Movement-Related Cerebellar Activation in the Absence of Sensory Input

ROBERT A. WEEKS, 1 CHRISTIAN GERLOFF, 1 MANABU HONDA, 1 MARINOS C. DALAKAS, 2 AND MARK HALLETT 1

1Human Motor Control Section and 2Neuromuscular Diseases Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892-1428

INTRODUCTION

Lesions of the cerebellum can cause serious motor deficits with minimal sensory, cognitive, or language effects (Holmes 1939). Cerebellar activation is also a consistent finding in functional imaging studies of motor function (Colebatch et al. 1991; Fox et al. 1985; Jenkins et al. 1994; Jueptner et al. 1997a,b; Kim et al. 1994; Nitschke et al. 1996). The traditional view is that the cerebellum is involved primarily in motor processing (Blomfield and Marr 1970; Eccles 1973; Glickstein 1992) and that sensory input to the cerebellum is important for sensorimotor integration. More recently, interest has arisen in “pure” sensory and cognitive processes within the cerebellum (Fiez 1996). Some groups have suggested that the cerebellum primarily processes sensory information during movement (Bower and Kassel 1990); accordingly, movement-related cerebellar activation would be produced by sensory processing, and motor deficits from cerebellar lesions would be caused by deficient proprioceptive processing. This viewpoint has received support from the results of human imaging studies (Gao et al. 1996; Jueptner et al. 1997b). However, it is difficult to differentiate sensory processing from motor processing during movement. Patients who have both sensory neuropathy and normal muscle strength are rare, but those who do provide a model for dissociating the sensory and motor components of movement (Cole and Sedgwick 1992; Dalakas 1986; Ghez et al. 1995; Rothwell et al. 1982; Sanes et al. 1984; Vercher et al. 1996). If the cerebellum processes sensory information exclusively, these patients should exhibit no movement-related cerebellar activation. We tested this hypothesis with the help of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

METHODS

Clinical assessment of sensation

We used standard clinical methods. Light touch was assessed with a cotton wisp, and vibration with a 128-Hz tuning fork. Joint position sense was tested with eyes closed in distal joints with manual movement over the full range of the joint. Pain sensation was tested using a pin; patients were asked whether they felt a prick, and, if so, whether the sensation was sharp or dull. Temperature sensation was assessed as present if they had a subjective cold sensation to the touch of metal.

Subjects

Patient 1 was a 66-yr-old, ambidextrous female. Her symptoms started 11 years ago with parasthesia in her left thumb. Over the following 2 years her symptoms gradually spread to involve all four extremities and have continued to be slowly progressive. She had pseudoathetoid (writhing) movements of her outstretched arms and a mild intention tremor. She was ataxic in all limbs and had truncal ataxia. Muscle power was normal, and there was no muscle wasting. Sensory examination revealed absent joint position and vibration sense; light touch and pain sensation were diminished and poorly localizable; cold temperature sensation was normal. Peripheral reflexes were absent. Investigations revealed absent transcuntenaneous sensory nerve action potentials with normal electromyographic (EMG) and motor nerve conduction studies. Reduced lacrimal secretion was evident with a Shirmer’s test. A lip biopsy showed lymphocytic mucosal infiltration, and a sural nerve biopsy showed perivascular infiltrates of lymphocytes. Although her serum never contained antibodies to the tissue antigens Ro/SSA and La/SSB, a diagnosis was made of an ataxic sensory neuropathy associated with Sjogren’s syndrome.

Patient 2 was a 54-yr-old, right-handed female. Her symptoms started 24 years ago with loss of sensation in her left arm. Her symptoms slowly spread so that her trunk and all extremities were affected. On examination she was areflexic, her gait was ataxic, and she had truncal ataxia. Motor examination showed pseudoathetoid movements but normal power and no muscle wasting. Sensory examination revealed absent joint position, vibration and light touch sensation; pain sensation was dull and nonlocalizable; and temperature sensation was normal. Nerve conduction studies confirmed a severe sensory neuropathy with normal EMG and motor conduction studies. Her serum contained polyclonal IgM immunoglobulin, but no monoclonal spikes; a diagnosis was made of a IgM paraproteinemic sensory neuropathy.

Patient 3 was a 61-yr-old, right-handed male. His symptoms started...
within the video segment. Proprioception was absent on the toes and impaired in the fingers. Pin prick was markedly reduced distally in both upper and lower extremity. Motor examination revealed limb ataxia, pseudoathetoid movements of the fingers, and minimally reduced muscle power. Sensory nerve action potentials were absent. Motor nerve conduction showed mild motor involvement. A diagnosis of chronic inflammatory polyradiculopathy with residual sensory impairment was made.

