Evidence for central command activation of the human insular cortex during exercise

J. W. Williamson,1 R. McColl,2 and D. Mathews2

Departments of 1Health Care Sciences, Physical Therapy, and 2Radiology, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75390-8876

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Williamson, J. W., R. McColl, and D. Mathews. Evidence for central command activation of the human insular cortex during exercise. J Appl Physiol 94: 1726–1734, 2003.—The purpose of this investigation was to determine whether central command activated regions of the insular cortex, independent of muscle metaboreflex activation and blood pressure elevations. Subjects (n = 8) were studied during 1) rest with cuff occlusion, 2) static handgrip exercise (SHG) sufficient to increase mean blood pressure (MBP) by 15 mmHg, and 3) post-SHG exercise cuff occlusion (PECO) to sustain the 15-mmHg blood pressure increase. Data were collected for heart rate, MBP, ratings of perceived exertion (SHG) and PECO, heart rate (7 time periods were compared when MBP was matched during using single-photon-emission computed tomography. When blood pressure elevations. Because prior studies (11, 27) have shown insular activation to be independent of mechanoreflex input, it was not presently assessed. These findings provide evidence that there are rCBF changes within regions of the insular and anterior cingulate cortices related to central command per se during handgrip exercise, independent of metaboreflex activation and blood pressure elevation.

heart rate (HR) and blood pressure (BP) (9). Central command and muscle afferent input also interact with baroreflex mechanisms (10). Studies investigating the functional anatomy of central command-induced changes in regional cerebral blood flow (rCBF) have identified a network of cortical structures involved, namely the insular cortex (4, 6, 12, 25–27) and anterior cingulate cortex (4, 6, 26, 27). These structures appear to be activated in response to an increased perception of physical effort during exercise when HR and BP are elevated. However, the exercise-mediated increases in BP, as well as skeletal muscle afferent activation, can independently act to alter rCBF within the insular cortex (22, 29).

Although the insular cortex has been implicated in the overall scheme of cardiovascular regulation (3, 14, 18, 19, 21), it can be selectively activated by simple changes in BP (29) and by muscle afferent input (22). Zhang and Oppenheimer (29) recorded firing patterns of both sympathoexcitatory and sympathoinhibitory neuronal units within the insular cortex after administration of phenylephrine (PE) in anesthetized rats. The PE-induced elevations in BP reduced firing of sympathoexcitatory units, whereas firing patterns for sympathoinhibitory units were increased. Waldrop and Iwamoto (22) reported that a group of sympathetic and/or cardiac-related insular neurons responded to muscular contraction, independent of arterial BP changes. These studies raise the possibility that the previously reported central command-related changes in patterns of brain activation may actually be governed by the concomitant changes in BP and/or muscle afferent input during exercise.

The purpose of this investigation was to determine whether central command activated regions of the insular cortex, independent of muscle metaboreflex input or BP elevations. Because prior studies (11, 27) have shown insular activation to be independent of muscle mechanoreflex input, this aspect was not specifically tested within the present study design. To address this question, patterns of brain activation were contrasted between conditions of static handgrip exercise (SHG) (increased central command, metaboreflex activation, BP elevation) and postexercise circulatory

DURING EXERCISE, CENTRAL COMMAND SIGNALS from the higher brain are thought to converge with afferent signals arising from the working skeletal muscle at medullary centers of cardiovascular integration to yield an overall cardiovascular response in proportion to the intensity of physical activity or perceived effort (5, 9, 23). Both of these mechanisms, central command and muscle afferent input, can act independently to elicit cardiovascular responses, namely elevations in

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Address for reprint requests and other correspondence: J. W. Williamson, UT Southwestern Allied Health Sciences School, 5323 Harry Hines Blvd., Dallas, TX 75390-8876 (E-mail: jon.williamson @utsouthwestern.edu).

