Differential Cerebellar Activation on Functional Magnetic Resonance Imaging During Working Memory Performance in Persons With Multiple Sclerosis

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ABSTRACT. Li Y, Chiaravalloti ND, Hillary FG, DeLuca J, Liu W-C, Kalnin AJ, Ricker JH. Differential cerebellar activation on functional magnetic resonance imaging during working memory performance in persons with multiple sclerosis. Arch Phys Med Rehabil 2004;85:635-9.

Objective: To explore the potential role of the cerebellum in working memory dysfunction in multiple sclerosis (MS).

Design: Blood oxygen level dependent functional magnetic resonance imaging (fMRI) was used to examine cerebellar activation during a working memory task.

Setting: University-affiliated medical rehabilitation facility.

Participants: Eight persons with MS and 5 healthy controls.

Interventions: Not applicable

Main Outcome Measure: Change in hemodynamic response. fMRI data were acquired and subsequently analyzed by using Statistical Parametric Mapping.

Results: Both the control and MS groups showed significantly greater activations in the right cerebellar hemisphere as compared with the left side. Persons with MS, however, showed no detectable activations in 4 cerebellar substructures that were significantly active in controls (ie, right vermis, right dentate nucleus, right tonsil, cerebellar peduncle).

Conclusions: The significantly decreased cerebellar activation in the MS group suggests that the cerebellum may play a role in the working memory impairment observed in MS.

Key Words: Cerebellum; Magnetic resonance imaging; Memory; Multiple sclerosis; Rehabilitation.

THROUGHOUT THE 20th CENTURY, the cerebellum was traditionally viewed as subserving purely motor functions, such as motor control and motor coordination. It was also widely held that the cerebellum only possessed connections to the primary motor gyrus. Surprisingly, however, it has been found that the human cerebellum itself possesses many more neurons than all other brain structures combined.[1,2] As shown in Lange's study, a human brain on average contains about 85 billion neurons[1] and the cerebellum alone comprises roughly 70 billion (or over 80%) of these neurons. In addition, the lateral cerebellar hemispheres and the dentate nuclei have been noted to be tremendously phylogenetically expanded, in direct correspondence to the enlargement of prefrontal cortex in humans.

Based on this observation, in 1986 Leiner et al[3] proposed a cerebellar role in cognitive functions. Their proposal triggered an exponential increase in cerebellar research since then, with a focus on the role the cerebellum plays in cognition. Neuroanatomic, neurobehavioral, and functional neuroimaging studies show that the cerebellum is functionally connected with virtually all major subdivisions of the central nervous system (CNS).[4-7] Functional magnetic resonance imaging (fMRI) in particular has been shown as an important tool to more assess directly neuronal activity in the functioning human brain.

A growing body of fMRI studies has provided evidence that the cerebellum plays a very important role in subserving a variety of nonmotor functions, such as sensory discrimination,[8] attention,[9] working memory,[10,11] semantic association,[12] verbal learning and memory,[13,14] and complex problem solving.[15] It is well known that the prefrontal cortex is critically involved in the execution of cognitive functions. Therefore, there are likely to be direct connections between the cerebellum and prefrontal cortex for the cerebellum to be truly involved in cognitive functions. Recently, by using novel retrograde tracing techniques, Middleton and Strick[7] have identified a neural pathway connection between prefrontal areas 46d, 9m, and 9l and cerebellar dentate nucleus.

Cognition and Multiple Sclerosis

It is now well established that cognitive dysfunction is prevalent in multiple sclerosis (MS). In fact, it has been estimated that 40% to 65% of patients with MS demonstrate impairment in attention, in speed of information processing, in learning new information, in problem solving, and in integrating new information with existing experience.[16,17] In particular, investigators[16] have noted impairment in working memory and this deficit has been linked to functional disability. However, the role that the cerebellum might play in leading to working memory dysfunction in MS is unknown. As is known, MS is a degenerative disease of the CNS, which is characterized by widespread plaques throughout the brain and spinal cord. Neuropathologic studies showed that there is axonal degeneration and axonal loss not only in the plaque region but also in normal-appearing white matter areas. For example, Evangelou et al[18] found that there is approximately a 16% to 56% axonal decrease in normal-appearing white matter in the corpus callosum when examined postmortem. In chronic MS (eg, disease duration 12–39y), there is even greater axonal loss (from

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45%–84% loss of axonal fibers).[19] Given such significant amounts of axonal loss, it is not surprising that people with MS are impaired in both motor and cognitive functions.