All three patients, therefore, had absent proprioception, diminished or absent cutaneous sensation with normal or near normal muscle power. All patients had extensive diagnostic neurophysiological testing within 6 mo of the PET study. The clinical features in patients 1 and 2 indicated predominant large-fiber neuropathies with some involvement of small fiber pathways. In patient 3, both large and small fiber pathways were equally affected. Formal testing of small fibers consisted of sensitivity to pinprick and hot and cold temperature appreciation. The patient’s deficits had all been present for at least 6 years, and all affected the right arm. Cerebellar function was regarded as normal as evidenced by normal speech and eye movements and normal cerebellar imaging on high-resolution MRI scans.

The control group for the PET study consisted of six age-comparable, right-handed normal subjects (5 women, 1 man), 44–66 yr of age (56.2 ± 7.4 yr, mean ± SD) who had no history of neurological disease and normal neurological examination results. The study protocol was approved by the Institutional Review Board, and all subjects gave their written informed consent for the study.

Experimental tasks

In the PET study, there were three experimental tasks and a rest (control) condition. Before the PET scans, subjects were trained in the movement tasks until they could perform the tasks without error or in the case of the patients to their maximal ability.

Condition 1 was an auditory-paced finger movement task under visual guidance (VG). Subjects performed repeated sequences of finger-to-thumb oppositions of the right hand so that the tip of their finger touched the tip of their thumb on each occasion. Each movement sequence consisted of four flexion movements, index-to-thumb, middle finger-to-thumb, ring finger-to-thumb and little finger-to-thumb movements. All movements were paced by an auditory tone of frequency 0.5 Hz.

Condition 2 was an auditory-paced sequential finger movement task without vision of hand (nonvisual guidance, NVG). Eyes were open during the scan and fixated onto a 0.75-cm cross on an opaque screen that was positioned between their moving hand and eyes. The screen was placed so that the fixation point was in front of their right hand, and thus the arm, head and ocular position, and all spatial coordinate reference frames were aligned in the two movement scans.

Condition 3 was a video monitoring (VM) condition, without finger movement. Before the PET scans, a video recording of each subject performing auditory-paced, sequential finger movements was made. The video recording was made to simulate the hand position visible to the subject during the movement scans of the PET session. The video was replayed during the PET scan via a television monitor positioned 30 cm in front of the subject’s face. The sound of the auditory cue was also recorded on the video and replayed in the scanner. Subjects were asked to monitor finger-to-thumb accuracy, maintenance of the pacing frequency, and errors in the sequence. At the end of each VM scan, subjects were asked whether movement errors had occurred within the video segment.

Condition 4 was a rest (R) condition. Subjects were asked to close their eyes, relax, and keep still; no other specific instructions were given. The lights in the PET room were turned off, and the background sound consisted of noise from the cooling fans.

EMG recording was performed throughout all PET conditions in all subjects. Bipolar EMG was recorded from surface electrodes placed over the thenar muscles of both hands. The active electrode was positioned over the muscle belly, and the reference electrode was attached to the radial aspect of the thumb at the level of the distal interphalangeal joint. The EMG was sampled at 5 kHz, high-pass filter was 5 Hz, and low-pass filter was 1.5 kHz (DANTEC Counterpoint electromyograph, DANTEC Medical A/S, Skovlunde, Denmark). EMG data were recorded continuously (oscilloscope mode) to permit constant on-line monitoring of performance.

The fMRI study involved two experimental tasks: active and passive movements of the fingers of the right hand in patients 1 and 2. Patient 3 was, unfortunately, excluded from fMRI scanning because he had an implanted metallic device. Patients were positioned within the scanner with their arms fully pronated and their hands resting just outside the machine. Their wrists were supported on cushions with their fingers flexed at the metacarpophalangeal joints. To standardize movement kinematics, the fingers of the right hand were taped together with the fingers extended at the interphalangeal joints. Finger movements were thus confined to around the metacarpophalangeal joints with the fingers moving as a single unit. Active movements consisted of voluntary finger extensions at the metacarpophalangeal joints until the fingers were fully extended followed by relaxation to the resting state. Each movement consisted of a radial excursion of ~7 cm when measured at the level of the fingertips. Passive movements were performed by an experimenter lifting a plastic rod attached to the terminal phalanges designed to mimic the kinematics of the active task. Each movement was paced at a rate of 2 Hz to the sound of the MRI scanner. All movements were visualized by the patient by using an angled mirror housed in the scanning gantry above the patient’s head.

