Activation of the insular cortex during dynamic exercise in humans

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1. The insular cortex has been implicated as a region of cortical cardiovascular control, yet its role during exercise remains undefined. The purpose of the present investigation was to determine whether the insular cortex was activated during volitional dynamic exercise and to evaluate further its role as a site for regulation of autonomic activity.

2. Eight subjects were studied during voluntary active cycling and passively induced cycling. Additionally, four of the subjects underwent passive movement combined with electrical stimulation of the legs.

3. Increases in regional cerebral blood flow (rCBF) distribution were determined for each individual using single-photon emission-computed tomography (SPECT) co-registered with magnetic resonance (MR) images to define exact anatomical sites of cerebral activation during each condition.

4. The rCBF significantly increased in the left insula during active, but not passive cycling. There were no significant changes in rCBF for the right insula. Also, the magnitude of rCBF increase for leg primary motor areas was significantly greater for both active cycling and passive cycling combined with electrical stimulation compared with passive cycling alone.

5. These findings provide the first evidence of insular activation during dynamic exercise in humans, suggesting that the left insular cortex may serve as a site for cortical regulation of cardiac autonomic (parasympathetic) activity. Additionally, findings during passive cycling with electrical stimulation support the role of leg muscle afferent input towards the full activation of leg motor areas.

6. The insular cortex has been implicated as an important site of cardiovascular regulation (Ruggerio, Mraovitch, Granata, Anwar & Reis, 1987; Yasui, Breder, Saper & Cechetto, 1991; Oppenheimer, Gelb, Girvin & Hachinski, 1992). Pathways project from the insular cortex to subcortical areas intimately involved in autonomic function, including the lateral hypothalamus (Yasui et al. 1991), the nucleus of the solitary tract (Saper, 1982) and the ventrolateral medulla (Yasui et al. 1991). Direct electrical stimulation of the insular region has been shown to produce changes in heart rate and blood pressure in both primates (Kaada, 1951; Hoffman & Rasmussen, 1953) and humans (Oppenheimer et al. 1992). However, there appears to be some degree of lateralization with respect to the specific cardiovascular responses elicited, as well as species differences.

Investigations of humans involving direct electrical stimulation of the posterior region of the left insula have reported a bradycardia (Oppenheimer et al. 1992). Conversely, a tachycardia coupled with a pressor response was observed upon right insular stimulation. This pattern of lateralization appears to be the opposite of that of the more commonly investigated rat model. Numerous studies have reported increases in sympathetic activity during stimulation of the rat left insular cortex (Oppenheimer & Cechetto, 1990; Oppenheimer, Wilson, Guiraudon & Cechetto, 1991; Yasui et al. 1991). Oppenheimer & Cechetto (1990) have further demonstrated an area of cardiac representation within the posterior confines of the rat left insular cortex. Yasui et al. (1991) have also reported reproducible cardiovascular responses, including a pressor response accompanied by an increase in heart rate, with stimulation of the rostral insular region. This pattern of cardiovascular response, with concomitant increases in heart rate and blood pressure, is similar to that typically observed during voluntary exercise.

The purposes of this investigation were to determine whether the insular cortex was activated during volitional exercise in humans and to further establish if lateralization existed. The concept of cortical cardiovascular control (central command) proposes a parallel activation of both the motor and cardiovascular systems. Despite a large amount of evidence supporting the existence of central command (Krogh & Lindhard, 1917; Goodwin, McChesney & Mitchell,
were displayed on screen and hard-copy prints were generated. Electrocardiographic electrodes were placed on the chest for continuous monitoring of heart rate. Mean arterial pressure was measured from the middle finger of the right hand using the Finapres device (Ohmeda 2300, Madison, WI, USA) with the hand supported at the level of the heart as shown in Fig. 1. Cardiac outputs were obtained using an acetylene rebreathing method modified for use with a mass spectrometer. This method has a correlation coefficient of 0.94 with the indocyanine-green dye dilution technique and has been previously described in detail (Triebwasser, Johnson, Burpo, Campbell, Reardon & Blomqvist, 1977). On-line measurements of oxygen uptake ($V_{\text{O}_2}$) and end-tidal carbon dioxide pressure ($P_{ET,\text{CO}_2}$) were also collected using the mass spectrometer.