Ataxia is a very common clinical motor sign noted in patients with MS, and ataxia typically indicates cerebellar involvement. However, there are no published data that address whether the cerebellum is also involved in concomitant cognitive dysfunction in MS. Given that there are so many cerebellar neurons, and that the cerebellum plays a role in so many cognitive functions, we hypothesized that the cerebellum may also play a mediating role in the cognitive dysfunction encountered in MS. The aims of this study were (1) to determine a pattern of cerebellar activation related to a working memory challenge in persons with MS, and (2) to examine the differences in cerebellar activation between people with MS and healthy controls.

METHODS

Participants

Eight people with clinically diagnosed MS and 5 healthy controls were recruited for participation. Participants were between the ages of 18 and 55 years with a mean age ± standard deviation of 47.8±4.8 years for persons with MS and 40.6±11.1 years for healthy controls. There was no statistically significant difference between the groups in terms of age, education, or estimated premorbid verbal intelligence quotient. Participants were excluded if they reported a history of chronic medical disorders (other than MS), alcohol or drug abuse, bipolar disorder, schizophrenia or other psychotic disorder, or head injury resulting in more than 30 minutes of loss of consciousness. Before fMRI scanning, all participants were screened for any surgical history that would suggest the presence of metal objects or electronic devices within the body. Persons with MS were at least 1 month post exacerbation or steroid treatment. Based on medical record review, 75% of the persons with MS were diagnosed with the relapsing remitting subtype of MS and 25% were diagnosed with the primary progressive subtype of MS.

Behavioral Task

Participants were first oriented to the behavioral task to be presented within the scanner before the planned fMRI procedures. An auditory monitoring task was used as the control condition. In this condition, participants are asked to press a button when they heard the number "7" within a sequential series of numbers presented through headphones.

The experimental paradigm assesses differential encoding and rehearsal demands, primarily within the phonologic loop.[20] The effects of cognitive load and delay on brain activation can also be measured. This paradigm requires (1) auditory perception of the numbers, (2) attention, (3) rehearsal and maintenance within working memory, and (4) motor response. Response accuracy was recorded by an observer during image acquisition.

We were primarily interested in the cerebellar activation under different levels of task load rehearsal and maintenance of the information during processing. Theoretically, the remainder of the brain activation associated with the long delay period—after subtracting the activation associated with the short delay period—would reveal the effect of delay on brain activity. That is, the remaining brain activation represents the hemodynamic response associated with the demands of holding information for an extended period.

Therefore, in this study, 2 separate experimental manipulations were used. The demands of low and high working memory load were manipulated by varying the length of a presented letter string. As used in this study, the presentation of 2 letters represented the low load condition, and 5 letters represented the high load condition. The demand of short or long delay was manipulated by requiring a target response at 4 or 12 seconds after the initial stimulus presentation. In the response condition, participants were required to respond by pressing a button if the letter presented as the target was included in a new stimulus string. If the target was not included in the initial stimulus string, the participant was asked not to respond. This paradigm was administered in 32 sets with equal numbers of task conditions.

fMRI Procedure

All neuroimaging was performed on a General Electric Signa Horizon echo-speed 1.5T magnetic resonance scanner.[a] Before functional imaging, sagittal T1-weighted localizer images were obtained, followed by whole brain axial T1-weighted conventional spin-echo images for anatomic overlays (repetition time [TR]=450ms; echo time [TE]=14ms; contiguous 5mm, 256×256 matrix, field of view [FOV]=24cm; number of excitations=1), yielding an in-plane resolution of .94mm^2.

Functional imaging consisted of multislice gradient echo images that were acquired with echoplanar imaging (EPI) methods (TR=4000ms; TE=60ms; FOV=24cm; flip angle=90; slice thickness=5mm contiguous). This yielded a 64×64 matrix with an in-plane resolution of 3.75mm^2. Twenty-eight images in the axial plane were acquired, providing coverage of the entire brain. A set of coplanar T2-weighted EPI images with identical parameters was also obtained without a task paradigm to provide an additional set of T2-weighted structural images.

