Cerebellum
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Lesion-Symptom Mapping of the Human Cerebellum

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Abstract High-resolution structural magnetic resonance imaging (MRI) has become a powerful tool in human cerebellar lesion studies. Structural MRI is helpful to analyse the localisation and extent of cerebellar lesions and to determine possible extracerebellar involvement. Functionally meaningful correlations between a cerebellar lesion site and behavioural data can be obtained both in subjects with degenerative as well as focal cerebellar disorders. In this review, examples are presented which demonstrate that MRI-based lesion-symptom mapping is helpful to study the function of cerebellar cortex and cerebellar nuclei. Behavioural measures were used which represent two main areas of cerebellar function, that is, motor coordination and motor learning. One example are correlations with clinical data which are in good accordance with the known functional compartmentalisation of the cerebellum in three sagittal zones: In patients with cerebellar cortical degeneration ataxia of stance and gait was correlated with atrophy of the medial (and intermediate) cerebellum, oculomotor disorders with the medial, dysarthria with the intermediate and limb ataxia with atrophy of the intermediate and lateral cerebellum. Similar findings were obtained in patients with focal lesions. In addition, in patients with acute focal lesions, a somatotopy in the superior cerebellar cortex was found which is in close relationship to animal data and functional MRI data in healthy control subjects. Finally, comparison of data in patients with acute and chronic focal lesions revealed that lesion site appears to be critical for motor recovery. Recovery after lesions to the nuclei of the cerebellum was less complete. Another example which extended knowledge about functional localisation within the cerebellum is classical conditioning of the eyeblink response, a simple form of motor learning. In healthy subjects, learning rate was related to the volume of the cortex of the posterior cerebellar lobe. In patients with focal cerebellar lesions, acquisition of eyeblink conditioning was significantly reduced in lesions including the cortex of the superior posterior lobe, but not the inferior posterior lobe. Disordered timing of conditioned eyeblink responses correlated with lesions of the anterior lobe. Findings are in good agreement with the animal literature. Different parts of the cerebellar cortex may be involved in acquisition and timing of conditioned eyeblink responses in humans. These examples demonstrate that MRI-based lesion-symptom mapping is helpful to study the contribution of functionally relevant cerebellar compartments in motor control and

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recovery in patients with cerebellar disease. In addition, information about the function of cerebellar cortex and nuclei can be gained.

Keywords Human · Cerebellum · Ataxia · Sagittal zone · Somatotopy · Motor learning

There are different ways to study the function of the human cerebellum. One method which has long been used is to study the impairments in human subjects with cerebellar lesions. The introduction of high-resolution structural brain imaging has helped to overcome some of the known limitations of human lesion studies [1]. Structural magnetic resonance imaging (MRI) in cerebellar lesion studies has different implications.

Firstly, to infer possible cerebellar function based on lesion localisation and volume, lesions need to be restricted to the cerebellum alone. Structural MRI is helpful to exclude extracerebellar involvement of the central nervous system, for example additional lesions of the brainstem in subjects with cerebellar stroke or degenerative disorders. Some shortcomings should, however, be noted. For example, patients with tumours may not present with hydrocephalus at the time of the testing, but tumours are frequently preceded by signs of increased intracranial pressure. The long-term effects of the latter and sudden surgical decompression are difficult to control. Furthermore, cranial MRI cannot detect concomitant disorders of the peripheral nervous system. For example, many patients with cerebellar degeneration show mild accompanying signs of polyneuropathy in the lower limbs. Additional clinical and/or electrophysiological measures are required.

Secondly, structural MRI can be used to determine the localisation and extent of cerebellar lesions. In patients with cerebellar degeneration volumetric measures have been applied to quantify the degree of atrophy of the whole cerebellum and its subdivisions [2]. In patients with focal cerebellar lesions, the affected cerebellar lobules are defined [3], and the cerebellar nuclei can be visualised allowing to analyse which parts of the nuclei are affected [4, 5]. Advances of MRI analysis tools and technology including available coils and increasing field strength lead to a constant improvement in precision of structural characterisation of the cerebellar lesions [6, 7]. It has to be noted that the majority of human cerebellar lesion models affect the cerebellar cortex. Additional lesions of the cerebellar nuclei may be present to various extents. However, human lesions affecting primarily the cerebellar nuclei are exceptionally rare.

Finally, and being the prime topic of this article, MRI-based lesion data can be used to correlate cerebellar lesion and behavioural data. Different statistical techniques have been introduced to compare lesion site on a voxel-by-voxel basis and behaviour in patients with focal brain lesions [1, 8, 9]. In patients with degenerative cerebellar disorders, behavioural data and cerebellar atrophy assessed by conventional MRI volumetry have been correlated. Voxel-based morphometry is another option, particularly in disorders with no obvious abnormalities in structural MRI [10].