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occlusion (PECO) with BP sustained at a level to match the exercise BP response (no central command, metaboreflex activation, BP elevation). Because PECO was initiated during the last seconds of SHG, the assumption was made that the magnitude of metaboreflex activation would be similar between conditions. Therefore, with levels of BP and muscle metaboreflex input “matched” between conditions, differences in rCBF would be related to the differences in the level of central command. We hypothesized that there would be regions of the insular cortex and anterior cingulate cortex activated only during the exercise condition, presumably by central command.

Additionally, the effect of prior SHG on rCBF distribution was assessed during postexercise recovery without circulatory occlusion. This was done to ensure that there was not a significant temporal lag between the time that exercise was terminated and brain blood flow returned to preexercise resting levels. rCBF distributions were determined for each condition in several cerebral cortical regions by using single-photon-emission computed tomography (SPECT) coregistered with magnetic resonance images (MRI).

METHODS

Subjects. Sixteen subjects volunteered to participate in this experiment. All participants provided written, informed consent before participating in this study, which was approved by the University of Texas Southwestern Medical Center Institutional Review Board and Radiation Safety Committee. The participants were provided information on the research protocols and were randomly assigned to one of three subjects. Three subjects, one assigned to the BP-match protocol three times on different days. A retained brain blood flow tracer was injected during a different portion of the test each time the protocol was performed, either during the rest portion, during the last minute of the handgrip portion, or during the postexercise circulatory occlusion portion. The portion of the test when the blood flow tracer was to be injected was randomized across test days and subjects. The primary goal of this protocol was to elevate mean BP (MBP) during SHG and then sustain the MBP during postexercise conditions (a target of 15 mmHg). For the SHG test, subjects began squeezing the dynamometer at 40% MVC. Depending on their individual MBP responses, subjects were provided verbal feedback to adjust their grip strength to achieve the target BP increase. This verbal cueing was continued as needed for 3 min of SHG to ensure that MBP remained within the target region. The brain blood flow tracer was injected during the last minute of exercise when MBP was stable. The verbal cueing was minimal during this last minute of exercise. A rating of perceived exertion (RPE) was taken every 20 s during the last minute of SHG by using a standard 6- to 20-unit scale (2). For PECO, the SHG was repeated, and an arm cuff was inflated to 250 mmHg during the last few seconds of exercise. Subjects were asked to stop squeezing and remain quiet while MBP was sustained. Over the next 40 s with PECO, HR was allowed to return toward baseline values while MBP was sustained. After 40 s, the brain blood flow tracer was injected, and the cuff remained inflated for an additional minute. A rating of discomfort produced by the arm cuff occlusion was also assessed at the end of each test by using a 10-point category scale.

For subjects involved in the postexercise recovery protocol, the tests involved a resting baseline (no cuff occlusion), handgrip exercise, and postexercise recovery without circulatory occlusion. Each subject performed this protocol three times on different days. A retained brain blood flow tracer was injected during a different portion of the test each time the protocol was performed (either during the rest portion, during the last minute of the SHG portion, or during the postexercise recovery portion). The portion of the test when the blood flow tracer was to be injected was randomized across test days and subjects. The goal of this protocol was to duplicate the SHG, as used in the other protocol, and assess postexercise responses to determine whether the exercise might have an influence on postexercise responses. For the SHG test, subjects again began squeezing the dynamometer at 40% MVC and were provided 3 min of verbal feedback, as needed, to adjust their grip strength so as to achieve and sustain the 15-mmHg target MBP increase. The brain blood flow tracer was again injected at minute 2 of the 3-min SHG test. For the postexercise recovery, the exercise protocol was repeated. At the end of SHG, subjects were asked to stop squeezing, relax, and sit quietly. Over the next 40 s, BP and HR were allowed to return toward baseline values. The brain blood flow tracer was then injected, and the subjects sat quietly for an additional minute.