Participants performed the behavioral task while lying supine in the scanner. Foam cushioning and tape were used to immobilize the head within the coil to minimize motion-induced signal degradation. Auditory stimuli were presented to subjects through MRI-compatible headphones designed in our laboratory. Sound volume was adjusted so that each participant could adequately hear the stimuli. Six scan images were acquired for every 24-second block during the acquisition of functional imaging.

Data Preprocessing

The fMRI data were initially analyzed on a voxel-by-voxel basis with a general linear model approach by using Statistical Parametric Mapping (SPM99) software.[b] The first 3 images were eliminated from analyses to control for saturation effects. To remove subvoxel motion-related signal change, all EPI data (192 images) were aligned to the first image during spatial realignment. The realigned EPI images were then coregistered to the participant's T1 anatomic image and resliced. After coregistration, the participant's T1 anatomic image was matched to the SPM99 T1 template (standardized T1 from the Montreal Neurological Institute) by using a 12-parameter affine approach. Thus, normalization of the coregistered EPIs was based on the linear and nonlinear normalization parameters for the T1 template in SPM99 and the study participant's T1. Bilinear interpolation was used during the normalization procedure. Normalized scans were then spatial smoothed to 8×8×10mm. The SPM maps were held to an α level of .001, with no minimum cluster size.[21,22]

Statistical Analysis

This study was designed to examine the differences in cerebellar activation between the MS group and the healthy con-

Table 1: Talairach Coordinates and *z* Scores of the Peak Activation and Voxels of Common Activation

Location	*x*	*y*	*z*	*z* Scores	Volume of Voxels
MS Group					
Cortex (L)	−32	−61	−16	3.5	19
Cortex (R)	32	−61	−15	3.5	69
Controls					
Cortex (L)	−32	−64	−24	3.6	46
Cortex (R)	22	−47	−37	4.1	265
DN (R)	26	−62	−32	3.3	2
Tonsil (R)	10	−48	−35	3.3	16
Peduncle	30	−62	−32	4.0	81
Vermis	0	−71	−23	3.9	37

Abbreviations: DN, dentate nucleus; L, left; R, right.

trol group in response to a working memory challenge. We were primarily interested in the common activations across all participants with each group. The commonality of the assessed mean activation over all subjects has been believed to be more robust so that it represents the population from which the subjects were sampled.[23] Conjunction analysis, developed by Friston et al[23] for multisubject fMRI studies, was also used. This statistical approach is used to maximize power in imaging studies when the number of participants in a group is fewer than 10. This approach is more sensitive than a random effect model because it uses more degrees of freedom.

For analysis, appropriate contrast and design matrices were specified for each task condition and each subject.[23] The functional imaging data were processed on a voxel-by-voxel basis. All voxels that were significant at *P* less than .001 across all participants were displayed as areas of common activation. Significant voxels (ie, areas considered representative of significant change in cerebral blood flow) were superimposed onto the standardized structural brain maps.

RESULTS

The Talairach coordinates,[24] *z* scores for the peak activation, and the volume of activated voxels are summarized in table 1. In both MS and control groups, there was cerebellar activity in response to the working memory task. Activations were present in both right and left cerebellar hemispheres but with greater activation noted in the right cerebellar hemisphere based on the volume of calculated activated voxels (table 1; figs 1, 2). This pattern of right-dominant activation was observed in both groups and is consistent with previously published findings from fMRI studies of cerebellar activations in healthy persons.[10,25-28]

In our control group, there were on average 265 activated voxels in the right cerebellar hemisphere and 46 in the left cerebellar hemisphere (table 1, fig 3). In contrast, there was significantly less activation in the MS group in both right and left cerebellar hemispheres. In the MS group, there was approximately 74% less activation in the right cerebellar hemisphere (ie, 69 activated voxels) and 59% less activation in the left cerebellar hemisphere (ie, 19 activated voxels) (table 1). More specifically, there was a greater amount of activation in 4 substructures in the control group (eg, 81 activated voxels in the peduncle; 37 in the vermis; 16 in the right tonsil; 2 in the dentate nucleus; figs 1, 2). In the MS group, however, there were no activations detected in any of these 4 cerebellar substructures (figs 3, 4).

