Lesion-Symptom Mapping

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Abstract

In this chapter, methods will be introduced which are currently available to perform lesion-symptom mapping in patients with focal and degenerative cerebellar disease. At the beginning of the chapter, strength and weaknesses inherent in studies on localization of cerebellar function in these different patient populations will be discussed. Next, methods of lesion-symptom mapping in focal cerebellar disease will be explained in more detail including lesion delineation, lesion normalization, and descriptive and inferential statistical analysis. Finally, methods of lesion-symptom mapping in cerebellar degeneration and available atlases of the cerebellum in stereotaxic space will be introduced.

Keywords

Cerebellar function · Mapping · Lesion-symptom · Lesion-deficit · Lesion-behavior

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74.1 Introduction

A traditional approach to studying cerebellar function is examining impairment in human subjects with cerebellar disease. High-resolution structural brain imaging coupled with tools that perform lesion-symptom mapping produced major advances in localization of function within the human cerebellum (Timmann et al. 2009, 2013). Lesion-symptom mapping is also called lesion-behavior mapping and lesion-deficit mapping. To localize function, patients should be included who have lesions restricted to the cerebellum. These patients are rare. Group sizes are commonly much smaller than in comparable studies with cerebral stroke. Methods will be discussed which are currently available to perform lesion-symptom mapping in patients with focal and degenerative cerebellar disease.

74.2 "Pure" Human Cerebellar Lesion Conditions

Although some might argue no patients have pure cerebellar lesions, there are conditions that affect the human cerebellum primarily. Lesion-symptom mapping studies are best done on patients with circumscribed focal lesions of the cerebellum. These include patients with cerebellar stroke and patients with benign tumor surgery (Timmann et al. 2009, 2013). Alternatively, patients with degenerative cerebellar disease can be studied. Cerebellar degeneration is more diffuse, and it commonly affects all parts of the cerebellum. Table 74.1 summarizes the strength and weaknesses inherent in studies on localization of cerebellar function in these different patient populations that are available for studying localization of cerebellar function.

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Table 74.1 Pros and cons of available "pure" human cerebellar lesion conditions

Cerebellar lesion condition	Strength	Weaknesses
Cerebellar stroke	Lesion-symptom mapping in acute stage is possible	Old age
SCA stroke		Brainstem and cerebral vascular lesions need to be excluded
PICA stroke		
Cerebellar tumor surgery	Young age	Delineation and normalization of acute lesions not reliable
Pilocytic astrocytoma	Accompanying cerebral disease unlikely	Possible sequelae of hydrocephalus
Vascular tumors		Possible influence of still developing brain
Chronic focal lesions	Easy lesion delineation on T1-weighted images	Study of fully compensated stage
Cerebellar stroke	Stable disease allowing use continuous variables in statistics (e.g., t tests)	
Cerebellar tumor surgery		
Acute focal lesions	Maximal deficits with no or incomplete compensation	Crossed cerebello-cerebral diaschisis as possible confounder
Cerebellar stroke		Special MRI sequences needed to show full lesion extent (e.g., DWI, FLAIR, Perfusion MRI or ASL)
Cerebellar degeneration	Good availability in many labs	Old age
SCA6		Mild extracerebellar involvement frequently present
SAOA		More diffuse disease

Abbreviations: SCA superior cerebellar artery, *PICA* posterior inferior cerebellar artery, *SCA6* spinocerebellar ataxia type 6, *SAOA* sporadic adult onset ataxia of unknown etiology, *DWI* diffusion-weighted imaging, *FLAIR* Fluid Attenuated Inversion Recovery, *ASL* arterial spin labeling

74.2.1 Cerebellar Stroke

Cerebellar stroke is a common lesion condition for lesion-symptom mapping. Because the three main cerebellar arteries supply parts of the cerebellum and the brainstem, brainstem lesions need to be excluded based on magnetic resonance brain imaging (MRI) (Tatu et al. 1996). Widespread use of MRI has shown that many such strokes are limited to the cerebellum and that they have a benign course. One must also exclude accompanying cerebral vascular disease. Cerebellar stroke is most common in the territories of the superior cerebellar artery (SCA) and the posterior inferior cerebellar artery (PICA). Strokes of the anterior inferior cerebellar artery (AICA) are rare and usually do affect the brainstem.

74.2.2 Cerebellar Tumors

Study of patients with benign tumors may provide more reliable data than studies of patients with malignant tumors. First, patients with metastasis of the cerebellum (the most common cerebellar tumor in adults) are frequently too sick to perform behavioral studies. Second, malign tumors require chemotherapy and radiotherapy which damage the nervous system. Pilocytic astrocytoma and vascular tumors (e.g., hemangioblastomas and arteriovenous malformations) do allow successful lesion-symptom mapping. Then, it is best to test behavior in the chronic stage after surgical removal of the tumor. Mass effects exacerbate the symptoms of cerebellar tumors so that the exact lesion site is difficult to determine with the tumor still in place (Karnath and Steinbach 2011). Furthermore, mass effects within the posterior fossa frequently cause accompanying hydrocephalus. In acute surgical lesions, there is usually a significant shift in neuronal structures because of edema, air, and cell detritus.

