to which all other images in the scanning run had been realigned) was aligned with that participant’s whole brain EPI acquired in the same scanning session. The second step involved coregistration of the participant’s whole brain EPI to the high-resolution T1-weighted anatomical image. Finally, the participant’s high-resolution T1-weighted anatomical image was warped to the MNI standard brain. Matrices representing the transformations of the three steps were multiplied to produce the global transformation from functional brain stem space to standard MNI space. This transformation matrix was applied to statistical parametric maps to perform higher levels of analyses described below. 

Analysis: preprocessing. Preparation and statistical analysis of functional brain stem images were performed with the Oxford Centre for FMRI B Software Library [Oxford, UK; FSL version 4.1 (http://www.fmrib.ox.ac.uk/fsl/)]. Sequential functional brain stem images from single-scanning runs were realigned spatially to the middle image of the run, to correct for any head movement during the scanning run using MCFLIRT (23). Images were spatially smoothed using a Gaussian kernel of 3-mm full width at half maximum. The time series of each scanning run was mean-based intensity normalized (all sequential volumes scaled by the same factor) and high pass filtered to remove low-frequency artefacts (58).

Statistical analysis. The first level of statistical analysis was performed on individual scanning runs using general linear modeling, including local autocorrelation correction, as instituted in the FMRI expert analysis tool [FEAT, FMRI B’s improved linear model (FILM)] (58). The regressor of interest for analysis was the simultaneously recorded electrodermal signal after scanning artifacts had been removed, and the signal was down-sampled to correspond to the timing of each functional brain stem image (once per 1.79 s). To adjust the appropriate relative timing, two factors were taken into account. The conduction delay between neural activity in the brain and the peak electrodermal response at the finger has been measured as 5 to 5.5 s (21). Therefore, the electrodermal regressors were translated backward in time by 5.37 s (TR × 3). Additionally, the hemodynamic response as measured by the BOLD signal lags 4 to 6 s after neural activation: compensation for this delay was factored into the standard FMRI analysis (19).

To remove the influence of known confounding factors, other regressors were added to the analysis of individual scanning runs. The brain stem is susceptible to physiological noise, including respiratory effects on local magnetic field properties and changes in the blood and cerebrospinal fluid associated with the cardiac cycle. To reduce the effects of physiological noise, regressors from three chosen regions were used in the model to account for variance associated with the cardiac and respiratory cycles, according to the procedures described by Birn et al. (3). Movement is also prevalent in the brain stem, so in addition to realignment of images as a preprocessing procedure (see above), the effects of movement were taken into account by including the six motion parameters (three translations and three rotations) into the modeling of signal changes.

The modeling of variance in BOLD signals across a time series in each scanning run was performed on a voxel-by-voxel basis. A parameter estimate was calculated for the fit of each regressor to the observed BOLD signal for each voxel in the native space of the preprocessed functional brain stem images, making a statistical parametric map for each scanning run. For subsequent analyses, these statistical parametric maps were warped to a standard template brain, as described above. A mask was applied to the grouped data to exclude voxels outside the brain stem. Statistical parametric maps were averaged between two runs for each individual, and then group averages were calculated for all participants in each condition (psychogenic or thermal sweating), as well as for contrasts between the two conditions.

Standard methods were used to calculate Z-scores for each voxel in standard brain stem space, accounting for the confounding factors noted above (1). The average statistical parametric map in each condition was then thresholded to include only voxels where Z > 2.3. Standard procedures were then used to determine significant clusters of activation by applying a cluster corrected threshold of P < 0.05 (59).

To test whether any brain stem region distinguished between thermal and psychogenic sweating events, voxelwise comparisons of BOLD signals were made between sweating-related activity in the two conditions. The results of these comparisons were then thresholded at a cluster-corrected threshold of P < 0.05.

To characterize the time course of sweating-related BOLD signals in regions of interest, (but only for that purpose), a sweating event was defined as an increase exceeding one SD above the baseline noise of the electrodermal signal, and its peak time was used as a trigger point. Electrodermal and preprocessed BOLD signals were averaged over a time window covering 30 s before and after the trigger time.

