NEUROPSYCHOLOGIA

Neuropsychologia 44 (2006) 171–177

www.elsevier.com/locate/neuropsychologia

Cerebellar activity switches hemispheres with cerebral recovery in aphasia

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Received 12 October 2004; received in revised form 10 May 2005; accepted 12 May 2005
Available online 12 July 2005

Abstract

The right postero-lateral cerebellum participates with the left frontal lobe in the selection and production of words. Using fMRI, we examined whether cerebellar activity switches hemispheres in parallel with recruitment of putative compensatory right homologous frontal regions in post-stroke aphasia. Re-examining the data of Blasi et al. [Blasi, V., Young, A. C., Tansy, A. P., Petersen, S. E., Snyder, A. Z., & Corbetta, M. (2002). Word retrieval learning modulates right frontal cortex in patients with left frontal damage. *Neuron*, *36*(1), 159–170], we asked: (1) if activity in the right cerebellum was disrupted by a left frontal lesion, (2) if activity switched to the left cerebellum, and (3) if activity in the left cerebellum was modulated by learning, as was right frontal cortex. Fourteen age-matched controls and eight mildly aphasic stroke patients participated. Aphasic participants all had lesions due to unilateral left hemisphere stroke at or near Broca's area. Subjects silently performed a word stem completion task with either novel or repeated items. Activity in right cerebellum of aphasic individuals was minimal and was not modulated by learning, as for controls. However, we observed robust learning-related attenuation of the BOLD signal in the left postero-lateral cerebellum consistent with learning-related effects in right frontal cortex. These findings support the hypothesis that right frontal and left cerebellar circuits are likely to be functionally relevant to recovered/residual verbal function.

Keywords: fMRI; Cerebellum; Aphasia; Language; Stroke; Recovery; Learning

Although the precise neuroanatomical underpinnings are only now becoming understood, the existence of reciprocal functional connections between the cerebellum and cerebral hemispheres has been long recognized for motor functions (e.g., Thach, 1987) and has, more recently, been recognized for cognitive functions including language (Fiez, Petersen, Cheney, & Raichle, 1992; Gebhart, Petersen, & Thach, 2002; Kelly & Strick, 2003; Marien, Engelborghs, Fabbro, & De Deyn, 2001; Middleton & Strick, 2000; Muller, Courchesne, & Allen, 1998; Schmahmann & Pandya, 1997). It has been known for several years that cerebellar lesions may result in dysarthria and transient mutism, especially in children (e.g., van Dongen, Catsman-Berrevoets, & van Mourik, 1994). More recently, Schmahmann and colleagues (e.g., Levisohn, Cronin-Golomb, & Schmahmann, 2000; Schmahmann & Sherman, 1998) have argued that individuals with cerebellar lesions frequently manifest with a cluster of deficits of cognition and affect, among them deficits of verbal production, that they term cerebellar cognitive affective syndrome. In addition, there are two case reports (Marien et al., 1996; Silveri, Leggio, & Molinari, 1994) specifically examining language deficits in individuals with cerebellar lesions. Both patients exhibited aphasic characteristics such as agrammatism and anomia without evidence of any supratentorial lesion. SPECT studies in both individuals showed

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doi:10.1016/j.neuropsychologia.2005.05.019

hypoperfusion of left frontal language regions; the language deficit was attributed to crossed cerebello-cerebral diaschisis. These cases emphasize that the cerebellum is an integral part of the neuroanatomical system underlying language output.

Functional neuroimaging studies in healthy individuals have also provided supporting evidence that the cerebellum, particularly right postero-lateral cerebellum, is involved in several aspects of language performance such as verb generation (Petersen, Fox, Posner, Mintun, & Raichle, 1988, 1989; Raichle et al., 1994), verbal fluency (Schloesser et al., 1998), difficult lexical search (Desmond, Gabrieli, & Glover, 1998), and semantic decisions (Roskies, Fiez, Balota, Raichle, & Petersen, 2001), processes traditionally thought to be largely the province of the left cerebral hemisphere. Moreover, individuals with frontal or cerebellar lesions demonstrate difficulty with verb generation further emphasizing that both frontal and cerebellar regions play essential roles in the performance of this task (Gebhart et al., 2002).

