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Cerebellar imaging with diffusion magnetic resonance imaging: approaches, challenges, and potential

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Diffusion magnetic resonance imaging (dMRI) is sensitive to the mobility of water in tissue and sensitive to cell geometry and organization in the central nervous system — providing unique insight into both local microstructure and white matter connectivity. Most dMRI methods were developed for studying cerebral white matter but can provide useful information about cerebellar white and gray matter. However, the small size and intricate structure of the cerebellum poses challenges for dMRI. In this review, we discuss these challenges, recent advancements in methodology, and insights from cerebellar applications of novel dMRI methods. While many limitations still remain and should be considered in conclusions regarding microstructure and connectivity, carefully designed experiments and analyses can provide new insight into behavioral and pathological aspects of cerebellar structure and function.

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Introduction

The cerebellum takes up a small proportion of total human brain volume, yet contains ~1600 cm^2 of cortical surface (78% of that of the neocortex) [1] and ~50% of the brain's neurons [2]. It supports motor and nonmotor behavior via spatially segregated structural connections that form reciprocal loops between cerebellar and cerebral cortical regions via the pontine nuclei (cerebral cortex → cerebellum) and cerebellar nuclei and thalamus (cerebellum → cerebral cortex) and basal ganglia [3]. The cytoarchitectural regularity of the cerebellar cortex implies that the roles of different cerebellar regions are primarily a function of their connectivity [4] — making investigations of cerebellar gray and white matter (both its microstructural properties and structural connectivity) of paramount importance to understanding this key brain region. Diffusion magnetic resonance imaging (dMRI) can be used to investigate the microstructure and connectivity of the brain noninvasively [5], and though the small volume and high axonal packing density makes dMRI in this region challenging for the reasons outlined below, recent improvements in dMRI hardware and acquisitions show significant promise for mapping the cerebellum with much greater microstructural and spatial precision.

Applications of diffusion magnetic resonance imaging in the cerebellum

Conventional dMRI utilizes variations of the pulsed field gradient spin-echo (PGSE) sequence that encodes and decodes particle positions in the phase of the MR signal. Particle spread (e.g. due to diffusion) results in a dispersion of phases and an attenuation of the signal [6]. For a simple medium with free diffusion and a Gaussian spread of particles, the signal attenuation is monoexponentially proportional to the particle's diffusivity and the diffusion weighting (b-value, determined by the length and strength of the diffusion-encoding gradients). Diffusion on the length scales that can be probed by dMRI interacts with typical cellular structure/geometry such as the diameter of somas (~5–20 μm) and axons (< 1 μm). The fibrous nature of axons and dendrites (and possibly glial processes) results in greater diffusivity along the direction of fibers (anisotropic) [6,7]. Fibers that align over the voxel (e.g. in white matter tracts) are characterized by macroscopic anisotropy. While *macroscopic* anisotropy decreases with increasing spread of fiber directions within a voxel, the diffusion

process that probes the microstructure on a μm scale may capture *microscopic* anisotropy locally within individual fibers. While a number of models have been proposed to interpret dMRI data in terms of microstructural features (cell density, size, shape, distribution etc.), such analyses depend on substantial effects in experimental data.

There are two main motivations for the use of dMRI in cerebellar research. The first applications discussed in this section are voxel-wise measurement as a probe for cellular microstructure. The second are based on using voxel-wise estimates of axonal directions to evaluate the trajectory of white matter pathways.

Diffusion magnetic resonance imaging for voxel-wise assessment of cerebellar microstructure