rCBF assessment. To determine the rCBF distributions during each testing condition, 20 mCi of freshly reconstituted
Tc-99m ethylcysteinate dimer (Neuro lite, Du Pont Pharma, Billerica, MA) was injected intravenously. This retained brain blood flow tracer is a photon emitter with a physical half-life of 6 h. Increases in rCBF to a particular region of the brain subsequently led to an increase in the amount of radioactivity recorded from that region (16). A technician administered the blood flow tracer and flushed the catheter with normal saline. The subjects continued their activity for an additional minute to facilitate appropriate distribution of the tracer. Because their eyes were closed during exercise, subjects were unaware of the exact time of injection and reported no noticeable side effects. All subjects were taken to the SPECT camera room 20 min after exercise, and scanning was completed within 50 min of injection for all subjects. Brain scanning procedures have been previously reported in detail (25).

Image processing and statistical analysis. Each individual's brain images were aligned in three dimensions by a computer using an automated volume coregistration algorithm widely used for PET-PET coregistration (28). Once the SPECT scans for a given subject were coregistered, normalization of total radioactive count variability was obtained by rescaling the image so that total counts were equal for all volumes. After SPECT-SPECT coregistration for each individual, SPECT-MR coregistration was obtained by using an interactive coregistration algorithm (8) implemented on the workstation after the SPECT voxel size was made to match the MR voxel size. The absolute and percent count differences for each pixel were obtained between scans. These differences were then displayed for a selected slice within the volume as a color overlay superimposed on the MR.

Specific brain regions and structures were located by using the coregistered MR as an anatomic reference. With the use of the computer, regions of interest (ROI) were drawn around these areas, as seen on the MR slice. This procedure was repeated on contiguous transaxial slices until the entire brain region/structure had been assessed across all slices. The number of 1.5-mm slices assessed varied by specific region and subject but was consistent across subjects.

On the basis of findings from prior human studies involving the insular cortex (4, 6, 14) and the spatial resolution of the SPECT methodology, the relatively large insular regions were divided into smaller divisions for analysis. The right and left insular regions were further subdivided into four equal quadrants on the basis of each individual and left insular regions were divided into smaller divisions for analysis. The right insular region and subject but was consistent across subjects. The SPECT methodology, the relatively large insular regions

RESULTS

SHG and PECO. This protocol involved SHG and postexercise circulatory occlusion with similar BP elevations and the assessment of cardiovascular changes and rCBF distribution as radioactive counts within the specific ROIs across conditions. Data for MBP, HR, force (%MVC) and RPE during SHG and perceived pain/discomfort during PECO are presented in Fig. 1.

There were significant elevations in MBP from rest during the last minute of SHG (94 ± 7 vs. 108 ± 5 mmHg; P < 0.05). Likewise, MBP remained elevated during PECO (107 ± 5 mmHg), and values did not differ from the last minute of SHG. HR was elevated during the last minute of SHG (7 ± 3.3 beats/min; P < 0.05) and returned to resting levels during PECO. There was a significant decrease in the force required to sustain MBP from the first to last minutes of exercise (39 ± 1 to 24 ± 5% MVC; P < 0.05) even though MBP and HR remained constant over the last minute of exercise. RPE also remained relatively constant at 15 ± 1 units (on a 6–20 point scale) over the last minute of exercise, despite the decrease in force over the same time period. During PECO, subjects rated the perceived level of pain at 2 ± 1 units on a 0–10 point scale.

Changes in cerebral cortical activation across conditions are shown in Table 1. The dominant and non-dominant hand sensorimotor regions showed significant increases in activity from rest during SHG at 9 ± 3 and 5 ± 2%, respectively. There was an increase in activation for the anterior cingulate (6 ± 2%) during SHG. The right inferior thalamus showed significant activation during both SHG (15 ± 3%) and PECO (12 ± 3%). Likewise, there was increased activation in the left inferior thalamus for both conditions. Although the right inferior anterior insula was activated during both SHG and PECO, the right inferior posterior insula was activated only during SHG (7 ± 3%). The SHG also elicited activation of the left inferior anterior insula (8 ± 2; P < 0.05), whereas PECO did not produce activation in this region (Fig. 2). There was no significant activation or deactivation for the other cerebral cortical regions assessed.
Rest vs. postexercise recovery. This protocol involved comparing patterns of brain activation between a pre-exercise resting period, exercise, and postexercise recovery period (40 s after termination of handgrip) for changes in rCBF distribution as radioactive counts within the specific ROIs across conditions. Data for MBP, HR, force (%MVC), and RPE during SHG were also collected.