For volitional cycling, the subjects were instructed to pedal at a cadence of 60 revolutions per minute (rpm) as led by a metronome. The metronome was used to strictly control the frequency of movement and remained on during all conditions. All cardiovascular and metabolic measurements were taken during steady-state conditions, between minutes 5 and 7 of cycling. To achieve passive movement, the subjects were asked to relax their legs while a second rider, seated on the rear of the bicycle, pedalled at 60 rpm. In this situation, the EMG also served as a biofeedback device to assist the subjects with relaxation of their leg muscles.

As a fourth condition, electrical stimulation of the quadriceps muscles was combined with the passive cycling movement in four of the subjects. The electrical stimulation was administered in a reciprocal pattern to mimic the frequency of quadriceps muscle activation during voluntary movement. As it was not possible to measure accurately muscle EMG activity during electrical stimulation, an attempt was made to match the subjects’ level of oxygen uptake during the active cycling condition. The level of electrical stimulation was initially adjusted to elicit a contraction sufficient to lift the leg against gravity and then increased to each subject’s tolerance. The final level of stimulation achieved the desired increase in $V_{\text{O}_2}$, and more importantly was not perceived by the subjects to cause any pain or discomfort.

To determine the regional cerebral blood flow (rCBF) during each testing condition, 15 mCi of freshly reconstituted $^{99m}$Tc-hexamethylpropyleneamineoxime (HMPAO, Ceretec, Amersham, UK) was injected intravenously (the retained radiopharmaceutical is a photon emitter with a physical half-life of 6 h). Increases in rCBF subsequently lead to an increase in the amount of radioactivity recorded from the respective region (Lassen, Andersen, Friberg & Paulson, 1988). Approximately 1 min prior to injection, the subjects were asked to close their eyes and an investigator gently lifted the left arm. A technician administered the tracer and the arm was supported for an additional 2 min while the subject continued their activity. The subjects were unaware of the time of injection and reported no noticeable side effects. Although the half-life of the tracer was 6 h, all subjects were taken to the SPECT facility and imaging was performed within 1 h.

The brain scans were obtained with a fast-rotating three-headed SPECT scanner (Toshiba 9300A, Japan). The subjects were uniformly positioned and then their heads were affixed using a strip of medical taping. The subjects were requested to remain still during the 20 min imaging session. This process was repeated for each test such that all eight subjects were imaged at least three times, and four subjects were imaged a fourth time.

On a separate occasion, each subject received an MRI scan. A 1.5 T system (Gyrocscan ACS-3, Philips Medical Systems, Shelton, CT, USA) was used to obtain approximately 100 contiguous, 1.8 mm-
thick gradient echo images (scan parameters: ratio of excitation to relaxation time, $T_E/T_R = 6/15$; field of view (FOV) = 20 cm; matrix = 256 x 256); this yielded a good grey-to-white-matter contrast and suppressed the cerebrospinal fluid signal. Each individual's MRIs were transferred over the campus network to the workstation for co-registration with SPECT data, to provide an anatomical reference for the flow difference measurements obtained during data analysis.

**Image processing and statistical analysis**

Initial data processing involved linearization (Lassen et al. 1988) and subsequent co-registration of each individual's SPECT scans, obtained during passive and active cycling, to the scan obtained during rest. This was done using an interactive volume co-registration algorithm (McColl, Blackburn & Peshock, 1996) implemented on the workstation (AVIS, Advanced Visual Systems, Waltham, MA, USA). Each individual's brain images were aligned in three dimensions using both surface anatomy and internal structure including the ventricles, cingulate gyrus and cerebellum. Once the SPECT scans for a given subject were co-registered, normalization of count variability was obtained by rescaling each volume so that the total count was equal over all volumes.