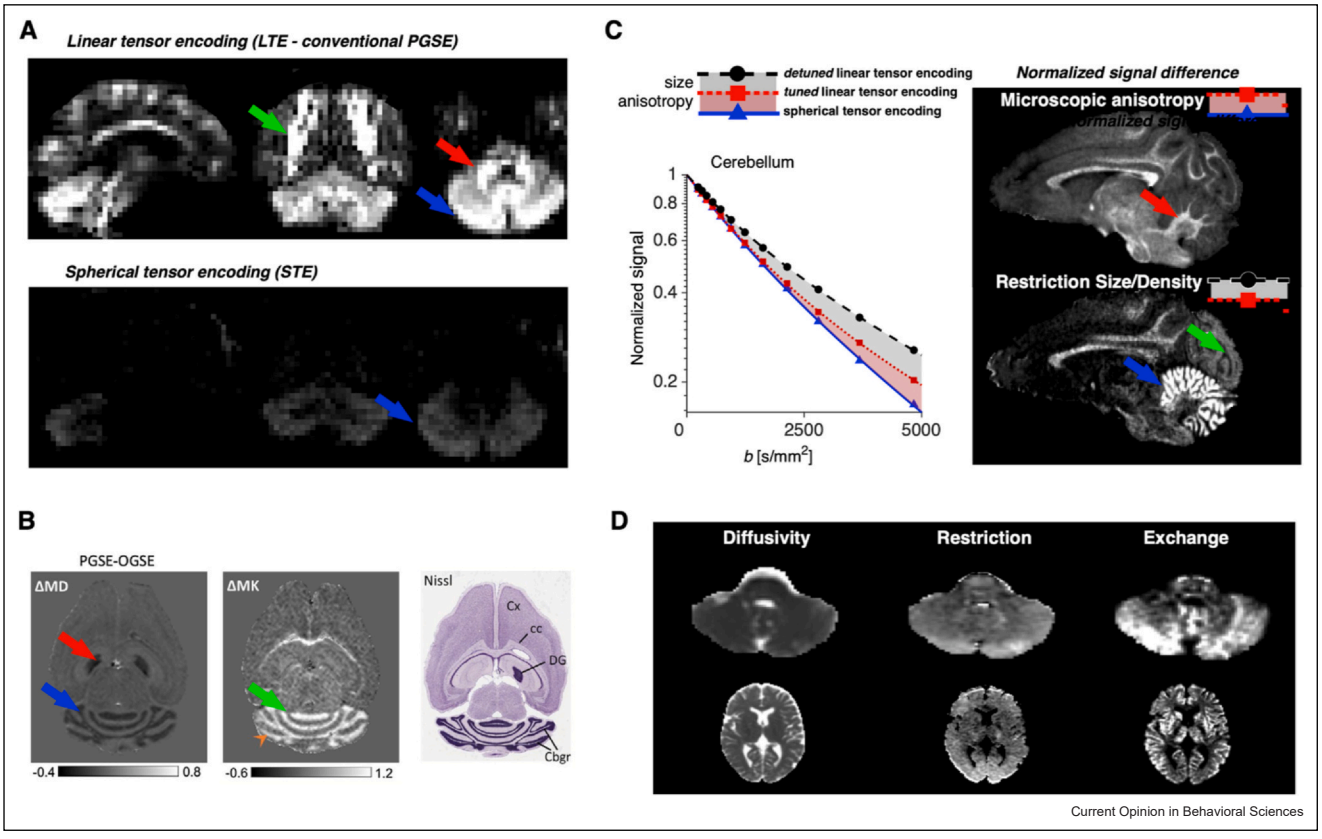
The vast majority of cerebellar research has historically utilized dMRI acquisitions and analyses from diffusion tensor imaging (DTI) [8]. The impact of DTI cannot be understated, and still stands as a useful and sensitive probe of subtle tissue differences/changes. However, DTI-based measurements suffer from a plethora of potential interpretations of their underlying mechanisms [9]. A key assumption in DTI is that the underlying diffusion process is Gaussian and that the displacement of particles conforms to an ellipsoidal shape under the experimental conditions. For this, acquisitions with a single nonzero b-value in at least six unique gradient directions (single-shell) are sufficient. However, if data disagree with this simple model, more information may be retrieved from a more elaborate analysis.

For voxel-wise estimates of fiber orientation distributions, an ellipsoidal shape can only capture a single main, or principal, direction of an axonal bundle. Data acquired with a high angular resolution (many gradient directions) reveal several orientations with high diffusivity in most voxels that reflects crossing, branching, or other more complex axonal configurations. This is a well-known challenge from the tractography literature, and analyses beyond DTI to resolve such situations are standard in most tractography software [10]. In general, the same models can be used for fiber orientation distribution estimates in cerebellar white matter, but implications for cerebellar tractography are reviewed in the next section.