However, the nature of cerebellar activity associated with language when frontal language regions are permanently damaged remains unclear. Frontal lesions may cause decrements in resting blood flow and metabolism in the contralateral cerebellum (crossed-cerebellar diaschisis (Baron, Bousser, Comar, & Castaigne, 1980; Pantano et al., 1986)), but the behavioral significance of this effect is not known. In the case of aphasia caused by frontal stroke, neuroimaging evidence has accumulated demonstrating that right hemisphere homologues are recruited during performance of language tasks over the course of recovery (Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996; Rosen et al., 2000) and the activity in these regions is modulated by task-specific manipulations (e.g., Rosen et al., 2000), such as through practice performing a word stem completion task (Blasi et al., 2002). Though Blasi et al. examined the functional activity throughout the cerebral hemispheres, they did not report whether right cerebellar activity was disrupted by left hemisphere lesion. In this study, we re-examine the data of Blasi et al. to answer three questions. First, is BOLD activity in the right cerebellum during a word stem completion task disrupted by a left frontal lesion? Second, does activity switch to the left cerebellum, as one would expect given the recruitment of homologous right frontal regions? Third, is the BOLD response in the cerebellum modulated by learning, as one would predict if it reflects fronto-cerebellar connections and if compensatory activity in the right frontal lobe is also modulated by learning?

1. Methods

1.1. Participants

Fourteen age-matched controls (mean age of 38.7 years) and eight mildly aphasic stroke patients (mean age of 48.6 years) participated. All aphasic participants had lesions due to unilateral left hemisphere stroke at or near Broca's area. All were 6 months or more post-stroke.

1.2. Procedure

Subjects participated in an fMRI session during which they silently performed a word stem completion task during whole-brain measurement of blood-oxygen level dependent (BOLD) signal. Forty-nine three-letter word stems (e.g., COU) were presented during each fMRI run. Each was presented for 3.5 s on a computer screen viewed on a mirror attached to the head coil on the scanner bed. Subjects were instructed to say silently to themselves a word that started with those three letters (e.g., couple). Novel stems were presented during runs 1, 6, 7, and 8; items from run 1 were presented in random order during runs 2 through 5. Behavioral responses and response latencies were measured in a prior session outside the scanner and with the scanner off after runs 1 and 5.

1.3. FMRI scan acquisition and data analysis

MR scans were acquired with a 1.5 T Siemens Vision scanner. An asymmetric spin-echo, echoplanar sequence was used to measure BOLD contrast (TR = 2.36 s, TE = 50 ms, flip angle = 90°). Eight BOLD runs of 128 frames were acquired in each subject with each frame including 16 contiguous 8 mm axial slices (3.75 mm × 3.75 mm in-plane resolution). In addition, we obtained sagittal T1-weighted MP-RAGE (TR = 9.7 ms, TE = 4 ms, flip angle = 12°, TI = 300 ms, 128 slices, 1 mm × 1 mm × 1.25 mm voxels) and T2-weighted fast turbo spin-echo (TR = 3800 ms, TE = 90 ms, flip angle 90°) anatomical images in each subject.

Images produced by each fMRI run were combined into one file organized as a 4D (*x*, *y*, *z*, time) time-series (4D stack). The 4D stack then passed through a sequence of unsupervised processing steps including compensation for asynchronous slice acquisition, realignment by six-parameter rigid body motion (Friston et al., 1995; Snyder, 1995) and whole brain normalization across scans and subjects. Functional data were realigned within and across runs to correct for head movement, and coregistered with anatomical data. Linear detrending was applied to eliminate drift in the MR signal. For each subject an atlas transformation was computed based on an average of the first frame of each functional run and T2 and MP-RAGE structural images. An eight-parameter (rigid-body plus in-plane stretch) cross-modal registration similar to the method of Andersson (Andersson, Sundin, & Valind, 1995) aligned the average first frame data to the T2 image. A similar procedure registered the T2 image to the MP-RAGE image.

The MP-RAGE image was registered to the atlas representative target using a 12-parameter general affine transformation. Functional data were interpolated to 2 mm cubic voxels in atlas space. The atlas representative MP-RAGE target was produced by mutual co-registration (12 parameter affine transformation) of images obtained in 12 normal subjects. This target image represents Talairach atlas space (Lancaster et al., 1995; Talairach & Tournoux, 1988). Atlas registration