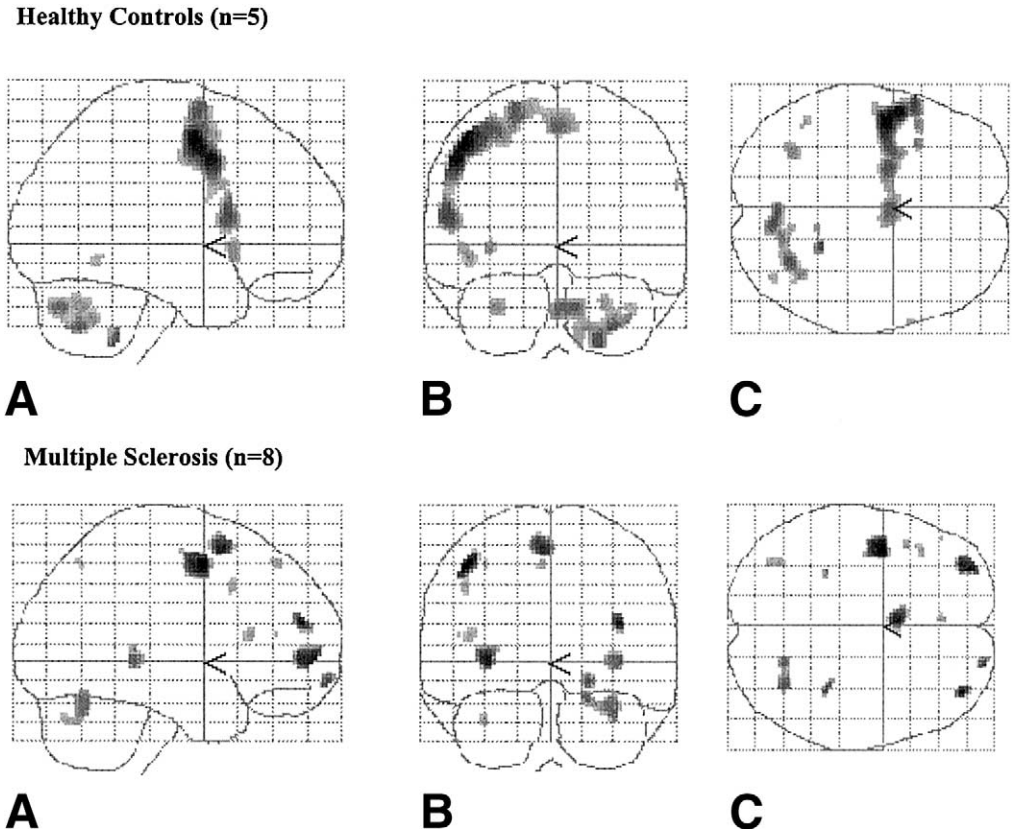

Fig 1. Brain regions active during working memory task; (A) sagittal view, (B) coronal view, and (C) horizontal view. Shaded areas represent regions of averaged activation in 5 controls and 8 persons with MS. Decreased and dispersed activation patterns characterize the persons with MS.

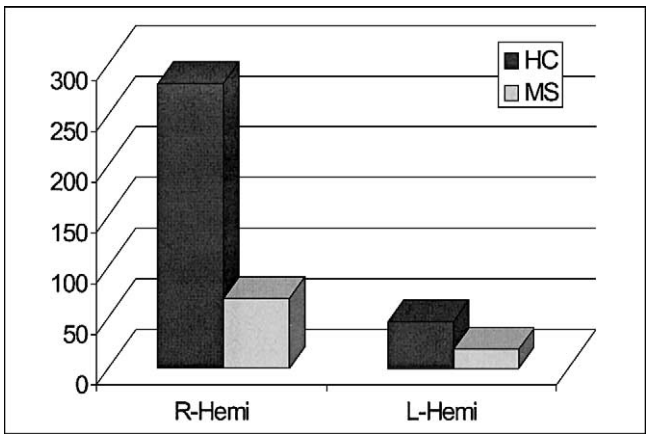

Fig 2. Averaged activation in cerebellar right and left hemisphere. Abbreviations: HC, healthy controls; Hemi, hemisphere; L, left; R, right.

