Localization of a cerebellar timing process using PET

M. Jueptner, MD; M. Rijntjes; C. Weiller, MD; J.H. Faiss, MD;
D. Timmann, MD; S.P. Mueller, MD; and H.C. Diener, MD

Article abstract—We used positron emission tomography (PET) to localize a cerebellar timing function. Six healthy volunteers estimated time differences by comparing a test interval (defined by two tones) with a standard interval. In the timing condition, subjects lifted their right index finger if the test interval was shorter and their right middle finger if it was longer than the standard interval. In the control condition, the two intervals were identical and subjects had to alternate between lifting their index and middle fingers. We examined regional cerebral blood flow (rCBF) using the standard $C^{15}O_2$ inhalation technique. Comparison of control and rest conditions revealed significant increases of rCBF during the control condition in the inferior parts of the ipsilateral cerebellar hemisphere, reflecting finger movements. Comparison of timing and control conditions showed additional activations of the cerebellar vermis and hemispheres bilaterally during the timing condition, reflecting the cerebellar timing process. We conclude that the cerebellum is involved in time-critical perception ("timing"). This nonmotor task can be separated from a motor task (finger movement).

NEUROLOGY 1995;45:1540-1545

In the beginning of this century, Holmes comprehensively described and summarized clinical signs and symptoms resulting from lesions of the cerebellum.[1-6] Lesions of the cerebellar hemispheres cause dyssynergia, dysmetria, dysdiadochokinesia, and dysarthria. Damage to the cerebellar vermis and the anterior lobe results in ataxia of stance and gait. Consequently, despite its homogeneous intrinsic anatomic structure,[7] the cerebellum is divided into functional compartments, with each of these subunits having specific functions.[8-10]

Apart from the cerebellar role in motor control, many recent studies demonstrated the involvement of the cerebellum in nonmotor tasks, eg, motor learning, classical conditioning, cognitive functions, and mental activity.[11-21] However, despite the increased information about activities involving the cerebellum, little is known about *how* the cerebellum processes all these different tasks. One important aspect of cerebellar function is the sequencing and *timing* of skilled action and perception, including thought.[11,22-25] For this reason, timing functions of the cerebellum have been studied in great detail and cerebellar patients are impaired in both motor and perceptual tasks that require accurate timing. Ivry and Keele[26] demonstrated an increased variability in response times when cerebellar patients tried to maintain a constant tapping rhythm with their fingers. These patients were also impaired when making perceptual judgments of differences in duration of time intervals or velocity of moving stimuli.[26,27]

The present study tested whether the cerebellum is involved in time-critical perception in normal human subjects. Using PET, we attempted to localize this cerebellar nonmotor function (estimation of time differences) in relation to an activation elicited by motor execution.

Methods. Regional cerebral blood flow (rCBF) was measured in six healthy volunteers aged 23 to 41 years. None of the subjects had a history of neurologic or psychiatric disease, and none took any medications. A routine clinical examination showed no signs of neurologic disease. Approximately 30 minutes prior to scanning, all subjects performed eight to 10 test trials on each experimental condition. All subjects gave written informed consent.

In each subject, we performed a total of six scans of rCBF in the following conditions:

A. Rest condition. During this condition, subjects kept their eyes closed and did not move their fingers; no tones were presented.

B. Control condition. In this condition, a first tone of 50-msec duration and a frequency of 1,000 Hz indicated the beginning of the first interval. After 300 msec, a second tone marked the end of this standard interval. An identical second interval was presented after a silent period of 600 msec. Subjects had to lift either the index or the middle finger of their right hand. If subjects lifted their index finger in one decision interval, they lifted

From the Departments of Neurology (Drs. Jueptner, Weiller, Faiss, Timmann, and Diener, and M. Rijntjes) and Nuclear Medicine (Dr. Mueller), University of Essen, Germany.

Supported by the Deutsche Forschungsgemeinschaft, grant Di-454/8-1.

Received September 9, 1994. Accepted in final form January 9, 1995.

Address correspondence and reprint requests to Dr. C. Weiller, Neurologische Universitätsklinik, Hufelandstrasse 55, D 45122 Essen, Germany.