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REVIEW

CURRENT ADVANCES IN LESION-SYMPTOM MAPPING OF THE HUMAN CEREBELLUM

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Abstract—While high-resolution structural magnetic resonance imaging (MRI) combined with newer analysis methods has become a powerful tool in human cerebral lesion studies, comparatively few studies have used these advanced imaging techniques to study lesions of the human cerebellum and their associated symptoms. This review will summarize the methodology of MRI-based lesion-symptom mapping of the human cerebellum and discuss its potential for gaining insights into cerebellar function. The investigation of patients with defined focal lesions yields the greatest potential for obtaining meaningful correlations between lesion site and behavioral deficits. In smaller groups of patients overlay plots and subtraction analysis are good options. If larger groups of patients are available, different statistical techniques have been introduced to compare behavior and lesion site on a voxel-by-voxel basis. Although localization in degenerative cerebellar disorders is less accurate because of the diffuse nature of the disease, certain information about the supposed function of larger subdivisions of the cerebellum can be gained. Examples are given which show that lesion-symptom mapping allows to investigate the function of the intermediate zone and cerebellar nuclei. We conclude that meaningful correlations between lesion site and behavioral data can be obtained in patients with degenerative as well as focal cerebellar disorders.

Key words: volumetry, voxel-based, intermediate zone, cerebellar nuclei, cerebellar stroke, functional compartmentalization.

Contents

A traditional approach to elucidate the function of the human brain, and the cerebellum in particular, is to study impairment in human subjects with brain lesions. However, the approach suffers from a number of limitations (Shallice, 1988). The cerebellum is part of a more extended brain circuitry. Thus, a specific behavioral deficit following a localized cerebellar lesion may result from functional disruption anywhere within that circuitry. Furthermore, in patients with chronic lesions, plasticity within the cerebellum and the connected areas may lead to changes in their function as the brain attempts to recover. In patients with

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Abbreviations: ADCA, autosomal dominant cerebellar ataxia; AICA, anterior inferior cerebellar artery; AVM, arteriovenous malformation; CT, computed tomography; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; EA2, episodic ataxia type 2; FF, force field perturbation; HVI, cerebellar hemispheral lobule VI according to Larsell; IB, impaired dynamic balance during gait; ICARS, International Cooperative Ataxia Rating Scale; IL, impaired leg placement; IPICA, lateral posterior inferior cerebellar artery branch; MNI, Montreal Neurological Institute; mPICA, medial posterior inferior cerebellar artery branch; MPRAGE, magnetization-prepared rapid-acquired gradient echo sequence; MRI, magnetic resonance imaging; MSA-C, multiple system atrophy, cerebellar type; mSCA, medial superior cerebellar artery branch; NIB, unimpaired dynamic balance during gait; NIL, unimpaired leg placement; PICA, posterior inferior cerebellar artery; ROI, region of interest; SAOA, sporadic adult onset ataxia; SARA, Scale for the Assessment and Rating of Ataxia; SCA, superior cerebellar artery; SCA(number), spinocerebellar ataxias type (number); SPM, statistical parametric mapping; SWI, susceptibility weighted imaging; TICV, total intracranial volume; VBM, voxel-based morphometry; VLSM, voxel-based lesion symptom mapping; VM, visuomotor rotation; WHO, World Health Organization; 3-D, three-dimensional.

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acute focal lesions, changes due to neural plasticity are not a problem. However, a temporary dysfunction in connected brain areas after abrupt changes in input is a serious problem in this patient group.

Although function of the cerebellum cannot be inferred from lesion data alone, it is still of major scientific and clinical interest if lesions of a given cerebellar area lead to specific behavioral deficits. The introduction of high-resolution structural brain imaging and new analysis methods has led to significant improvement in our ability to draw such conclusions (Rorden and Karnath, 2004). This review highlights these implications for human cerebellar lesion studies.

Despite the good quality of new generation computed tomography (CT), magnetic resonance imaging (MRI) is the method of choice for visualization of structures within the posterior fossa. In patients with cerebellar degeneration, volumetric MRI measures can be applied to quantify the degree of atrophy of the whole cerebellum and its major subdivisions (Makris et al., 2005; Brandauer et al., 2008). In patients with focal cerebellar lesions it is possible to define affected cerebellar lobules (Schmahmann et al., 2000; Gerwig et al., 2003, 2005). Furthermore, the cerebellar nuclei can be visualized with increasing precision, and it is now possible to determine which parts of the nuclei are affected in each patient (Dimitrova et al., 2002; Deoni and Catani, 2007).