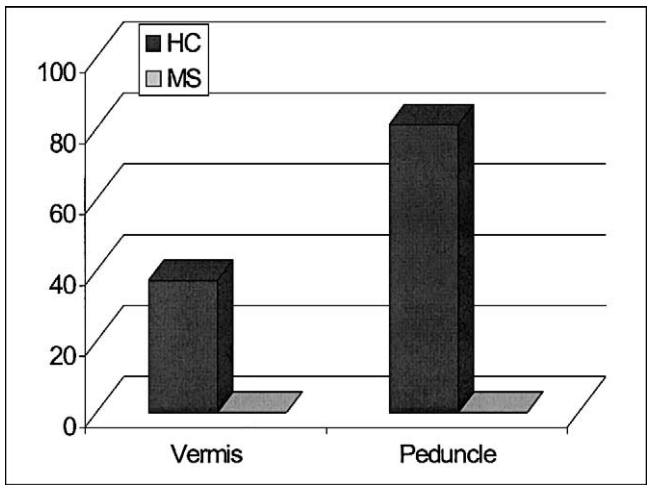

Fig 4. Averaged activation in cerebellar vermis and peduncle.

DISCUSSION

The predominant activations in the right cerebellar hemisphere are consistent with a number of previously published findings of fMRI studies in healthy persons.[25-28] In contrast to the pattern of activation noted in the control group, persons with MS showed much lower levels of cerebellar activation. Furthermore, there was no activation detected in cerebellar substructures that were quite active in healthy individuals (ie, right vermis, right dentate nucleus, cerebellar peduncle, right tonsil). Although it is unclear why persons with MS would exhibit this pattern of activation, such a finding is consistent with other clinical samples.[29]

Our findings remain preliminary and require replication. Even so, there are 2 possible explanations for the between-group differences. First, decreased external information input because of axonal loss may cause decreased activation in both left and right cerebellar hemispheres. If this is the case, then people with MS may not be acquiring (ie, encoding) as much new information and thus perform more poorly when asked to recall or recognize information at a later time, even if the delay is rather brief. Second, impaired internal information transport may compromise the cerebrocerebellar interaction between right cerebellum and left prefrontal lobe. There is little known about how the cerebellum influences the functional activity of cerebral cortex, in particular the prefrontal cortex, during the performance of working memory tasks.[20] However, it has been proposed that left prefrontal activation reflects response selection, and the right cerebellar activation reflects the search for responses, which increases with increase in difficulty.[10] Given the contralateral connections between prefrontal and cerebellar hemisphere confirmed by a neuroanatomic study,[6] the significantly decreased cerebellar activation in the right hemisphere observed in MS group in this study supports this possibility.

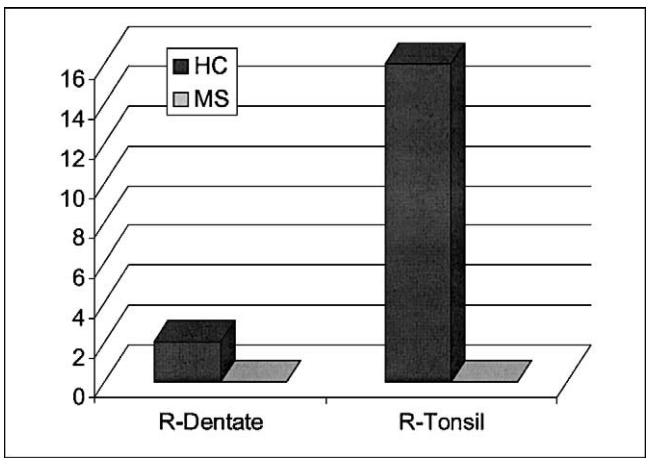

Fig 3. Averaged activation in cerebellar dentate nucleus and tonsils.

CONCLUSIONS

Future studies will need to use larger samples to verify the generalizability of our findings for persons with MS. In addition, an event-related fMRI design would allow investigators to examine the dysfunctional components of the working memory system and how they contribute to working memory deficits in MS. Finally, as human tracer methods and other approaches to studying human functional neuroanatomy in vivo are developed, functional neuroimaging procedures will need to be refined and expanded in the examination of cognitive dysfunction in the presence of neurologic compromise.

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