PET

Each subject had two H215O-PET scans per condition performed with a Scanditronix PC 2048–15b PET camera with an axial field-of-view of 9.75 cm and an in-plane resolution of 6.1 mm at the center of the field of view. Data were collected from superior cerebellar sections, including areas previously shown to be activated in motor tasks, but not from the most inferior cerebellar sections. For each scan, a 30-microliter (μl) bolus of H215O was injected, and data were collected in the 2D acquisition mode with a 10-min interscan interval. Attenuation-corrected emission data were reconstructed as 15 contiguous axial planes of 6.5-mm slice thickness. All head images were aligned using an image registration algorithm and transformed into standard stereotactic space. Each image was smoothed with 15-mm isotropic Gaussian filter.

MRI

MRI was performed with a whole-body 1.5 Tesla MRI scanner (Signa, General Electric, Milwaukee, WI) equipped with a head coil. Patient 3 was excluded from MRI scanning because he had an implanted metallic device. The anterior-posterior commissural line (AC–PC line) was identified on T1-weighted anatomic images, followed by a series of six 3D spoiled gradient-echo (SPGR) axial images (TR/TE/flip/NEX/FOV/matrix 33/4/20/1/24/256 × 256) of 7-mm slice thickness, parallel to the AC–PC line, and covering the entire cerebellum. High-resolution echo-planar imaging scans were then collected in the same axial planes using a T2*-weighted acquisition (TR/TE/flip 3000/4090), which produced a 64 × 64 matrix with an 18-cm field of view and voxel size of 2.81 × 2.81 × 7 mm. A time course series of 60 images/slice was acquired in a 3-min trial, with two trials per condition, in an off–on cycle paradigm of 30 s of rest and 30 s of movement. T2*-weighted and...
proton density anatomic images were also collected using the same scanning planes. The time course series of images from each subject were realigned, with the first image of each slice used as a reference. No spatial normalization or smoothing of the data were performed. Global differences in intensity between scans were removed by means of proportional scaling.

Statistical analysis

Data from the PET study patients were pooled and analyzed using conventional subtraction techniques with contrasts of the experimental tasks with the rest condition. Statistical comparisons between patients and normal (control) subjects were also made. Statistical parametric mapping (SPM 95; Wellcome Department of Cognitive Neurology, London, UK) was used for statistical analysis of the PET and fMRI data. For the PET study, an analysis of covariance, applied on a single-subject basis, was used to remove the confounding effect of global activity. The resulting $t$ values constituted a SPM$[t]$, which was transformed to the unit normal distribution to give a SPM$[Z]$. The Z map threshold was set at 3.09 ($P < 0.001$), and the values were corrected for the number of nonindependent comparisons.

For the fMRI study, correlations between the input function, modeled as a temporally smoothed box-car reference waveform, and the signal intensity were calculated for each voxel to produce a SPM$[t]$. This was transformed to the unit normal distribution to give a SPM$[Z]$. The Z map threshold was set at 3.09 ($P < 0.001$), and the values were corrected for the number of nonindependent comparisons. The two patients were analyzed individually, group analysis was not performed in the fMRI study.

RESULTS

EMG recordings during the nonmovement scans, rest, and video monitor in both patients and controls showed no muscle activity. In particular, pseudoathetoid movements were not present in the patient cohort, most likely because their hands and forearms rested comfortably on pillows. In the movement conditions (NVG and VG) each flexion movement was represented by a phasic EMG burst in the thenar muscles of the performing hand. Regular EMG bursts occurred in the patients even in the NVG condition and the number of movements made in each scan was the same in patients and controls. In the video monitoring condi-

<table>
<thead>
<tr>
<th>TABLE 1. Statistical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Regions</td>
</tr>
<tr>
<td>Increased rCBF during the nonvisually guided movement (NVG)†</td>
</tr>
<tr>
<td>Increased rCBF during the visually guided movement (VG)†</td>
</tr>
<tr>
<td>Contralateral anterior cerebellum</td>
</tr>
<tr>
<td>Increased cerebellar signal during voluntary movement‡</td>
</tr>
<tr>
<td>Ipsilateral dentate nucleus</td>
</tr>
<tr>
<td>Contralateral anterior cerebellum</td>
</tr>
<tr>
<td>Contralateral dentate nucleus</td>
</tr>
</tbody>
</table>

* With a Bonferroni correction for multiple comparisons. † Positron emission tomography with $H_2^{15}$O. ‡ Functional magnetic resonance imaging.
tion all subjects correctly identified any movement errors on the video segment, and thus compliance during the cognitive task was ensured.

