Activation of the insular cortex is affected by the intensity of exercise


Departments of Physical Therapy and Radiology, and the Moss Heart Center, University of Texas Southwestern Medical Center, Dallas, Texas 75235-8876

Williamson, J. W., R. McColl, D. Mathews, M. Ginsburg, and J. H. Mitchell. Activation of the insular cortex is affected by the intensity of exercise. J. Appl. Physiol. 87(3): 1213–1219, 1999.—The purpose of this investigation was to determine whether there were differences in the magnitude of insular cortex activation across varying intensities of static and dynamic exercise. Eighteen healthy volunteers were studied: eight during two intensities of leg cycling and ten at different time periods during sustained static handgrip at 25% maximal voluntary contraction or postexercise cuff occlusion. Heart rate, blood pressure (BP), perceived exertion, and regional cerebral blood flow (rCBF) distribution data were collected. There were significantly greater increases in insular rCBF during lower (6.3 ± 1.7%; P < 0.05) and higher (13.3 ± 3.8%; P < 0.05) intensity cycling and across time during static handgrip (change from rest for right insula at 2–3 min, 3.8 ± 1.1%; P < 0.05; and at 4–5 min, 8.6 ± 2.8%; P < 0.05). Insular rCBF was decreased during postexercise cuff occlusion (−5.5 ± 1.2%; P < 0.05) with BP sustained at exercise levels. Right insular rCBF data, but not left, were significantly related, with individual BP changes (r² = 0.80; P < 0.001) and with ratings of perceived exertion (r² = 0.79; P < 0.01) during exercise. These results suggest that the magnitude of insular activation varies with the intensity of exercise, which may be further related to the level of perceived effort or central command.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
respectively (20). We hypothesized that increased levels of exercise intensity would elicit greater activation of the insular cortices.

METHODS

Eighteen healthy subjects, fifteen men and three women (age 25 ± 2.8 yr), provided written informed consent before their participation in this study, which was approved by the University of Texas Southwestern Medical Center Institutional Review Board and the Environmental Health and Safety Committee. All subjects were nonsmokers and normotensive (resting BP <140/90 mmHg), and none was taking any cardiovascular medications or reported any history of cardiovascular or neurological disorders.

Dynamic exercise protocol. Subjects (n = 8) were studied under three conditions performed randomly on separate days: 1) low-intensity cycling (LIC) with ergometer resistance adjusted to yield a steady-state heart rate (HR) response of between 80 and 90 beats/min (bpm; workload ranged from 10 to 40 W), 2) higher intensity cycling (HIC) with resistance adjusted to yield a HR response of between 150 and 160 bpm (workload ranged from 130 to 150 W), and 3) seated rest on the bicycle ergometer. Subjects were seated on a semirecumbent bicycle (Ergys I, Dayton, OH), and their feet were secured to the pedals. Subjects were instructed to cycle at a cadence of 60 rpm and were paced by an investigator. HR and BP measurements were recorded at rest and during exercise conditions when subjects achieved the predetermined target HR range. Ratings of perceived exertion (RPE) were also obtained during exercise by using a 6-to-20-unit Borg scale (2). Time required to reach the target HR during low-intensity exercise ranged from 2 to 4 min, whereas higher intensity exercise times ranged from 5 to 6.5 min. Subjects were reminded to use only their legs during exercise and to keep their upper body relaxed.

Static exercise protocol. Subjects (n = 10) were studied under three conditions of sustained static handgrip (HG) exercise at 25% of their maximal voluntary contraction (MVC). They were randomly assigned to perform two of four HG protocols, as well as a control study by holding the HG (MVC). They were familiarized with all of the procedures and methodologies to be used during the study. A venipuncture was made in the antecubital vein of the right hand by using a Finapres device (Ohmeda 2300, Madison, WI) with the hand supported at the level of the heart.