By extending the range of b-values in a conventional diffusion encoding, a deviation from monoexponential signal attenuation is observed in most brain regions and in particular the cerebellum. A simple interpretation from this observation can be the combined signal from multiple regions with a spread of high and low diffusivities. Initial decay faster than free diffusion of water could be due to flow effects, for example, in randomly oriented small blood vessels (known as intravoxel incoherent motion [11]), while signals retained at very high b-values isolate the very slow components from, for instance, highly restricted intracellular water. This effect is apparent in raw dMRI data from the cerebellum and can be attributed to the high number of neuronal cell bodies (Figure 1a), and also in dense white matter tracts for diffusion-encoding directions perpendicular to the axons. It further illustrates the inherent lack of specificity of conventional dMRI and shows that strong model assumptions specific to different tissue types are needed for interpretation — introducing a risk of misinterpretations, which the small structural features of the cerebellum further exacerbate with partial voluming. To overcome these issues, alternatives to the conventional PGSE approach have been proposed to provide specificity in dMRI data rather than in later modeling. This can be achieved with multiple encoding pulses before the image readout or completely free gradient waveforms designed for specific questions [12–14]. One possibility is to sensitize the signal to diffusion in all directions, that is, isotropic or spherical tensor encoding (STE, in contrast to a conventional linear tensor encoding (LTE)). A strong STE provides a strong attenuation that disregards the orientation of fibrous anisotropic structures, such as axons, while signals from spherical restrictions, such as in the granular layer of the cerebellar cortex, will still be retained (Figure 1a, bottom panel, from Ref. [15]). Since LTE captures all restrictions and STE only spherical restriction, the difference between them reflects microscopic anisotropy. Another approach for probing highly restricted diffusion in cell bodies is to probe the transition from low restricted diffusivity at long diffusion times to more free diffusion at shorter diffusion times. While this, in theory, can be done by changing the timing of a PGSE, the limited gradient strength on scanners provides too weak b-values to provide sufficient contrast. Oscillating gradient spin echo (OGSE) offers a solution by keeping a long encoding time, while short diffusion processes are probed by oscillating the gradient. In the cerebellum, the granular layer demonstrates a very strong effect of restricted diffusion with decreasing mean diffusivity (MD) (Figure 1b) [16–18].

The combined separation of microscopic anisotropy and time-dependent diffusion can be accomplished by considering combinations of LTE and STE acquisitions with modulated oscillation frequencies similar to the considerations for OGSE (Figure 1c, [19]). A related approach, modulating both the sensitivity to microscopic anisotropy and time-dependent diffusion using double-diffusion encoding, has also been applied in humans *in vivo* and has demonstrated a similar combination of effects in the cerebellum [21]. Longer diffusion times not only increase sensitivity to restricted diffusion but will also increase the impact of exchange from, for example, the permeability of cell membranes. This leads to a homogenization of diffusivities and a more monoexponential signal attenuation at longer diffusion or mixing times, and has previously been investigated as an isolated effect with conventional dMRI methods [22]. By using free gradient waveforms, recent work has proposed a framework to design experiments that separate

Figure 1



Novel time-dependent and multidimensional diffusion encoding strategies. **(a)** Top panel shows raw diffusion-weighted data from a conventional PGSE (LTE) experiment at high b-value in a healthy human averaged over gradient directions. The remaining signal indicates restricted diffusion observed especially in the cerebellar cortex (blue arrow) but also in the dense white matter such as the cerebral penduncles (red arrow) and the corticospinal tract (green arrow). The signal in white matter stems from gradient directions perpendicular to the axons. The bottom panel shows the signal from a STE, which is sensitive to diffusion in all directions. This encoding attenuates the signal from microscopically anisotropic restrictions but not signals from water in small spherical restrictions such as in the granular layer (blue arrow) (from Ref. [15]). **(b)** Data from a postmortem mouse probed at long and short diffusion times with PGSE and OGSE [17]. Increasing diffusion times provide a strong drop in MD from the granular layer (blue arrow) and an increase in mean kurtosis (green arrow) (MK) reflecting a separation of slow restricted intracellular diffusion and fast extracellular diffusion. The cell body-rich dentate nucleus of the hippocampus also exhibits a large drop in diffusivity (red arrow.) Rightmost panel in B is a Nissl stain showing regions with high cell body density. **(c)** Combining separation of microscopic anisotropy from the difference between LTE and STE acquisitions (as in A) and an additional LTE probing slow diffusion (as in B) with three different measurements [19]. Maps to the left are raw diffusion signals averaged over directions with microscopic anisotropy in white matter (green arrow) and high restriction density in the cerebellar cortex (blue arrow). Also note the strong effects in the visual cortex (green arrow). **(d)** Separation of time-dependent effects from restricted diffusion and exchange, both showing effects in the human cerebellum *in vivo* [20].