There were significant elevations in MBP from pre-exercise rest during the last minute of SHG (97 ± 8 vs. 110 ± 7 mmHg; \(P < 0.05\)). After 40 s of recovery, the postexercise resting MBP was not different from pre-exercise resting MBP (96 ± 7 vs. 97 ± 8 mmHg). Although HR was elevated during the last minute of SGH (+8 ± 6 beats/min; \(P < 0.05\)), values had returned to resting levels during postexercise recovery (68 ± 5 vs. 66 ± 5 beats/min). Similar to the other protocol, there was a significant decrease in the force from the first to last minutes of exercise as needed to achieve a MBP increase of ~15 mmHg (41 ± 1 to 22 ± 4% MVC; \(P < 0.05\)). RPE also remained relatively constant at 15 ± 1 units (on a 6–20 point scale) over the last minute of exercise, despite the decrease in force. During postexercise recovery, subjects rated the perceived level of pain at 1 ± 1 units (on 0–10 point scale).

With respect to changes in cerebral cortical activation across conditions, the dominant and nondominant hand sensorimotor regions showed significant increases in activity from rest during SHG at +8 ± 3% and +5 ± 2%, respectively. However, there were no significant changes from preexercise rest during the
showed significant activation during SHG. Both the right and left inferior thalamic regions showed significant activation during SHG (+12 ± 3
d and +8 ± 3%, respectively). The right inferior anterior insula (+5 ± 2%), right inferior posterior insula (+7 ± 2%), and left inferior anterior insula (+7.5 ± 2) all showed significant activation during SHG. These re-