There are important limitations to infer from correlation between a lesion and a behavioural measure on the function of a given cerebellar area [11]. The cerebellum is part of a more extended brain circuitry. Thus, it is not meaningful to assign a specific behavioural function or deficit to a specific lesioned area within the cerebellum, since the lesion is part of a wider network involving intact parts of the cerebellum as well as the cerebellar projections. Furthermore, in patients with chronic lesions, plastic changes have taken place. It is likely that both the cerebellum and connected areas change their function in an attempt to recover. Recovery has not taken place in patients with acute focal lesions. However, effects of temporary malfunctions in connected brain areas due to abrupt disconnection have to be considered in this patient group. Therefore, results of human cerebellar lesion studies need to be complemented by animal and human data using other techniques, for example functional brain imaging and electrophysiological studies including transcranial magnetic stimulation.

Despite these limitations, functionally meaningful correlations between cerebellar lesion site and behavioural data can be obtained both in subjects with degenerative as well as focal cerebellar disorders. One example is to correlate clinical data with lesion data that are in good accordance with the known functional compartmentalisation of the cerebellum. We used conventional MRI-based volumetry to quantify the degree of atrophy of the cerebellum and its three longitudinal subdivisions in patients with cerebellar cortical degeneration. Total clinical ataxia rating scores showed a significant negative correlation with the volume of the entire cerebellum (normalised to the total intracranial volume) [12, 13]. Oculomotor disorders were highly correlated with atrophy of the medial cerebellum. Posture and gait ataxia subscores revealed the highest correlations with the medial and intermediate cerebellum. Disorders in limb kinetic functions correlated with atrophy of lateral and intermediate parts of the cerebellum. The subscore for speech disorders showed the highest correlation with the intermediate cerebellum [13].

Findings are in good agreement with animal data showing that the medial zone is of particular importance for control of stance, gait and eye movements and the intermediate and lateral zones for control of limb movements and speech [14–16]. Atrophy of the intermediate zone, however, was not only correlated with limb ataxia and dysarthria but also with ataxia of stance and gait.

Likewise, studies of our group in subjects with chronic focal cerebellar lesions revealed that postural sway and disordered balance control during gait were associated with lesions affecting both the fastigial (that is medial zone) and interposed nuclei (that is intermediate zone) [17, 18]. In the gait study, lesions of the intermediate but not the medial zone were associated with abnormalities in the temporal characteristics of joint coordination patterns in lower limb control both during leg movements and gait [18]. One possible explanation is that lesions of the intermediate zone lead to disordered leg and trunk coordination, which adds to disordered balance control during stance and gait.

In another experiment, the correlation with clinical ataxia rating scores and MRI-defined lesions was performed in patients with acute and chronic focal cerebellar lesions using voxel-based lesion-symptom mapping (VLSM [9]) [19]. In acute patients, a somatotopy in the superior cerebellar cortex was found which is in close relationship to animal data and functional MRI data in healthy control subjects [20]. Upper limb ataxia was correlated with lesions of cerebellar lobules IV–VI, lower limb ataxia with lesions of lobules III and IV, and dysarthria with lesions of lobules V and VI.

Furthermore, in the acute lesions, limb ataxia was significantly correlated with lesions of the interposed and part of the dentate nuclei (Fig. 1A) and ataxia of posture and gait with lesions of the fastigial nuclei including part of interposed nuclei. In the subgroups with chronic focal lesions, similar correlations were observed with lesions of the cerebellar nuclei but no such correlations mentioned for the acute group with lesions of the cerebellar cortex (Fig. 1B). The lesion site, therefore, appears to be critical for motor recovery. Findings agree with animal studies showing that a recovery after lesions to the nuclei of the cerebellum is often less complete [21].

Another example with extended knowledge about functional localisation within the cerebellum is classical conditioning of the eyeblink response, a simple form of motor learning [22]. Most authors agree that some forms of neuronal or synaptic plasticity develop in both cortex and cerebellar nuclei as a result of training [23, 24]. There are, however, ongoing controversies about the relative contributions of cerebellar cortex and nuclei.

A study of our group found that in healthy human subjects, the number of acquired conditioned eyeblink responses was significantly related to the volume of the grey matter of the posterior lobe but not to the volume of the grey matter of the anterior lobe, the cerebellar white matter or cerebrum [25]. In a group of patients with cerebellar cortical degeneration, however, no significant correlations between acquisition of conditioned responses and any of the cerebellar volumes were observed. Floor effects most likely explained this observation with significantly reduced eyeblink conditioning early in the disease and no possible further reduction during disease progression.