time-dependent effects from exchange and restrictions under the assumption that they occur on different timescales [23]. In the human cerebellum, this method detects both effects, but in particular, apparent exchange provides a strong contrast under the experimental conditions [20]. The resolution of these *in vivo* data does not allow delineation of the granular and molecular layers, but it is likely that the restriction effects originate from the granular layer as shown in high-resolution animal data. While the restriction effects are likely to originate from the granular layer similar to the findings from animal OGSE studies discussed above, the high exchange rates could also arise across the membranes of the unmyelinated parallel fibers in the molecular layer.

Diffusion magnetic resonance imaging for assessing white matter structural connectivity

Fiber orientations derived from the local voxel-wise models can be followed in a piecewise manner from one region to another to infer the connecting pathways of the brain with diffusion tractography [5,10]. As the only method for noninvasively assessing putative structural connectivity at the systems level, tractography is a key tool for understanding the connectivity of the human

cerebellum [24–30], can serve as an important bridge to postmortem fiber microdissection in humans [31,32], and has huge potential as a clinical tool to assist in surgical approach planning to, for example, understand and limit the impact of cerebellar mutism [33]. To fully understand how the cerebellum contributes to brain function and behavior in health and disease, we must develop a comprehensive understanding of how its anatomical connectivity is organized. This includes characterization of the gross anatomy (the inferior [ICP], middle [MCP], and superior [SCP] cerebellar peduncles) [27,29,34,35] but also requires detailed mappings of trajectories and connectivity within the cerebellar circuit, including the deep cerebellar nuclei [24], pons [25], SCP [36,37], ICP, and MCP. Identification of the peduncles provides global connectivity information, while detailed mappings confer specific spatial information about tract endpoints and trajectories that are important for understanding functional topology and interpreting local connectivity. Similar to ongoing work in cerebral stroke [38], detailed local connectivity models can be used to better quantify, track, and eventually predict the impact and optimal treatment for cerebellar damage or disease.