Table 1. Changes in cerebral cortical activation across conditions

<table>
<thead>
<tr>
<th>Cortical Region</th>
<th>Rest</th>
<th>SHG</th>
<th>Change, % from rest</th>
<th>PECO</th>
<th>Change, % from rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant arm sensorimotor (BA 1-4)</td>
<td>493 ± 36</td>
<td>535 ± 40</td>
<td>+8.5 ± 3%</td>
<td>488 ± 41</td>
<td>-1.0 ± 4%</td>
</tr>
<tr>
<td>Nondominant arm sensorimotor (BA 1-4)</td>
<td>489 ± 33</td>
<td>515 ± 36</td>
<td>+5.3 ± 3%</td>
<td>480 ± 34</td>
<td>-1.6 ± 3%</td>
</tr>
<tr>
<td>Anterior cingulate cortex (BA 24 &amp; 32)</td>
<td>472 ± 30</td>
<td>501 ± 33</td>
<td>+6.1 ± 2%</td>
<td>480 ± 34</td>
<td>+1.7 ± 2%</td>
</tr>
<tr>
<td>Right superior thalamus</td>
<td>418 ± 29</td>
<td>424 ± 40</td>
<td>+1.4 ± 3%</td>
<td>430 ± 48</td>
<td>+2.9 ± 3%</td>
</tr>
<tr>
<td>Right inferior thalamus</td>
<td>401 ± 32</td>
<td>459 ± 34</td>
<td>+14.5 ± 3%</td>
<td>448 ± 42</td>
<td>+11.7 ± 3%</td>
</tr>
<tr>
<td>Left superior thalamus</td>
<td>411 ± 34</td>
<td>429 ± 41</td>
<td>+4.3 ± 3%</td>
<td>428 ± 45</td>
<td>+4.1 ± 3%</td>
</tr>
<tr>
<td>Left inferior thalamus</td>
<td>408 ± 36</td>
<td>447 ± 39</td>
<td>+9.6 ± 3%</td>
<td>443 ± 44</td>
<td>+8.6 ± 3%</td>
</tr>
<tr>
<td>Right superior, anterior insular</td>
<td>397 ± 33</td>
<td>402 ± 38</td>
<td>+1.3 ± 3%</td>
<td>406 ± 37</td>
<td>+2.2 ± 4%</td>
</tr>
<tr>
<td>Right superior, posterior insular</td>
<td>388 ± 43</td>
<td>395 ± 41</td>
<td>+1.8 ± 4%</td>
<td>401 ± 44</td>
<td>+3.3 ± 3%</td>
</tr>
<tr>
<td>Right inferior, anterior insular</td>
<td>402 ± 31</td>
<td>422 ± 35</td>
<td>+5.0 ± 2%</td>
<td>427 ± 37</td>
<td>+6.2 ± 3%</td>
</tr>
<tr>
<td>Right inferior, posterior insular</td>
<td>416 ± 42</td>
<td>444 ± 33</td>
<td>+6.7 ± 3%</td>
<td>428 ± 30</td>
<td>+2.9 ± 3%</td>
</tr>
<tr>
<td>Left superior, anterior insular</td>
<td>405 ± 40</td>
<td>418 ± 37</td>
<td>+3.2 ± 3%</td>
<td>398 ± 47</td>
<td>-1.7 ± 2%</td>
</tr>
<tr>
<td>Left superior, posterior insular</td>
<td>396 ± 42</td>
<td>402 ± 34</td>
<td>+1.5 ± 3%</td>
<td>399 ± 32</td>
<td>+0.7 ± 2%</td>
</tr>
<tr>
<td>Left inferior, anterior insular</td>
<td>405 ± 33</td>
<td>438 ± 29</td>
<td>+8.1 ± 2%</td>
<td>410 ± 37</td>
<td>1.2 ± 3%</td>
</tr>
<tr>
<td>Left inferior, posterior insular</td>
<td>389 ± 42</td>
<td>371 ± 27</td>
<td>-4.6 ± 2%</td>
<td>378 ± 32</td>
<td>-2.8 ± 2%</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>517 ± 44</td>
<td>529 ± 42</td>
<td>+2.3 ± 4%</td>
<td>534 ± 49</td>
<td>+3.3 ± 4%</td>
</tr>
<tr>
<td>Corpus callosum (white matter corr.)</td>
<td>317 ± 25</td>
<td>322 ± 27</td>
<td>+1.6 ± 1%</td>
<td>325 ± 31</td>
<td>+2.5 ± 2%</td>
</tr>
</tbody>
</table>

Values are for means ± SD of radioactive counts recorded from each region of interest (ROI) across conditions for rest, static handgrip (SHG), and postexercise circulatory occlusion (PECO). BA, Brodmann’s areas. *Significance from rest; †Significance between SHG and PECO conditions at P < 0.05.

postexercise rest. There was an increase in activation for the anterior cingulate (7 ± 3%), but only during SHG. Both the right and left inferior thalamic regions showed significant activation during SHG (+12 ± 3 and +8 ± 3%, respectively). The right inferior anterior insula (+5 ± 2%), right inferior posterior insula (+7 ± 2%), and left inferior anterior insula (+7.5 ± 2) all showed significant activation during SHG. These re-