The PET study of the patients showed that the anterior cerebellar hemisphere was activated ipsilaterally (to the moving hand) in the NVG condition, and bilaterally in the VG condition (Table 1 and Fig. 1, A and B), but there was no cerebellar activation in the VM condition. There was no statistically significant difference in cerebellar activation between patients and normal subjects in any of the contrasts analyzed.

The fMRI study demonstrated that during the active movement task the patients activated two foci bilaterally; one in the anterior cerebellar hemisphere and another in the dentate nucleus (Table 1 and Fig. 1, C and D). There was no cerebellar activation during the passive movements, even at a low threshold of Z > 2.33 (without Bonferroni correction).

DISCUSSION

The PET and fMRI studies showed that movement-related cerebellar activation occurs without proprioception. In the PET study, prominent cerebellar activation was observed during the NVG condition. Because the patients could not see their hand moving, the cerebellar activation could not be attributed to visual or somatosensory input. There was no cerebellar activation during the VM condition, which replicated the retinal and auditory input of the motor tasks and had similar visual attention demands. In the fMRI study, failure of the passive movements task to produce cerebellar activation in the patients suggests that any residual somatosensory information was insufficient to activate the cerebellum. The results of this study suggest that cerebellar activation during movement in patients with severe pansensory neuropathies is not due to sensory, attentional, or other cognitive aspects of behavior. Importantly, the cerebellar areas activated in the patients are the same ones that are activated by hand movements in normal subjects (Colebatch et al. 1991; Fox et al. 1985; Jenkins et al. 1994; Nitschke et al. 1996). (Unpublished somatotopic fMRI experiments conducted in our own laboratory using the same imaging parameters have also shown cerebellar activation during finger movements in healthy control subjects in the same areas as in the present study.)

Visual, auditory, and somatosensory input to the cerebellum has been recognized for many years (Snider and Stowell 1944). The prevailing view is that this sensory input is processed for sensorimotor integration (Blomfield and Marr 1970; Eccles 1973; Glickstein 1992), but interest increasingly has focused on the role of the cerebellum in sensory and cognitive processing (Allen et al. 1997; Fiez 1996; Grill et al. 1994; Keele and Ivry 1990; Leiner et al. 1986). The functional relevance of cerebellar activation during pure sensory or cognitive tasks is uncertain, but there is evidence that the cerebellum may be important for the temporal aspects of sensory processing (Allen et al. 1997; Fiez 1996; Grill et al. 1994; Keele and Ivry 1990; Leiner et al. 1986). Many of the imaging studies showing cerebellar activation with nonmotor tasks found activation of the lateral hemisphere. The present work indicates that activation of the anterior cerebellar hemisphere and dentate nucleus can be due to the motor aspects of movement and does not depend on sensory input. It remains possible that lateral cerebellar hemisphere structures, which are greatly enlarged in humans, contribute to nonmotor functions, but the suggestion that the cerebellum has exclusively a sensory role (Gao et al. 1996) is probably incorrect.

The cerebellum receives extensive somatosensory input via spino cerebellar pathways, and the failure to find some reduction in activation is surprising. Eff erence copy from the motor command to the cerebellum is likely to be intact in the neuropathy patients and may be overactive in an attempt to overcome their sensory deficits. Such activity may obscure any lack of somatosensory cerebellar activation. Although our data shows cerebellar activation in the patient group, this does not indicate normal sensorimotor integration, which is clearly deficient in these patients.

We thank Drs. Leonardo Cohen, Steve Wise, and Steve Massaquoi for a critical reading of the manuscript, the members of the PET Imaging Section of the Clinical Center for their expertise, N. Dang for technical assistance, and B. J. Hesse and D. Schoenberg for skillful editing. Address for reprint requests: M. Hallett, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bldg. 10, Rm. 5N226, 10 Center Dr. MSC-1428, Bethesda, MD 20892–1428.

Received 16 June 1998; accepted in final form 1 March 1999.

REFERENCES


SNIDER, R. S. AND STOWELL, A. Receiving areas of the tactile, auditory and visual systems in the cerebellum. J. Neurophysiol. 7: 331–357, 1944.