Specific challenges for cerebellar diffusion magnetic resonance imaging

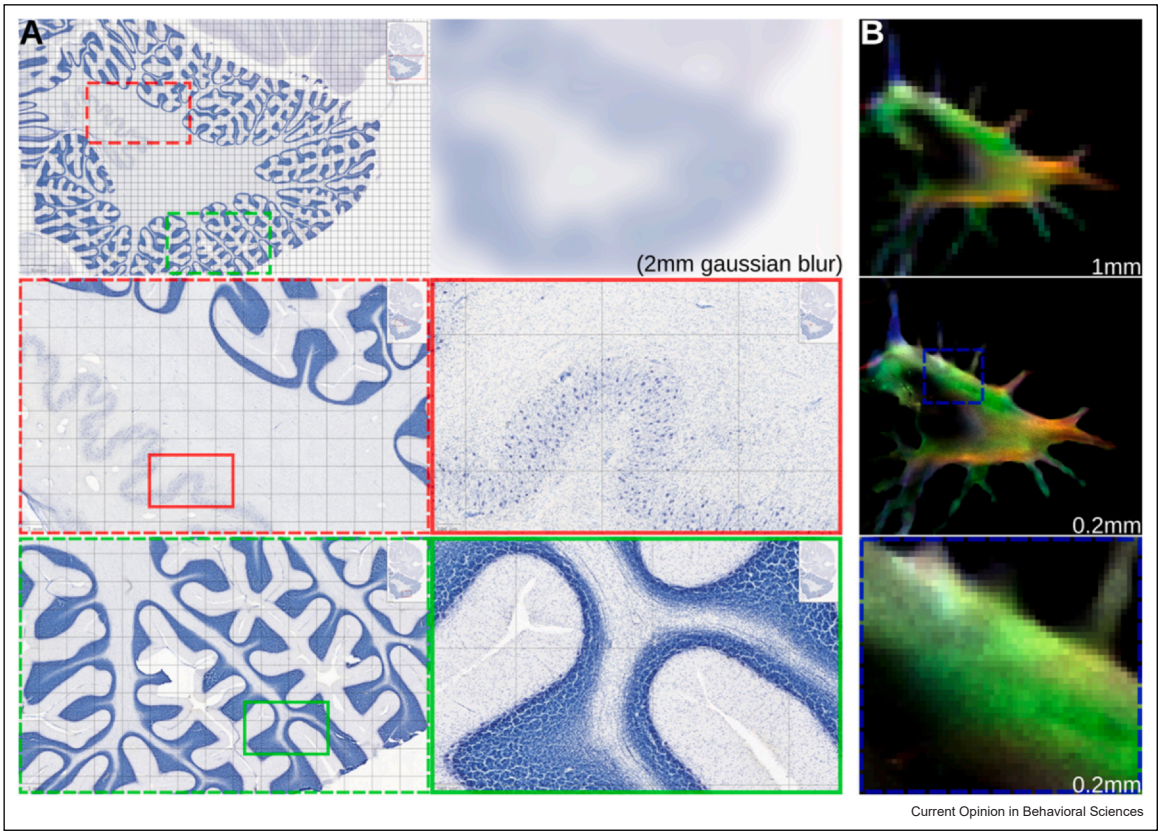
As with any technique or method, there are a set of known challenges for dMRI, including physiological inference of voxel-wise metrics [9] and tractography biases and limitations [39]. The size, cellular density, cortical folding, and position of the cerebellum within the posterior cranial fossa gives rise to additional issues that we will focus on here. Its position at the back of the brain makes it the furthest major structure from the magnet isocenter, leading to potentially stronger eddy current effects, and it also corresponds with poorer coverage in standard head coils. The small size and intricate folding of the folia of the cerebellar cortex [1,26] means that imaging resolution is an even larger issue than in the cerebral cortex. Voxel-wise metrics are particularly susceptible to partial voluming between WM, GM, CSF, and/or different tracts at even sub-mm resolution (Figure 2) [24,26]. The improvement of image resolution and the use of diffusion-encoding waveforms with high efficiency and specificity calls for higher field strengths and stronger gradient systems. However, such hardware may also have to be paired with efficient correction methods or compensated acquisition techniques to account for additional image distortions from field inhomogeneities or eddy currents.

Tractography is also a unique challenge in the cerebellum, with relatively little space to contain the dense connections between the cortex, nuclei, and pons; most (if not all) voxels at standard resolution contain multiple fiber orientations that serve to blur across the axonal curvature present at a finer spatial scale [26]. This interacts with the high cortical surface area granted by the folia [1] and the three-dimensional organization of the arbor vitae as it branches into the lobules and folia, leading to bottlenecks at the bases of the lobules (where all tracts entering/exiting the lobule converge) and axons that may follow multiple curving trajectories before reaching the folia (Figure 2a, bottom). Tractography close to cerebellar gray matter may also be influenced by the strong alignment of parallel fibers in the molecular layer that are readily visible in high-resolution DTI [41]. dMRI-derived fiber orientations within the MCP, which occupies most of the central cerebellar white matter, are dominated by the direction running to/from the pons (which interacts with algorithmic curvature constraints to produce a posterior bias in tractography originating in the pons). In addition, the boundaries of the cerebellar nuclei are difficult to identify at standard resolution (introducing uncertainty in inclusion/exclusion masks that may bias analyses). These challenges are not unique to the cerebellum, but are particularly salient within this small and tightly packed region (Figure 2). Another challenge is the mapping of the cortico-ponto-cerebellar projections, which synapse in ipsilateral pons where the majority decussate before continuing along the middle cerebellar peduncle to terminate in the contralateral nuclei or cerebellar cortex. Additional complications include difficulties identifying specific pontine nuclei with MRI (to serve as regions of interest) and the inability to separate the contributions of ipsilateral ponto-cerebellar fibers with dMRI tractography [42]. Putting aside the known difficulties with transsynaptic tract tracing, it is also important to consider that streamlines representing cortico-pontine projections are highly differentiable in the medial–lateral/anterior–posterior plane and less so in the superior–inferior dimension (in humans), while ponto-cerebellar projections are highly differentiable in the anterior–posterior/superior–inferior plane and less so in the medial–lateral dimension (this is equivalent in nonhuman animal models). This disconnect in projection spaces makes it very difficult to infer streamline continuity through the pons without very careful methodological consideration. Though it is important to identify the entirety of the cortico-cerebellar loops, it is problematic to definitively conclude based on diffusion tractography of a multisynaptic pathway and transformation between projection planes.