To determine the rCBF distributions during each testing condition, 20 mCi of freshly reconstituted 99mTc-ethyl cysteinate dimer (Neurolite, DuPont Pharma) 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 lead to an increase in the amount of radioactivity recorded from that region (6, 9). Approximately 1 min before injection, the subjects were asked to close their eyes while continuing their activity. A technician administered the blood flow tracer and flushed the catheter with normal saline. During HG, injections were made at onset, 2 min, and 4 min, while the subjects continued their activity for an additional minute to facilitate appropriate distribution of the tracer. Subjects were unaware of the exact time of injection and reported no noticeable side effects. All subjects were immediately taken to the SPECT camera room, and imaging was completed within 1 h of injection for all subjects.

The brain scans were obtained with a fast-rotating three-headed SPECT scanner (Picker 3000, Cleveland, OH). The subjects were placed in the camera with their head held in position with a forehead strap and a chin strap. The cameras were optimally positioned by a trained technician, and the exact coordinates were recorded for subsequent scans. The camera was repeated for each of the rest protocols on separate days. Acquired data were fan-beam and uniformity corrected. Images were reconstructed in the transaxial plane, and a three-dimensional postprocessing low-pass filter was then applied. Coronal and sagittal images were generated from the transaxial image set, which was corrected with an angle parallel to the orbito-meatal line. Images were displayed at a thickness of four pixels (~7 mm). SPECT images were then transferred over the campus network to a computer workstation (AVIS, Advanced Visual Systems, Waltham, MA).

On a separate occasion, each subject also underwent a magnetic resonance imaging (MRI) scan. A 1.5-T system (Gyroscan NT, Philips Medical Systems, Shelton, CT) was used to obtain ~100 contiguous, 1.5-mm-thick gradient-echo axial slices. Each individual’s magnetic resonance images were transferred over the campus network to a workstation for coregistration with SPECT rCBF data.

Data processing and statistical analysis. Data processing involved coregistration of each individual’s SPECT scans, obtained during the exercise protocols, to the scan obtained during the resting trial. This was done by using an automated volume coregistration algorithm widely used for positron emission tomography–positron emission tomography coregistration (30). Each individual’s brain images were aligned in three dimensions by computer. Once the SPECT scans for a given subject were coregistered, normalization of total radioactive count variability was obtained by rescaling each volume so that total counts were equal for all volumes.

After SPECT-MRI coregistration for each individual, SPECT-MRI coregistration was obtained by using an interactive coregistration algorithm (15) implemented on the workstation (AVIS, Advanced Visual Systems), after the SPECT voxel size was made to match the MRI voxel size. With the resulting SPECT used as a baseline, absolute and percent count differences for each pixel in the nonresting SPECT volumes were obtained. These differences were then displayed, for a selected plane through the volume, as a color overlay superimposed on the MRI (4).

The right and left insular regions were located by using the MRI as an anatomic reference. With the use of the computer, regions of interest (ROIs) were drawn around the insular region as seen on the transaxial MRI image. This procedure was repeated on contiguous transaxial slices until the entire
insula had been assessed. The number of 1.5-mm slices ranged from 16 to 22 among individuals. Based on findings reported by Oppenheimer et al. (18), who demonstrated select regions of cardiovascular representation that appeared to be located in the inferior insula, coupled with the 8- to 10-mm spatial resolution for this technique, we chose to divide the insular cortices into equal halves representing superior and inferior regions. The number of radioactive SPECT counts within the inferior regions for the right and left insular cortices was then compared across the three conditions for each subject as absolute counts and as changes from the resting condition. Additionally, volumetrically identical ROIs were drawn around leg motor areas for cycling, hand/forearm motor regions for HG, and a white matter region encompassing the anterior commissure for all trials.

The SPECT data were corrected for any changes in rCBF to white matter regions between conditions and were compared by using Friedmann’s test with a main effect of condition. Cardiovascular data were also analyzed by using Friedmann’s test with a main effect of condition. If significant F-ratios were detected, a Student-Newman-Keuls post hoc analysis was used to determine specific mean differences by condition. Specific correlation analyses were performed on individual data sets. Associations between rCBF and cardiovascular and rating of perceived exertion (RPE) data were assessed by using a Spearman analysis. The significance level was set at P < 0.05 for all analyses, and all data are presented as means ± SD.