RESULTS

Experimental procedure. Sweating events were measured as abrupt increases in skin conductance and were detected as peaks in the electrodermal trace. Representative electrodermal traces from psychogenic and thermal sweating runs (after down-sampling) are shown in Fig. 2. While the baseline was smooth during psychogenic sweating runs (Fig. 2A), low-level ongoing activity was present between the large peaks during thermal sweating (Fig. 2B). That low ongoing activity, indicating small sweating events, would have made a minor contribution to the regressor for brain stem voxel analysis. Both the thermal stimulus and the mental task were adjusted to keep the frequency of large sweating events low, so as to minimize overlap and to preserve the contrast between those events and

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Fig. 2. Examples of electrodermal recordings that were used to extract sweating event-related activity from the brain stem. These show representative records of 7.9-min scanning periods during the mental task (upper trace) and during heating (lower trace). Previously, scanning artifacts were removed from the raw AC recording, and the signal was down-sampled to once per 1.79 s so as to match the imaging sequence (see MATERIALS AND METHODS). The straight dotted line in each trace denotes one SD greater than the mean. Further details are given in the text.
the intervening periods. The mean numbers of sweating events during each 7.9-min scanning sequence that exceeded the mean level by 1 SD (horizontal lines in Fig. 2) were 7.3 ± 2.1 and 10.2 ± 2.5 for psychogenic and thermal sweating runs, respectively.

Brain stem sites activated in association with thermal and psychogenic sweating events. The brain stem regions that showed significant clusters of voxels activated in association with thermal and psychogenic sweating events are listed in Table 1. The principal regions are illustrated in Fig. 3 and will be described further below.

No brain stem clusters were found to show a significant reduction in BOLD signal (“deactivation”) associated with electrophysiological events during either thermal or psychogenic sweating.

To test whether any brain stem regions were preferentially activated with thermal or with psychogenic sweating events, a voxelwise comparison was made between sweating-related BOLD signal changes in the two conditions. This revealed no brain stem region that was activated significantly more during thermal than psychogenic sweating events, or vice versa ($P$ (corrected) > 0.05).

Principal regions of activation. Although there was no statistical difference between regions activated during thermal and psychogenic sweating events, the thresholded activation maps from each condition were not identical. As with other human fMRI studies, such minor anomalies are to be expected when detecting small signals against a noisy background (25). Two features were used to select the activated regions that were most likely to be significant. First, on the basis that thermal and psychogenic sweating events were evidently equivalent (see above) “consensus” voxels that were activated significantly by both stimuli were identified. These were collected green in Fig. 3.

Second, on the basis that sweating events occur bilaterally over the body but the descending brain stem tracts drive sweating unilaterally (see introduction), we infer that the medullary pathways on the left and the right sides must be activated together (by an unidentified antecedent source). Therefore, we sought areas that were activated roughly symmetrically on either side of the brain stem. This “logical filter” highlighted two areas: the dorsal midbrain and the rostral lateral medulla.

Dorsal midbrain activation. The dorsal midbrain region showing bilateral consensus activation was ventral to the superior colliculi, level with the rostral end of the cerebral aqueduct. The locus of consensus activation appeared to be centered lateral to the periaqueductal gray matter (PAG) but may have involved lateral parts of the PAG. The mean BOLD signals extracted from these voxels during thermal and psychogenic sweating events are shown in Fig. 4, A and B. Their relative timing coincided closely, reflecting the fact that the hemodynamic response to generate the BOLD signal and the conduction-plus-neuroeffector time to generate the electrodermal response both imposed delays of about 5 s. The peak increase in mean BOLD signal there was 0.7 to 1.0%.

Rostral medullary activation. This bilateral region of consensus activation extended through the rostral medulla up to the lower pons. This cluster was centered near the lateral margin of the brain stem, ventral to the facial nucleus and dorsal to the pyramidal tract. The mean BOLD signals from this region are shown in Fig. 4, C and D. The peak signal increase here was 1.2 to 1.4%.

### DISCUSSION

So far as we are aware, this is the first neuroimaging study to investigate the human brain stem regions involved in sweating, although a number of studies have investigated the forebrain structures involved (e.g., 8, 14, 37, 46, 57). In answer to the first question that we posed, we found several regions in the midbrain, pons, and medulla that were activated in association with thermal and psychogenic sweating (detailed in Table 1). In answer to our second question—Was any region associated specifically with psychogenic or thermal sweating?—no region showed any such preference. To our final question—Could we identify the human homolog of the rostral medullary cell group that drives sweating in cats (49)?—the answer is yes (discussed below).

Sweating occurs in bursts (54), driven by the bursting pattern of sympathetic sudomotor nerve activity (2). Each burst generates a volume of sweat, which dilutes the sweat duct and lowers transdermal resistance, measured as the electrodermal response. At low levels of sweating (as here) the precursor sweat is reabsorbed and disperses over the next few seconds, the duct collapsens, and skin conductance falls again. An AC-coupled skin resistance signal gives an index of bursts of sudomotor nerve activity (28), and we have used it here to measure the strength and timing of sweating bursts. Because sweating bursts show clear synchrony across body regions (17, 38, 45, 56), the electrodermal signal from the fingers of one hand served as a suitable measure of the whole body response.