74.2.3 Cerebellar Degeneration

There are many different forms of hereditary, non-hereditary, and acquired degenerative cerebellar ataxias. Only very few are primarily confined to the cerebellum. The two most common "pure" cerebellar ataxias are spinocerebellar ataxia type 6 (SCA6), with an autosomal dominant inheritance, and sporadic adult onset ataxia of unknown etiology (SAOA). For some other, rare forms of hereditary ataxias, a benign course with a more cerebellar phenotype has been described as well (Klockgether 2011). Although SCA6 and SAOA are considered "pure" cerebellar ataxias mild extracerebellar involvement is common (e.g., mild polyneuropathy, brisk tendon reflexes, mild pollakiuria). Cerebellar cortical degeneration is the hallmark of both ataxias. More recent studies show that there is (likely secondary) degeneration of the cerebellar nuclei as well, at least in SCA6 (Stefanescu et al. 2015; Deistung et al. 2022).

74.3 Lesion-Symptom Mapping in Focal Cerebellar Disease

The general idea is to delineate lesions on high-resolution structural MRI images. Next, in order to allow group analysis, the delineated lesions are normalized into a standard stereotaxic space, very similar to normalization of functional MRI data. If lateralization is not part of the scientific question, lesions are frequently mirrored to the same side of the cerebellum to increase group size. Finally, lesion sites and

behavioral data are compared using descriptive and statistical methods (de Haan and Karnath 2018). These results are displayed as overlays on atlases of the cerebellum for localization. Because analysis is based on spatially normalized lesions, atlases are used which show the cerebellum in the same stereotaxic space.

74.3.1 Lesion Delineation

The gold standard of lesion delineation remains manual tracing. This is most commonly done on T1-weighted MRI scans using image processing software such as the freely available MRIcroN program (https://www.nitrc.org/projects/mricron). Semiautomatic lesion demarcation methods are available (e.g., de Haan et al. 2015; https://www.medizin.uni-tuebingen.de/de/das-klinikum/einrichtungen/kliniken/kinderklinik/kinderheilkunde-iii/forschung-iii/software). Limitations of automatic tracing methods are discussed in Wilke et al. (2011).

Cerebellar nuclei are not seen in T1-weighted images. Susceptibility weighted imaging (SWI) and quantitative susceptibility imaging (QSM) can be used to visualize the cerebellar nuclei directly and delineate their lesions (Maderwald et al. 2012; Deistung et al. 2022).

74.3.2 Lesion Normalization

The individual cerebellum and the traced lesion are simultaneously spatially normalized into a standard stereotaxic space. Normalization of the cerebellum is performed while the lesioned region is ignored ("masked"; (Brett et al. 2001)). The freely available SPM program is one of a number of software packages available for this purpose (https://www.fil.ion.ucl.ac.uk/spm/). A good practice is to use the Spatially Unbiased Infra-Tentorial atlas template (SUIT template) of the human cerebellum which allows optimized normalization of the cerebellum (Diedrichsen 2006). The SUIT template and software are freely available as a toolbox for SPM and other image analysis software http://www.diedrichsenlab.org/imaging/suit.htm). Normalization with the SUIT template has been extended for specific normalization of the dentate nuclei (Diedrichsen et al. 2011).

74.3.3 Descriptive Statistical Analysis

The simplest use of normalized lesions is to collect patients with the same disorder and superimpose lesions. Because locations of brain damage are not randomly distributed, simple overlay plots may be biased, that is they may simply show commonly damaged areas. A more advanced method is the comparison of lesion site between two groups of patients with and without impairment in a given task (Rorden and Karnath 2004). Subtraction analysis is a way to quantify group differences (Karnath et al. 2002). In MRIcroN, for each lesion end voxel, the percentage of unimpaired patients with a lesion in that voxel is subtracted from the percentage of impaired patients with a lesion in that voxel. For example, in case 80% of the impaired patients and 40% of the unimpaired patients are lesioned for a voxel, then subtraction of the two numbers gives 40% consistency. Subtraction analysis is a useful tool in small patient populations which is frequently the case in human cerebellar lesion studies. The method, however, is descriptive. Furthermore, behavior is classified as normal or abnormal, and the severity of the abnormality is not considered.

74.3.4 Inferential Statistical Analysis

Binomial statistical tests can be applied when behavior can be categorized as either normal or abnormal based on a specific threshold of performance. These include Fisher's exact test, chi-square test, and Liebermeister test. For example, the Liebermeister test can be performed to support the descriptive results of subtraction analysis. If symptom severity is a continuous variable, multiple t tests or a non-parametric alternative (e.g., the Brunner–Munzel test) can be applied without the need to group patients by a behavioral cut-off (Bates et al. 2003; Rorden et al. 2007). A t test is conducted at each voxel comparing the behavioral scores of the patients for whom that voxel is intact and lesioned on the parameter of interest. Voxel-wise lesion-symptom mapping has the same multiple-comparison problem as standard techniques in functional MRI. Bonferroni correction can be applied, and less conservative methods like false discovery rate (FDR) and permutation thresholding are also available to correct for this. Focusing analysis on a specific region of interest or only on those voxels where some patients have lesions (Rorden et al. 2009) are other ways to reduce the number of comparisons. Some authors include lesion size as nuisance regressor (Karnath and Smith 2014).