Following SPECT-SPECT co-registration for each individual, SPECT-MRI co-registration was obtained following a similar procedure. With the resulting SPECT used as a baseline, absolute and percentage count differences for each pixel in the non-resting SPECT volumes were obtained. These differences were then displayed, for a selected plane through the volume, as a colour overlay superimposed on the MRI (Faber, McColl, Opperman, Corbett & Peshock, 1991). The insular region was located using the MRI reference and potential areas of activation identified. To be considered a significant change in rCBF, the site had to appear as a 5% or greater change in at least four consecutive transaxial slices.

<table>
<thead>
<tr>
<th>Condition</th>
<th>$V_i$ (ml min⁻¹)</th>
<th>Cardiac output (l min⁻¹)</th>
<th>Heart rate (beats min⁻¹)</th>
<th>Stroke volume (ml)</th>
<th>BP (mmHg)</th>
<th>Total peripheral resistance (mmHg ml⁻¹ min⁻¹)</th>
<th>End-tidal $P_{CO_2}$ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>434 ± 45·2</td>
<td>54 ± 0·40</td>
<td>74 ± 6·1</td>
<td>73 ± 10·9</td>
<td>95 ± 4·5</td>
<td>17·5 ± 5·3</td>
<td>39·5 ± 4·1</td>
</tr>
<tr>
<td>AC</td>
<td>648 ± 31·4*</td>
<td>8·0 ± 0·37*</td>
<td>89 ± 8·2*</td>
<td>89 ± 12·4*</td>
<td>96 ± 3·1</td>
<td>11·9 ± 5·7*</td>
<td>38·8 ± 3·3</td>
</tr>
<tr>
<td>PC</td>
<td>436 ± 41·8</td>
<td>6·6 ± 0·45</td>
<td>76 ± 8·3</td>
<td>88 ± 17·7*</td>
<td>105 ± 4·8*</td>
<td>15·9 ± 5·9</td>
<td>39·9 ± 4·1</td>
</tr>
<tr>
<td>PC + ES</td>
<td>618 ± 46·5*</td>
<td>7·6 ± 0·74*</td>
<td>74 ± 9·1</td>
<td>102 ± 15·6*</td>
<td>108 ± 5·6*</td>
<td>14·1 ± 5·8*</td>
<td>39·1 ± 4·4</td>
</tr>
</tbody>
</table>

Values are means ± s.d. AC, active cycling; PC, passive cycling; ES, electrical stimulation; BP, blood pressure. Significance from rest is indicated by * at $P < 0.05$.

**Figure 1. Experimental set-up showing the adapted tandem bicycle**

During the passively induced cycling, the rider on the rear seat pedalled while the subject kept his legs relaxed. Metabolic and haemodynamic responses were recorded during all experimental protocols.
To address the questions posed in this study, activation patterns were first determined for the active cycling protocol. For the foci of activation, the computer was used to define a region of interest (ROI) around the site of activation. After calculating the mean level of activation for the four slices, this region of interest was saved. The other conditions were then analysed using the identical slices and with the same ROI as used for the active cycling. Individual data for all subjects were compared across conditions using an ANOVA. A similar procedure was employed to determine differences in leg motor activation. Cardiovascular and metabolic data were also analysed using an ANOVA with a main effect of condition. If a significant $F$ ratio was detected, a Tukey's post hoc analysis was used to determine specific mean differences.

RESULTS

Metabolic and haemodynamic responses

The metabolic and haemodynamic data are presented for each condition in Table 1. During the active cycling protocol, cardiac output, $V_O$, heart rate and stroke volume were all significantly elevated above the resting condition, while total peripheral resistance was significantly reduced. There were no changes in blood pressure or $P_{ET,CO_2}$. Passive cycling elicited increases in blood pressure and stroke volume, with no changes in any of the other variables. Likewise, passive cycling combined with electrical stimulation also produced increases in blood pressure and stroke volume, with no change in heart rate. Additionally, electrical stimulation elicited increases in both cardiac output and $V_O$, with a fall in resistance. The increases in cardiac output and $V_O$ were similar to those observed during active cycling. The amplitude of EMG responses during active cycling were markedly higher than during passive cycling. As no changes in $P_{ET,CO_2}$ from resting levels were present, no rCBF corrections for changes in the arterial $CO_2$ pressure ($P_a,CO_2$) were necessary.