Fig. 2. Differences in brain activation from rest for SHG (left) and PECO (middle) matched for the same MBP elevation. Coregistered single-photon-emission computed tomography (SPECT) and MRI data representing a transaxial slice from one subject. The coronal and sagittal MRI figures (right) show lines of orientation for the transaxial slice. Top and bottom of the transaxial figures correspond to an anterior and posterior orientation, respectively. Changes in rCBF distribution from SPECT data were mapped on the MRI by using an arbitrary color scale with a positive range from 5 to 25% (from green through yellow to red) and negative range from −5 to −25% (from purple through dark blue to light blue). The white lines denote the specific regions of interest assessed (in this brain slice) and encompass the right and left insular cortices for inferior anterior (ICa) and inferior posterior (ICp) regions, right and left inferior thalamic regions (THa), and anterior cingulate cortex (AC). The image shows the significant increases in activation for both anterior cingulate and insular regions for this subject during SHG with blood pressure matched to PECO. Although these regions were not activated during PECO, there is significant activation in the thalamus and right inferior anterior insula, similar to that observed for the SHG.

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DISCUSSION

The primary finding of this investigation was that there were distinct regions of the insular cortex and anterior cingulate cortex activated during SHG by central command, independent of muscle metaboreflex activation or BP elevations. Regions of the insular cortex and thalamus also showed activation during both handgrip and postexercise circulatory occlusion, suggesting that these specific sites may be related to the muscle afferent input or BP elevations as reported in prior studies (22, 29). When preexercise rest was compared with postexercise recovery without circulatory occlusion, there were no significant differences in rCBF distribution. This indicates that the responses observed during postexercise circulatory occlusion did not result from the preceding exercise bout. Taken together, these data support the hypothesis that regions of the insular cortex and anterior cingulate cortex can be activated by central command per se. Human studies investigating central command-induced changes in rCBF have consistently reported activity within insular cortex (4, 6, 12, 25–27) and anterior cingulate cortex (4, 6, 26, 27). However, the potentially confounding effects of concomitant BP elevations (29) and muscle afferent input (22) on insular cortex activation had not been previously addressed during exercise in humans.

Central command-related responses. A goal of this investigation was to uncouple the effects of central command on rCBF from those of BP elevations occurring during exercise. Central command is generally thought to have a greater effect on HR and cardiac output (7, 24) than on BP, with the latter being attributed to a pressor reflex response generated by the contracting skeletal muscle (5, 9). The handgrip force was continually adjusted such that MBP could be elevated by ~15 mmHg and then sustained, via reductions in force as needed. At the end of SHG, the arm cuff was rapidly inflated to trap the metabolites within the muscle and sustain metaboreflex activation. As shown in Fig. 1, BP elevations were similar between SHG and PECO, suggesting that muscle metaboreflex activation was most likely driving the MBP increases during both conditions. Over the last minute of the SHG with MBP maintained, the RPE remained relatively constant at 15 ± 2 units, indicating that the level of central command was sustained during this period (9). As would be expected with central command activation during SHG, HR was elevated, but returned toward resting levels during PECO (Fig. 1). Thus, with similar activation of muscle metaboreflexes and BP elevation between conditions, differences in patterns of rCBF are likely related to the presence of central command during SHG.

To assess patterns of brain activation within the insular cortex, the right and left insular cortices were subdivided into four equal quadrants (superior anterior, superior posterior, inferior anterior, inferior posterior) by using standard planes of reference for human study. This was done to determine whether there were more specific regions of central command-induced activation within this relatively large cortical structure than previously reported without compromising the spatial resolution of the SPECT technique. With regards to the functional anatomy of central command per se, the right inferior posterior and left inferior anterior insular regions were activated to a greater extent during exercise, but not during PECO with BP elevated (Fig. 2). In closer examination of data provided by King et al. (6) during a brief bout of SHG, it appears that the right posterior insular region was activated during the handgrip but not immediately postexercise. Critchley et al. (4) also reported activation of the right posterior insular region during handgrip, as well as in response to mental stress. If the classical definition of central command is broadened to one’s “sense of effort” independent of actual exercise (26), then a variety of “effortful” tasks (i.e., mental arithmetic) resulting in cardiovascular activity could activate similar cortical networks to elicit cardiovascular responses. Findings of the left inferior anterior activation are consistent with previous work demonstrating a significant correlation with HR (25). It should be noted that activation of the right inferior posterior insular region was also reported to covary with BP (4, 25). However, present data would suggest that this insular activation may be more related to central command or effort sense than to actual changes in BP.