74.4 Lesion-Symptom Mapping in Cerebellar Degeneration

Conventional MRI volumetry and voxel-based morphometry (VBM) are two options to assess the correlation of behavioral data and regional atrophy of the cerebellar cortex. Both methods are based on T1-weighted MRI images. Conventional MRI volumetry accesses atrophy in predefined cerebellar regions, for example, the anterior and posterior lobes or individual cerebellar lobules. Several semiautomatic

and automatic methods are available (e.g., SUIT, Diedrichsen et al. 2009; the Johns Hopkins atlas, Yang et al. 2016). SWI and QSM images can be used to assess changes in the volume of the cerebellar nuclei (Stefanescu et al. 2015; Deistung et al. 2022).

No anatomical regions need to be predefined in VBM. Local concentration of gray matter is assessed on a voxel-wise basis. Furthermore, analysis is automatized. VBM data, however, need to be normalized to standard stereotaxic space (e.g., SUIT space). Furthermore, it has the same multiple-comparison problem as outlined above. VBM is also of interest in patients with chronic focal cerebellar disorders. Here, VBM is a useful option to access secondary changes in preserved cerebellar tissue and in connected cerebral areas (Clausi et al. 2009). Diffusion-weighted imaging (DWI) sequences (including neurite orientation dispersion and density imaging, NODDI; Zhang et al. 2012) enable the study of abnormalities in white matter of the cerebellum. Similar to gray matter changes of the cerebellar cortex, alterations of cerebellar white matter tracts (e.g., cerebellar peduncles) can be correlated with behavioral findings.

74.5 Atlases of the Cerebellum in Stereotaxic Space

For many years, Schmahmann et al.'s MRI atlas of an individual cerebellum was a major tool in identifying cerebellar lobules and fissures in functional and structural imaging studies (Schmahmann et al. 2000). Diedrichsen et al. (2009) have published a probabilistic atlas of the cerebellar cortex. This atlas is also available as a flat representation of the cerebellar cortex (Diedrichsen and Zotow 2015), which can be helpful when presenting the results of lesion symptom mapping. Furthermore, later versions include the cerebellar nuclei (Diedrichsen et al. 2011). These atlases are available for imaging data normalized to different stereotaxic spaces including SUIT space. More recently, cerebellar templates have been made available based on resting state networks, that is cerebellar regions that are functionally coupled to cerebral networks, and functional MRI, that show motor and cognitive areas of the cerebellum (Buckner et al. 2011; King et al. 2019; Guell and Schmahmann 2020). These templates can be downloaded at http://www.diedrichsenlab.org/imaging/suit.htm and https://xaviergp.github.io/littlebrain/.

74.6 Limitations

Several limitations of lesion-symptom mapping in general and of human cerebellar lesion conditions and analysis methods in particular have to be taken in mind. 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, plastic changes have occurred and behavior is confounded by compensatory effects. In patients with acute focal lesions, a temporary dysfunction in connected brain areas (i.e., crossed cerebro-cerebellar diaschisis) after abrupt changes in input can be a confounder. Furthermore, much of recovery is happening in the very initial days and weeks after an acute brain injury. Unless patients are tested at the same time after the injury, statistical tests using continuous variables are biased by lesions in patients with less time of recovery (Rorden and Karnath 2004). Therefore, subtraction analysis and binomial statistical tests are more reliable in acute lesions. Lesion delineation is another problem in acute lesions. In acute surgical lesions there is usually a significant shift in neuronal structures which hampers reliable lesion delineation and normalization. In acute stroke, special MRI sequences are needed to show the full extent of the lesion. In very early stages, lesions may only be visualized on diffusion weighted (DWI) or Fluid Attenuated Inversion Recovery (FLAIR) images (Wintermark et al. 2013). Furthermore, to show areas that are structurally intact but not functioning normally, perfusion MRI or arterial spin labeling is required (Rorden and Karnath 2004). Voxel-wise lesion-symptom mapping cannot fully rule out the possible bias by the natural distribution of the underlying brain lesions, e.g., stroke territories (Mah et al. 2014). Furthermore, voxel-wise lesion-symptom mapping has limitations when multiple regions are involved in a given task. In order to deal with these problems, multivariate pattern analysis has more recently been introduced (Karnath and Smith 2014; Mah et al. 2014). Large data sets, however, are required which are commonly not available in human cerebellar lesion studies. Despite these limitations, it remains of major scientific and clinical interest if lesions of a given cerebellar area lead to specific behavioral deficits.

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