Cerebral activation

Changes in rCBF distribution are presented in Table 2. The active cycling produced a mean increase of 8.5% in the left insular cortex. This change occurred primarily in the posterior insula (Fig. 2). The rCBF distribution was significantly greater than the changes produced during passive cycling or passive cycling when combined with electrical stimulation. There were no significant rCBF changes for the right insular cortex between the conditions. Active cycling also produced a 17% increase bilaterally in the primary leg motor region. This value was significantly greater than the change recorded during passive cycling. However, when electrical stimulation was added to passive cycling the rCBF was increased to 13.7%, closer to that seen during active cycling (Fig. 3), but still less ($P < 0.05$).

DISCUSSION

This study provides the first evidence that the left insular cortex is activated during mild dynamic exercise in humans. Metabolic and haemodynamic results are consistent with those previously reported by Nobrega et al. (1994) for active and passive cycling. The focus of rCBF increase was localized in the posterior insular cortex of the left hemisphere and was only observed during the active cycling protocol, when heart rate was elevated. Although an area of selective cardiac representation has been identified within the rostral posterior confines of the rat left insular cortex (Oppenheimer &
(Cechetto, 1990), investigation of humans involving electrical stimulation of the left posterior insular cortex in epileptic patients consistently yielded a bradycardia (Oppenheimer et al. 1992). Direct extrapolation between our present findings and those of Oppenheimer et al. (1992) is made difficult given the differences in experimental procedures, specifically electrical stimulation versus an exercise-induced activation. However, if the human left posterior insular cortical region is indeed an area of parasympathetic control, as implied by Oppenheimer et al. (1992), there may be a unifying theme explaining the apparent discrepancies in the heart rate responses.

Focal increases in relative rCBF are related to an increased local metabolic demand which is mainly due to increased excitatory or inhibitory synaptic activity (Raichle, 1987). As we cannot assess the specific type of synaptic activity (excitation or inhibition) produced by direct electrical stimulation or exercise-induced activation, it is possible that they may elicit different responses from this parasympathetic region. Direct stimulation could elicit a bradycardia, while an exercise-induced vagal withdrawal of parasympathetic activity common to mild exercise with heart rates below 100 beats min⁻¹ (Robinson, Epstein, Beiser & Braunwald, 1966) could produce a tachycardia. In support of this concept, infusion of amobarbital into the left internal carotid, essentially paralysing the left hemisphere, results in a pronounced tachycardia (Zamrini et al. 1990).

Blood pressure elevations were found to be most frequently elicited from stimulation of the right posterior insula (Oppenheimer et al. 1992). While both the passive cycling and electrical stimulation protocols selectively elevated blood pressure, insular activation was inconsistent with respect to loci and lateralization. Interestingly, the two subjects showing right insular activation had the highest

<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>PC</th>
<th>PC + ES</th>
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<tbody>
<tr>
<td>Leg motor area (M1)</td>
<td>17.1 ± 3.6</td>
<td>6.9 ± 4.7*</td>
<td>13.7 ± 2.7*†</td>
</tr>
<tr>
<td>Left posterior insular cortex</td>
<td>8.5 ± 1.7</td>
<td>3.7 ± 2.5*</td>
<td>4.1 ± 2.0*</td>
</tr>
<tr>
<td>Right posterior insular cortex</td>
<td>3.5 ± 2.5</td>
<td>2.7 ± 2.4</td>
<td>4.3 ± 3.4</td>
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</tbody>
</table>

Increases in rCBF distribution from rest are presented (means ± s.d.; * P < 0.05 from active condition; † P < 0.05 between passive and passive with electrical stimulation) during conditions of active cycling (AC), passive cycling (PC) and passive cycling combined with electrical stimulation (PC + ES).