RESULTS

Dynamic exercise HR, mean arterial pressure (MAP), and RPE data are presented in Table 1. During the LIC, HR was elevated from rest by 20 bpm (P < 0.05) with no significant change in MAP. The RPE was increased 2 ± 1 units (P < 0.05). The LIC significantly increased HR to 154 ± 6 bpm (as dictated by the study design) and also elicited significant elevations in MAP (+30 mmHg) and RPE values (to 15 ± 1 units).

Changes in rCBF distribution are presented in Table 1 as radioactive counts (within the ROI) and as a percent change from rest for the low- and higher-intensity conditions. LIC exercise was associated with a 6.3 ± 5.4% increase for the right insular cortex (P < 0.05) and a 7.8 ± 2.7% rise for the left insula. The LIC also produced a 12.4 ± 4.5% increase (P < 0.05) in the leg motor region of the superiomedial precentral gyri.

HIC elicited an increase in rCBF distribution for both the right (13.0 ± 4.5%, P < 0.05) and left (12.8 ± 4.1%) insular cortices, as shown in Table 1. Leg motor regions showed a 20.9 ± 4.6% (P < 0.05) increase during HIC, which was significantly greater than that observed during LIC.

Static exercise HR, MAP, and RPE data are presented in Table 1. During the first minute of HG (0–1 min), HR was increased by 5 bpm (P < 0.05), MAP by 6 mmHg (P < 0.05), and RPE by 3 units (P < 0.05). Between minutes 2 and 3 of HG, HR was elevated from rest by 9 bpm (P < 0.05), MAP by 13 mmHg (P < 0.05), and RPE by 6 units (P < 0.05). During minutes 4–5, HR was increased by 18 bpm (P < 0.05), MAP by 25 mmHg (P < 0.05), and RPE by 8 units (P < 0.05). Postexercise cuff occlusion maintained MAP elevations above rest levels by 20 mmHg (P < 0.05), whereas HR returned to resting levels.

Changes in rCBF distribution are presented as radioactive counts in Table 1 and as a percent change from resting conditions for insular cortex activation. During the first minute of HG, neither the right nor left insula achieved a significant activation. During minutes 2–3, both the right (3.8 ± 1.1%) and left (4.2 ± 1.5%) insulae were significantly activated. Similarly, both the right (8.6 ± 2.8%) and left (6.9 ± 2.5%) insulae were activated during minutes 4–5 of HG (Fig. 1). However, postexercise cuff occlusion elicited insular deactivation in the same regions, with the right side decreased by 5.5 ± 1.2% (P < 0.05) and the left by 3.5 ± 1.5%.

The contralateral hand/forearm motor regions showed a significant increase in rCBF (from rest) at minutes 2–3 (7.1 ± 2.8%, P < 0.05) and minutes 4–5 (12.2 ± 3.9%, P < 0.05) of static HG, as shown in Table 1. Ipsilateral hand motor activation reached significance after 4–5 min of HG (7.2 ± 3.1%, P < 0.05).

Individual data. Individual data for changes in MAP and right insular activation (or deactivation) across all conditions are shown in Fig. 2. A significant positive relationship was found between MAP and right insular cortex activation (r² = 0.80; P < 0.001) during exercise.

Table 1. Cardiovascular and relative regional cerebral blood flow responses during exercise