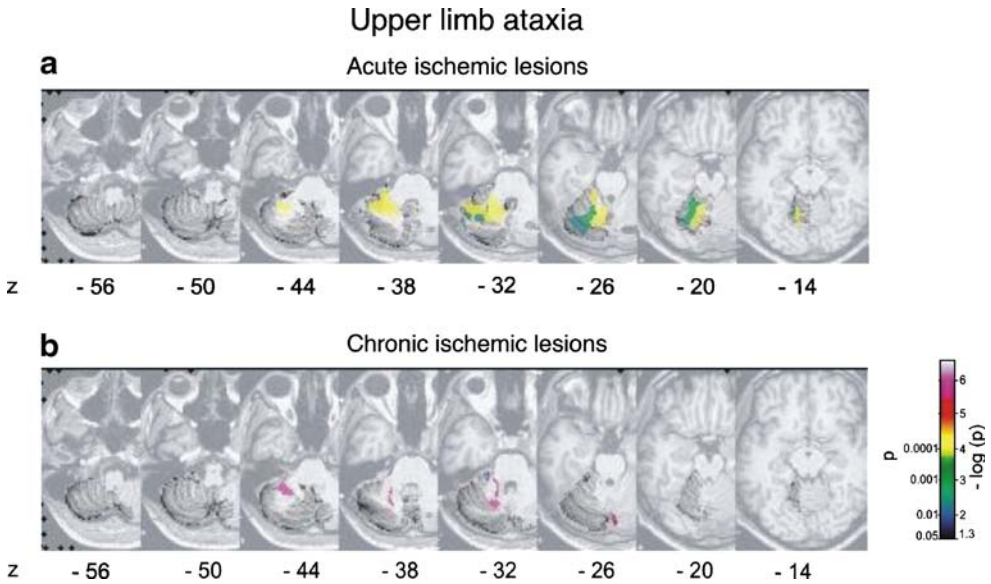

Fig. 1. VLSM [9] of upper limb ataxia rating score (ICARS; [29]) in **A** 21 subjects with acute and **B** 33 subjects with chronic ischemic cerebellar lesions. VLSMs are superimposed on axial slices of the cerebellum of a healthy subject normalised to MNI space. Right-sided lesions are flipped to the left. **A** Acute lesions: Relating cerebellar lesion sites to the ICARS subscore "upper limb" the highest *t* values (8.5) were found within paravermal lobules V and VI. In addition, interposed and dentate nuclei were affected (highest value (*yellow area*) refers to $p<$ 0.0001, Bonferroni-corrected). **B** Chronic lesions: statistical significant correlations were found primarily in areas including the dentate and interposed nuclei ($p<0.0001$, Bonferroni-corrected; shown in *violet*) but not the cerebellar cortex (adapted from [19])

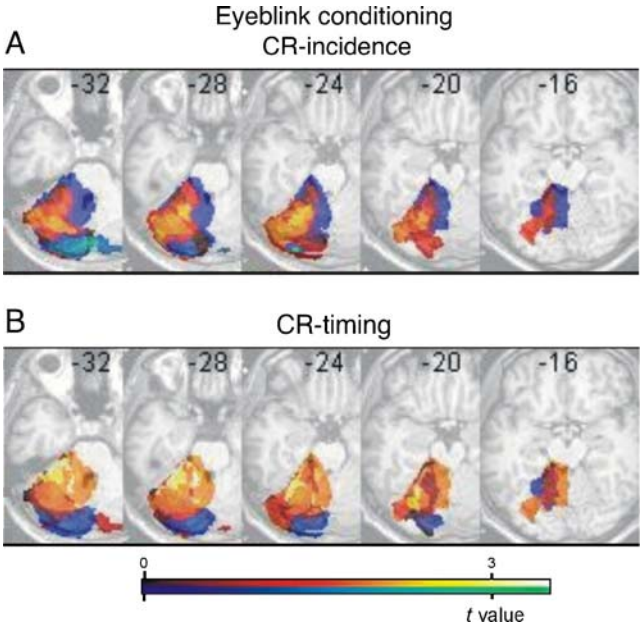

Fig. 2. VLSM [9] of classical eyeblink conditioning in 22 subjects with unilateral cerebellar lesions. VLSMs related to learning rate (**A**) and timing (**B**) of conditioned eyeblink responses are superimposed on axial slices of the cerebellum of a healthy subject normalised to MNI space. Right-sided lesions are flipped to the left. **A** Relating cerebellar lesion sites with learning rate (that is CR-incidences normalised to the unaffected side) revealed highest positive *t* values (that is lowest CR-incidences) primarily within hemispheral lobule VI (Larsell HVI) extending to posterior parts of adjacent lobule V (shown in *dark yellow*). **B** Regarding the relationship of lesion sites and timing of conditioned responses (that is CR-onset latencies), highest positive *t* values (that is shortest CR-onsets) were found within hemispheral lobule V (Larsell HV) extending to adjacent lobules IV and anterior parts of HVI (shown in *yellow*; adapted from [26])