Correlation of cerebellar lesion and behavioral data has greatest spatial precision in patients with focal lesions. In smaller groups of subjects, lesion overlay plots and subtraction analyses are useful approaches. These techniques allow comparison of lesion site between two groups of patients with and without impairment in a given task. Likewise, patients can be divided into a group with and a group without lesion in a specific area, and then behavior can be compared between the two groups. If larger groups of patients with focal lesions are available, innovative statistical techniques have been introduced to compare behavior and lesion site on a voxel-by-voxel basis (Bates et al., 2003; Rorden and Karnath, 2004; Rorden et al., 2007).

In patients with degenerative cerebellar disorders conventional MRI volumetry has been used to assess the correlation of behavioral data and regional cerebellar atrophy. Voxel-based morphometry (VBM) is an alternative with the potential for better spatial resolution. VBM is particularly appropriate in disorders with no obvious abnormalities in structural MRI (Rorden and Karnath, 2004). As yet, few studies have explored VBM as a tool to compare behavior and lesion site in patients with degenerative cerebellar disease (Lasek et al., 2006).

In the first part of this review the pros and cons of available human cerebellar lesion conditions will be discussed. In the second part examples of lesion-symptom mapping both in focal cerebellar disorders and cerebellar degeneration will be given.

HUMAN CEREBELLAR LESION CONDITIONS

In principle, lesions need to be exclusively restricted to the cerebellum in order to infer possible cerebellar function based on lesion localization and volume. However, patients with lesions restricted to the cerebellum are rare and it can be argued that there are no patients with 100% pure cerebellar lesions. Yet, several conditions lead to lesions that primarily affect the human cerebellum. In general three patient groups can be distinguished: patients with focal lesions due to stroke, patients with focal lesions due to tumors, and patients with slowly progressive degenerative disorders. Each of the available human cerebellar lesion conditions has its specific limitations, which will be discussed below (see Table 1 for summary).

Structural MRI makes it possible to exclude patients with extracerebellar involvement of the CNS, such as additional lesions of the brainstem in subjects with cerebellar stroke or degenerative disorders. Cranial MRI, however, cannot detect concomitant disorders of the peripheral nervous system or spinal cord. For example, many patients with cerebellar degeneration show mild accompanying signs of polyneuropathy in the lower limbs. Additional clinical and electrophysiological measures are required in order to reach definitive conclusions.

Cerebellar stroke

Patients with cerebellar stroke provide the only human lesion condition where symptoms can be studied following an acute lesion in a previously healthy cerebellum. Although tumor surgery causes an acute cerebellar lesion, the growing tumor has caused cerebellar dysfunction for an unknown time. Infarction of the cerebellum is a rare event representing up to 15% of all cerebral strokes (Tohgi et al., 1993; Amarenco, 1991; Weimar et al., 2002). First with the introduction and later with better availability and quality of CT and MRI scanners the number of detected cerebellar infarcts has increased. Furthermore, it became clear that the “classical” cerebellar ischemic syndromes including brainstem signs as well as life-threatening brainstem compression and hydrocephalus from postinfarct edema are comparatively rare (Kase et al., 1993; Chaves et al., 1994). The majority of cerebellar infarctions have a benign clinical course.

The main cerebellar arteries are the posterior inferior cerebellar artery (PICA), the anterior inferior cerebellar artery (AICA), and the superior cerebellar artery (SCA) (Caplan, 1996). Branches of the PICA supply the inferior aspects of the cerebellar hemispheres and inferior vermis extending up to the primary horizontal fissure. Branches of the AICA supply the flocculus, and adjacent lobules of the inferior and anterior cerebellum and the middle cerebellar peduncles. The SCA supplies the superior parts of the cerebellum down to the horizontal fissure. It supplies all cerebellar nuclei and most of the cerebellar white matter. In some cases the PICA supplies parts of the dentate nucleus. The SCA and PICA have two main branches, supplying the more dorsomedial (mPICA, mSCA) and the more ventrolateral (lPICA, lSCA) parts of each territory. Medial branches supply mostly the vermis and paravermian parts of the hemispheres, and lateral branches the more lateral parts of the hemispheres. The cerebellar vascular territories are nicely illustrated in Tatu et al. (1996) based