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**Figure 3. Co-registered SPECT and MRI data for one subject at the level of the motor cortex**

A, active cycling; B, passive cycling; C, passive cycling combined with electrical stimulation. This view represents a transaxial slice with the top and bottom (of A, B and C) corresponding to an anterior and posterior orientation, respectively. The brain is viewed from below such that the right side is actually the left hemisphere. The horizontal reference line in all panels denotes the central suture. The SPECT activation seen in A, B and C represents the percentage increase from the resting control (see Table 2) mapped on the MRI using an arbitrary colour scale with a range of 5—20% (from green to yellow to red). During active cycling (A), there is activation of the leg motor area, which is similar to that seen in during passive cycling combined with electrical stimulation (C). In B, there is no activation of this area during passively induced cycling. Additionally, there is activation of a pre-motor area (in the right hemisphere) during all three conditions. D and E show the exact level of the brain slice with reference to the coronal (D) and sagittal MRI data (E).
blood pressure elevations during the electrically stimulated passive cycling. However, in the majority of subjects, the changes in rCBF were very small (<5%) and fell below our a priori criteria for activation as shown in Table 2. Given this, no systematic analysis of blood pressure-induced insular responses was performed.

As a means of assessing our methodology and increasing confidence in our insular data, we also chose to analyse the superiomedial precentral gyri (leg motor control area) given recent findings demonstrating activation of this area during leg activity (Fink et al. 1996). Our 17% increase found using SPECT during volitional cycling is consistent with the 16% increase reported by Fink et al. (1996) during volitional leg kicking as assessed by PET. The rCBF increases observed during active cycling were significantly greater than that observed during passively induced cycling movement (Table 2). However, the addition of quadriceps electrical stimulation to passive cycling produced rCBF increases closer to those found during active cycling. Electrical stimulation cannot mimic the exact patterns of motor activation evoked during active cycling nor match exact levels of proprioceptive feedback. These discrepancies may explain the differences noted in rCBF to primary leg motor areas. These findings strongly support the importance of afferent input for cerebral motor activation and are in agreement with studies demonstrating that rCBF increases induced by hand movement can be blocked by regional anaesthesia (Friedman, Friberg, Mitchell & Secher, 1991; Friedman, Friberg, Payne, Mitchell & Secher, 1992). The specific type of muscle afferent responsible for the rCBF changes remains unknown, but there does not appear to be significant involvement of either the metabolically sensitive fibres (groups III and IV) or the muscle spindles (group Ia) in this type of motor response (Williamson, Friedman, Mitchell, Secher & Friberg, 1996).

Findings from this study suggest that cardiovascular changes during mild volitional exercise could potentially result from activation of the insular cortical region, possibly via central command, and that this left insular region could serve as a site of cortical autonomic regulation of cardiac parasympathetic activity during exercise. While Gardevia et al. (1993) have found that central command can elicit increases in both heart rate and blood pressure, some evidence suggests that heart rate is controlled primarily by central command (Victor, Seals & Mark, 1987; Williamson, Olesen, Pott, Mitchell & Secher, 1996), with the parasympathetic response requiring muscle afferent input (Strange, Secher, Pawelczyk, Christensen, Mitchell & Salim, 1993; Williamson, Mitchell, Olesen, Raven & Secher, 1994; Williamson et al. 1996). It should also be noted that non-exercise-induced activation of the insular cortex has been reported in response to pain (Coghill et al. 1994) and phobic stimuli (Rauch et al. 1995) both of which can elevate heart rate. While such findings do not preclude the insular cortex as a site of cortical autonomic control, they do suggest that the insular cortex is probably not the origin of central command, as there is presumably no motor component during the specific pain or phobic stimuli. As the technology advances, further investigations delineating the temporal sequence of activation of various cortical and midbrain structures will certainly yield more definitive conclusions concerning the cardiovascular regulation during exercise.


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