More detailed information was observed examining patients with focal cerebellar lesions, most of them due to ischemic stroke. Eyeblink conditioning was significantly reduced on the ipsilesional side in subjects with lesions within the common territory of the superior cerebellar artery (SCA; lobule Crus I and above) but within normal limits on the contralesional side. In subjects with lesions restricted to the common territory of the posterior inferior cerebellar artery (PICA; Crus II and below), no significant difference in eyeblink conditioning was found comparing the affected and unaffected side [3]. VLSM [9] analysis revealed that learning rate was significantly reduced in subjects with focal lesions including superior parts of the posterior lobe, particularly lobule HVI (Fig. 2A [26]). Findings are in good accordance with animal data [27].

Regarding timing of the conditioned response, we found that conditioned eyeblink responses occurred significantly earlier in subjects with cerebellar lesions in the SCA territory and with cerebellar cortical degeneration but not in subjects with PICA infarctions. Corresponding to animal findings of Mauk's group [28], VLSM analysis revealed that CR onset was significantly earlier in subjects with cortical lesions including parts of the ipsilateral anterior lobe, in particular lobule HV (Fig. 2B). Findings suggest that cortical areas of the anterior lobe may be involved in conditioned response timing and superior parts of the posterior lobe in stimulus association in humans. This does not speak against an additional role of the cerebellar nuclei.

In summary, lesion-symptom mapping is helpful to study the contribution of functionally relevant cerebellar compart-

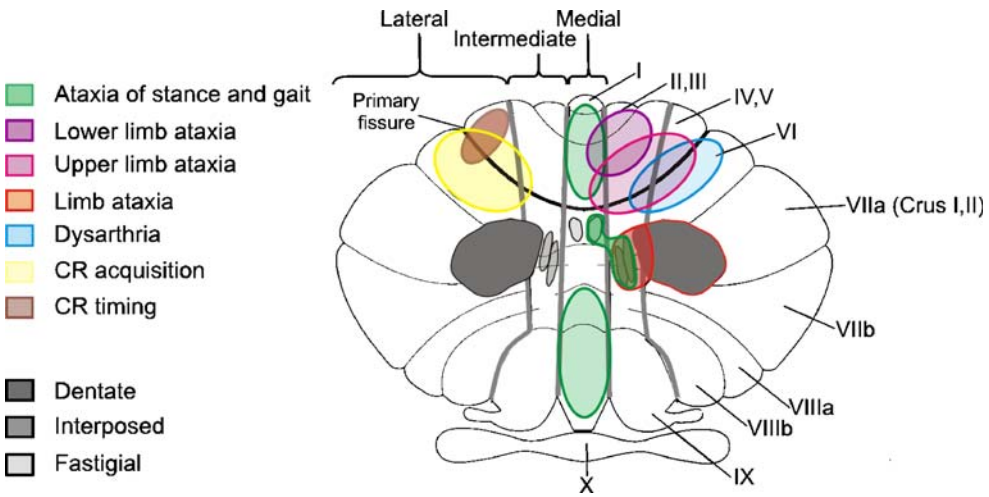

Fig. 3. Schematic sketch of main findings in patients with focal cerebellar lesions. The figure summarises the results of lesions-symptom mapping in our studies on eyeblink conditioning [26], cerebellar ataxia rating scores [19], balance in stance [17] and gait [18] and upper and lower limb coordination [17, 18]. Note that two studies [17, 18] found a relationship between limb ataxia and lesions of interposed nuclei and adjacent dorsomedial dentate nucleus, whereas lesions of ventrolateral parts of the dentate nucleus were also related to limb ataxia in a third study [19]. *I–X* cerebellar lobules according to [30]; *dentate*, *interposed*, *fastigial* cerebellar nuclei; *medial*, *intermediate*, *lateral* cerebellar sagittal zones; *CR* conditioned eyeblink response

ments in motor (and non-motor) control and recovery in humans with focal and degenerative disorders (Fig. 3). Although the study of participants with focal lesions is preferable, studies in participants with degenerative disorders do also lead to meaningful results. In focal lesions, additional information about the function of cerebellar cortex and nuclei can be gained. Application of new techniques, for example higher resolution structural imaging of the cerebellar nuclei using high-Tesla MRI, will improve lesion-symptom mapping in the future

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