The insular cortex has been implicated in the central modulation of autonomic function with reciprocal connections to limbic structures (3, 18, 19, 21). The primary limbic structure implicated in exercise-related brain activation has been the anterior cingulate cortex (4, 6, 26, 27). Activation of the anterior cingulate was presently observed during SHG, but not during PECO, implicating it in the functional anatomy of central command. Although the anterior cingulate cortex has been shown to be involved in the perceived unpleasantness of painful stimuli (17), the absence of activation during PECO indicates that it did not respond to a metaboreflex stimulus sufficient to drive BP elevations. The rating of perceived pain during PECO was a 2 ± 1 unit on the 0–10 point scale, corresponding to a sensation of being “uncomfortable,” and was well below a “painful” level denoted by a rating of 6 units. This indicates that the metaboreflex activation was not perceived as painful stimuli and that the anterior cingulate activation was likely related to sense of effort or central command.

With regard to a specific role of the anterior cingulate cortex as related to central command, it is largely involved in the discrimination of peripheral somatosensory input. Thus it could serve to interpret an individual’s level of central command (or sense of effort...
or exertion). This region defined as the anterior cingulate cortex by both Critchley et al. (4) and the present study is included within the region termed the medial prefrontal cortex by King et al. (6). They reported that activation of this medial prefrontal region during SHG was associated with cardiovascular activation. Reviews by Cechetto and Saper (3) and Verberne and Owens (21) have defined a significant role for the medial prefrontal cortex in cardiovascular regulation, and this area appears to have a role in central command (26, 27). This suggests that the anterior cingulate cortex may function in cooperation with portions of the insular cortex as a “central command network,” functioning to interpret an individual’s sense of effort and elicit an appropriate autonomic adjustment to affect cardiovascular responses.

Noncentral command-related responses. During SHG, hand sensorimotor regions showed significant activation (Table 1), as found in previous work (4, 11, 13, 25–27). This sensorimotor region was not activated during postexercise circulatory occlusion, suggesting that it may not have encompassed a significant sensory region for the hand or that the metabolic afferent signals may be integrated in a different region of the brain. Sensorimotor regions are typically activated during exercise with the execution of movement but are not requisite for modulation of cardiovascular responses (27). Nowak et al. (11) have previously concluded that it is unlikely that activation of sensorimotor cortex represents a central command influence on the cardiovascular system.

With regard to common sites of activation between exercise and postexercise circulatory occlusion at similar BP, the thalamus and right inferior anterior insular region showed significant activation. Given the similarity in responses between conditions, these regions are most likely responding to baroreceptor activation (29) and/or muscle afferent input (22). The present study design does not allow for differentiation between these two mechanisms. However, the finding is consistent with data from King et al. (6), who showed right anterior insular activation during SHG, Valsalva’s maneuver, and maximal inspiration procedures, during which time BP was elevated.

As noted previously, PE-induced elevations in BP in rats reduced firing of insular sympathoexcitatory units, whereas firing patterns of sympathoinhibitory units were increased (29). On the basis of the overall distributions of excitatory and inhibitory neurons within the insula, both increases and decreases in insular activity might be expected in response to BP elevations. In the present study, the left inferior posterior insular also showed a tendency for decreased activity when BP was increased, and it has previously been reported that PECO can result in decreased rCBF for the insular cortex (25). Waldrop and Iwamoto (22) located a group of sympathetic and/or cardiac-related insular neurons that responded to muscular contraction. These same neurons showed decreased firing when PE was used to elevate arterial BP. Thus the insular cortex appears to be capable of responding to multiple inputs from arterial baroreceptors, muscle afferents, and central command. Further comparisons regarding activation patterns of the insula between studies is complicated by the potential species differences, coupled with possible anatomic and neurophysiological variations within species.