The experimental design used these sporadic sweating events, which were unsynchronized to any experimental intervention, as a regressor; established methods were then used to identify...
brain stem regions whose BOLD signals were correlated with that regressor.

The generator of sweating bursts is unknown. At high rates of sweating, they become regular and occur at $\approx 80–100$ bursts/min (2, 42), suggesting that they are driven by a central “oscillator”. While it is conceivable that left-right connections between the bilateral regions identified here could generate that rhythm [by analogy with the respiratory rhythm (52)], it seems more likely that they receive periodic drive from an oscillator located elsewhere. This inference is based on the finding that forebrain structures also show activity related to sweating bursts (6), and the likelihood that the pontomedullary locus of activation represents the descending output pathway from the brain (see below). Further work is needed to answer this.

To the best of our knowledge the midbrain site we identified as activated with sweating has not been highlighted as such in previous human work. In cats, Davison and Koss (10) used electrical stimulation to map sudomotor pathways from the hypothalamus to the caudal medulla and found that the excitatory tract passed through the midbrain ventrolaterally to the periaqueductal gray matter. Their use of electrical stimulation prevented them from identifying synaptic relays in the pathway, because this method does not distinguish between cell bodies and fiber tracts. An excitatory BOLD signal, however, suggests a synaptic relay. The anatomical correspondence between the cat and human data is plausible, so this region could represent a synaptic relay in the descending sudomotor pathway.

By contrast, the site of strong bilateral activation in the rostral medulla was expected on the basis of animal work. McAllen (35) identified a region near the ventral surface of the rostral medulla, which, when activated with microinjections of excitant amino acid, drove sweating in the cat’s paw. That region was anatomically distinct from, and rostromedial to, the vasomotor premotor neurons of the rostral ventrolateral medulla (RVLM; subretrofacial nucleus) (9). A subsequent study on cats (49) mapped the sudomotor cell group to a discrete locus between the facial nucleus and the pyramidal tract. Excitant amino acids activate neurons but not fiber tracts (15), so this juxtafacial region represents a synaptic relay within the cat sudomotor pathway. The bilateral region with sweating-related activity identified here in the human rostral medulla (Fig. 3) was also centered between the facial nucleus and the pyramidal tract (Fig. 4). The strong sweating-related BOLD signal in the juxtafacial region of the human medulla (Fig. 4) also indicates the presence of a synaptic relay rather than a fiber tract.

Limitations. As with all human imaging studies, the conclusions reached here are based on correlation rather than proof of causation. In the case of psychogenic sweating, for example, it is conceivable that each sweating event signals a “mini-arousal,” to which the medullary and midbrain regions identified here respond in parallel with, but not directly linked to,
sweating. Indeed, this could also apply during thermal sweating. However, previous work has demonstrated that transient sweating events and “arousal” (measured by mean skin conductance) are linked to activation of distinct cerebral regions (37). Sweating events can, thus, be used to discriminate sweating-related brain activity over and above any background arousal. This suggests that the BOLD signals correlated with sweating events reflect sweating per se.

The participants were unselected volunteers, with only one female in each group. Thus, although we expect brain stem mechanisms to apply equally to both sexes, we could not test this from our sample.

We recorded electrodermal responses from the palmar surface of fingers on one hand, and used this as a general index on the basis that sweating events across the body occur synchronously. However, sweating responses may differ in amplitude over body regions (33). Therefore, if any body map exists within brain stem sweating pathways, our view would be biased toward the hand.

Perspectives and Significance

It is encouraging to find the human homolog of a brain stem cell group identified in animals: it gives confidence that both findings are correct and demonstrates the evolutionary conservation of a basic physiological mechanism. In two previous cases, fMRI studies of the human brain stem have found a remarkably accurate correspondence between functional maps of autonomic control and anatomical predictions based on animal studies. These were the demonstration of the involvement of the rostral medullary raphé in cold-defense (36) and of the RVLM (and caudal ventrolateral medulla) in vasomotor control (29, 30). We consider that the sweating-related juxtafacial activation identified here adds a third example. Animal studies indicate that, like the cell groups in the rostral medullary raphé and RVLM, neurons in this region (called rostral ventromedial medulla, RVMM, in rats) send their axons directly to sympathetic preganglionic neurons (22, 53). This juxtafacial region in the human brain stem may, therefore, contain the final common premotor pathway that transmits to the spinal sympathetic neurons the descending signals that drive both thermal and psychogenic sweating. In each case, it remains to be determined which antecedent pathways drive those neurons to cause sweating.

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AUTHOR CONTRIBUTIONS


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