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate</th>
<th>Mean Pressure</th>
<th>RPE</th>
<th>Left Insula</th>
<th>Right Insula</th>
<th>Leg Motor Area</th>
<th>Ipsilateral Hand Motor Area</th>
<th>Contralateral Hand Motor Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>62 ± 8</td>
<td>93 ± 6</td>
<td>6</td>
<td>584 ± 56</td>
<td>590 ± 59</td>
<td>645 ± 46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC</td>
<td>82 ± 6*</td>
<td>95 ± 4</td>
<td>8</td>
<td>629 ± 11*</td>
<td>627 ± 13*</td>
<td>724 ± 33*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIC</td>
<td>154 ± 6⁺</td>
<td>123 ± 8⁺</td>
<td>14</td>
<td>658 ± 14⁺</td>
<td>664 ± 21⁺</td>
<td>780 ± 41⁺</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 Min</td>
<td>64 ± 4</td>
<td>92 ± 2</td>
<td>6</td>
<td>591 ± 38</td>
<td>597 ± 43</td>
<td>668 ± 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–3 Min</td>
<td>59 ± 5*</td>
<td>98 ± 4*</td>
<td>8</td>
<td>603 ± 54*</td>
<td>609 ± 63*</td>
<td>687 ± 45 (2.8%)</td>
<td>698 ± 55 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>4–5 Min</td>
<td>73 ± 8⁺</td>
<td>105 ± 5⁺</td>
<td>12</td>
<td>615 ± 37⁺</td>
<td>620 ± 33⁺</td>
<td>722 ± 36⁺</td>
<td>756 ± 43⁺ (12.2%)</td>
<td></td>
</tr>
<tr>
<td>Postexercise</td>
<td>86 ± 7⁺</td>
<td>117 ± 4⁺</td>
<td>14</td>
<td>632 ± 74⁺</td>
<td>648 ± 68⁺</td>
<td>716 ± 37⁺ (7%)</td>
<td>756 ± 43⁺ (12.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD for n subjects. Cardiovascular and rating of perceived exertion (RPE) data, along with regional cerebral blood flow distributions as radioactive counts and percent changes from rest (in parentheses) are presented across conditions of rest, low-intensity cycling (LIC), and higher intensity cycling (HIC); during sustained handgrip exercise at 25% maximal voluntary contraction for minutes 0–1, 2–3, and 4–5; and during postexercise cuff occlusion. Significance is denoted at P < 0.05: * from rest, † between cycling conditions for LIC and HIC, and † between handgrip conditions for minutes 2–3 and 4–5.
The relationship between MAP and left insular activation was much weaker ($r^2 = 0.44$). Data for three subjects whose BP decreased during mild dynamic exercise were not included in the correlation, but there tended to be a greater magnitude of insular activation with the small drop in BP during exercise (Fig. 2A). During postexercise cuff occlusion, with BP elevated, the relationship between BP and insular activity was negative ($n = 5$) as seen in Fig. 2C, such that increases in BP produced insular deactivation. Additionally, there was a strong positive relationship between right insular activation and RPE ($r^2 = 0.79$; $P < 0.001$) and between MAP and RPE ($r^2 = 0.87$; $P < 0.001$). Left insular activity was most strongly related to HR ($r^2 = 0.84$; $P < 0.001$), but only when HR was below ~100 bpm.

As contralateral hand motor region activation tended to increase over time, comparisons were made between changes in motor activity and insular activity. There was no significant relationship for the individual data between contralateral hand motor activity and right ($r^2 = 0.47$) or left ($r^2 = 0.35$) insular rCBF. There was a significant relationship between hand/forearm motor region activation and RPE ($r^2 = 0.69$; $P < 0.001$), as well as between hand/forearm motor activity and MAP ($r^2 = 0.61$; $P < 0.001$).

**DISCUSSION**

The primary finding from this investigation was that there were differences in the magnitudes of insular cortex activation between varying intensities of static and dynamic exercise, such that a greater physical effort produced a greater magnitude of insular activation. This increased effort also yielded greater increases in leg and hand/forearm motor region activity for cycling and static HG, respectively. These findings are consistent with previous exercise studies (5, 7, 28).

Increased rCBF to motor regions during exercise appears to be related to the level of afferent input from the working limb (7, 27), as opposed to an increased level of volitional effort. Although rCBF distribution to both motor regions and insular cortices was related to the intensity of exercise, when individual subject data were examined, there was no significant relationship between changes in motor activity and insular cortex activation. This suggests that the magnitude of insular cortex activation was not solely related to the magnitude of afferent input from the working muscle. However, it does not discount the possibility that some level of afferent input is required for insular activation to occur during volitional exercise.

Whereas both right and left cortices showed increased rCBF with increasing exercise intensity, only changes in right insular activity were significantly related to individual changes in BP, as well as in individual RPE. Zhang and Oppenheimer (32) reported a predominance of SE units in the right insula. As shown in Fig. 2, changes in BP were associated with changes in insular activity. This is not surprising given that the insular cortex has reciprocal connections with
Elevations elicted during volitional exercise and postexercise cuff occlusion (Fig 2A). Saleh and Connell (24) have reported a role for the insular cortex in the modulation of baroreflex sensitivity; however, further investigation is warranted to establish the relationship between changes in insular cortex activation and baroreflex modulation in humans.