The thalamus was subdivided into superior (dorsal) and inferior (ventral) portions for right and left sides. There was significant activation of the right and left inferior thalamic regions during both handgrip exercise and postexercise circulatory occlusion. The inferior (or ventral) region of the thalamus presently activated appears to be analogous to the ventroposterior region previously demonstrated to have reciprocal connections with the insular cortex (3, 19) and may be further related to baroreceptor activation (3). BP changes have been shown to elicit activity in the thalamus (3, 30). Zhang and Oppenheimer (30) determined that a significant portion of baroreceptor-related neurons from the ventrobasal thalamus were reciprocally connected with the posterior insula in the rat. It has been reported that regions of the human ventrocaudal nucleus of the thalamus are involved in the integration of afferent baroreceptor information (15). When directly stimulated, these thalamic regions can elicit increases in HR and BP in humans (20). Taken together with the present findings, regions of the human thalamus appear to have a key role in the overall regulation of BP via baroreflex mechanisms, and further study is needed to better define its specific function.

Limitations. The cerebral cortical regions identified in this study may not be inclusive of all brain regions involved in the functional anatomy of central command as the spatial resolution of the SPECT technique (~10–12 mm) does not allow us to assess, with confidence, smaller structures that may also play an important role in cardiovascular regulation, such as midbrain regions. Also, regions of increased or decreased rCBF distribution, relative to a baseline condition, have been identified, but it is not possible to determine the specific type of neural activity (i.e., excitatory or inhibitory) related to these changes in rCBF.

Although a muscle metaboreflex signal may have been similar between conditions of SHG and PECO, it is likely that SHG would produce a greater degree of muscle mechanoreflex activation. It could be suggested that differences in insular activation may be related to this mechanical afferent input; however, prior studies during imagined exercise, with no muscle afferent input, activated similar regions of the insular cortex as those presently reported (27). Furthermore, Nowak (13) has reported insular activation during attempted movement in spinal cord injured subjects with no afferent feedback. These findings argue in favor of a central command effect with regard to insular activation as opposed to a muscle mechanoreflex effect. However, these studies cannot definitively rule out a possible role for muscle mechanoreceptor involvement in the observed insular activation.
The insula has also been implicated in an auditory network. Thus it is possible that the verbal cueing to squeeze given to some subjects during SHG could have contributed to insular activity. This cueing was only provided as needed, typically once or twice during the last minute of SHG, and was not consistent. It would appear that such cueing would not lead to significant activation of the insular cortex (1), but the possibility of an auditory-related activation cannot be discounted.

Changes in PCO2 during exercise can alter global cerebral blood flow; however, we would not expect significant changes in PCO2 during the SHG used. Although no direct measures of PCO2 were made, the rCBF data were corrected for the small white matter flow changes (+2 ± 1%) that reflect global cerebral blood flow. Novel information regarding patterns of cerebral cortical activation has been provided for one level of BP change (−15 mmHg), but it is not clear whether the present findings can be extrapolated for higher (or lower) BP changes.

In conclusion, findings from this investigation show distinct regions of the right and left insular cortices and the anterior cingulate cortex activated during SHG, presumably by central command. Although prior (13, 27) studies have demonstrated insular activation dependent of the muscle mechanoreflexes, the present study design does not eliminate the possible involvement of muscle mechanoreceptor input. There were also regions of the insular cortex and thalamus activated during both exercise and postexercise circulatory occlusion, most likely responding to muscle metaboreflex activation and/or BP elevations resulting in arterial baroreceptor activation. When postexercise recovery without circulatory occlusion was compared with preexercise rest, there were no significant differences in rCBF. Thus regions of the insular cortex and anterior cingulate cortex appear to play a significant role in neural circuitry of central command. Future investigations must be performed to more clearly define the sites of signal integration for central command, muscle afferent input, and arterial baroreflex mechanisms.

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