Limitations. With respect to the potential limitations of our study, we cannot define the specific type of neuronal activity by using SPECT, and no specific testing was performed to assess hemispheric dominance. Whereas the majority (6:1 ratio in the rat) of baroreceptor responsive neurons within the insular cortex were reported to be SE units (32), the observed increases in rCBF may be caused by activity of SE or SI neurons. Given the volume of tissue analyzed and the spatial resolution of the SPECT images, it is possible that a significant number of SE and SI units may be located within the insular regions assessed. Thus we cannot totally discount the possibility that right insular cortex activity is related to two different types of neurons responding to BP changes. However, assuming a predominance of SE units within the ROI and the patterns of activation observed, it is probable that there are differences in patterns of insular activation between conditions of rest and exercise.

Traditionally, the hemisphere that manages language is called the dominant hemisphere, and in ~95% of people the dominant side is the left hemisphere (14). Although it appears that some degree of laterality exists for autonomic function with respect to low- and
higher intensity exercise, studies in persons with right-hemispheric dominance could potentially yield different results with respect to patterns of insular activation. Also, changes in $\text{PCO}_2$ (or end-tidal $\text{PCO}_2$ ($\text{PET}_{\text{CO}_2}$)) can alter global cerebral blood flow and in turn systemically alter rCBF (15). Whereas we would expect no significant $\text{P CO}_2$ changes from rest during HG or LIC, the HIC at 155 bpm (roughly 70% of age-predicted maximal HR) would in all likelihood decrease $\text{PET}_{\text{CO}_2}$ from resting levels as ventilation increased. One would expect a decrease in global cerebral blood flow with a decrease in $\text{CO}_2$. Although no direct measures of $\text{CO}_2$ resting levels as ventilation increased. One would expect a decrease in global cerebral blood flow with a decrease in $\text{CO}_2$. Although no direct measures of $\text{CO}_2$ (pCO$_2$) or end-tidal $\text{CO}_2$ ($\text{PET}_{\text{CO}_2}$) levels were made, we noted only minimal changes in white matter blood flow (−3.2%) during heavy exercise. The findings and conclusions drawn from this study are similar both with and without the small correction to rCBF distributions for changes in white matter rCBF.

Conclusions. Findings from this study indicate that there are differences in the magnitude of insular cortex activation between varying intensities of static and dynamic exercise. Whereas both right and left cortices showed increased rCBF with increasing exercise intensity, only changes in right insular activity were significantly related to individual changes in BP and RPE. However, when BP was elevated during postexercise cuff occlusion, there were decreases in insular rCBF. These differences could be related to different types of neuronal activation. Leg motor activity was higher during HIC, and hand/forearm motor activity increased over time during sustained HG exercise, yet these changes alone were not significantly related to changes in insular rCBF. Taken together, these findings suggest that changes in the level of volitional effort (central command or perceived effort), either alone or in combination with concomitant motor input, may govern, at least in part, activation of the insular cortex. Further investigations will be required to clearly define the specific contributions of systemic BP changes and perceived effort toward insular activation during exercise.

We thank the subjects for their cooperation and also acknowledge the expert technical assistance of Peter Hughes, Michael McLaughlin, and Michael Viguet, as well as the cooperation of Zale Lipshy University Hospital. We also thank Dr. Lars Friberg for helpful comments and insights.

This study was supported by an American Heart Association grant-in-aid from the Texas Affiliate (to J.W. Williamson, principal investigator).

Address for reprint requests and other correspondence: J. W. Williamson, UT Southwestern Allied Health Sciences School, Dept. of Physical Therapy, 5323 Harry Hines Blvd., Dallas, TX 75235-8876 (E-mail: jwill4@mednet.swmed.edu).

Received 8 October 1998; accepted in final form 26 May 1999.

REFERENCES
25. Sander, J., and J. Klingelhöfer. Changes in cardiac blood pressure patterns and cardiovascular parameters indicate later-