Current state and future perspectives

We have reviewed recent methodological developments/approaches in dMRI applied to the cerebellum. While some challenges remain to be resolved in order to fully recover the finer anatomical details, a rich set of newly developed tools exist to isolate and probe both white matter connectivity and features of cellular morphology. Recent general developments in scanner hardware,

Figure 2



The impact of spatial resolution on the interpretation of cerebellar structure and connectivity. Panel A. Anatomical structure of the human cerebellum. Top: High-resolution image of a single Nissl-stained coronal slice of the human brain overlaid with a 1 × 1-mm grid and red/green ROIs for the middle and lower panels, respectively. A 2-mm Gaussian blur was applied to the image on the right to demonstrate the approximate level of detail available to standard dMRI acquisitions. Middle: Dentate nuclear cortical sheath folding detail. Partial voluming of the deep cerebellar nuclei may lead to biased microstructural measures and improperly terminated streamlines. Bottom: Cerebellar cortical surface detail with distinguishable granular, Purkinje, and molecular layers. Note the clear separation between GM (or GM layers) and WM at all scales, except in the 2-mm blurred image. Partial voluming between cortical layers (and WM) is a significant issue with standard dMRI acquisitions and tractography into/out of folia is not currently possible. Data obtained from the BrainSpan reference atlas (Allen Institute for Brain Science; www.brainspan.org; tissue index: 2274, left hemisphere), downloaded at 2 × 2-μm resolution and overlaid with a 1 × 1-mm grid. Panel B. dMRI-based tract density reconstruction of the cerebellum in a similar coronal slice as in A. Data are presented as 1-mm (Top) and 0.2-mm isometric resolution super-resolved reconstructions (Middle, Bottom). With only the first branch of the arbor vitae into the lobules resolved at this scale. Folia are also not resolvable, but the higher-resolution reconstruction is able to capture finer boundary details that may be important for defining masks for tractography. The dominance of the MCP (green, running in/out of plane) and the smooth boundary between the white matter and dentate nucleus (in comparison to Panel A: Middle) are apparent at both resolutions. Data derived from directionally encoded tract density images in a single subject from the HCP [40] (native dMRI resolution: 1.25-mm isometric, 10 million streamlines within the cerebellum seeded from the WM/GM interface, minimum length of 5 mm). Red: medial–lateral; Green: anterior–posterior; Blue: inferior–superior.

acquisition protocols, and analyses have yet to be applied in cerebellar research and could resolve some of the challenges. One important limitation is the gradient strength of human MRI systems, but recent developments have demonstrated successful research implementations reaching up to (and soon above) 300 mT/m compared with 80 mT/m in high-end clinical systems [43,44]. Stronger gradients can both allow for quicker diffusion weightings and thereby shorter echo time and higher signal to noise, but also allow for more intricate gradient waveforms probing, for example, shorter diffusion times [14]. The human *in vivo* methods presented in Figure 1a and d have already demonstrated the value of systems with strong gradients in cerebellar dMRI [15,20]. Strong gradients have also enabled development of new acquisition protocols with submillimeter resolution in whole-brain settings [45]. This could benefit both delineation of voxel-based measures in the cortical lamina and also allow for improved tractography of smaller white matter pathways in the cerebellum. Despite the challenge of partial voluming, lower resolution but higher specificity could still provide input to analyses of structural and microstructural variation in the cerebellum across populations/diseases. One example is the

specificity to restricted diffusion mapped with OGSE or STE that appears to be isolated to the granular layer, and could act as a surrogate measure of the layers' thickness or density. Enhancing specificity with multidimensional diffusion encoding could also provide better estimation of axonal directions from other microstructural features to improve tractography, as recently proposed in cerebral white matter [46]. Additional specificity can also be obtained by projecting voxel-wise measurements along tracts within the tractography space [47], exploiting both the super-resolution effects of streamlines (Figure 2b) and tract-based smoothing that can help to overcome resolution challenges in the cerebellum. Beyond characterizing diffusion properties alone, hybrid methods, including diffusion-relaxation correlations, would also help stratification of signals from, for example, myelinated and unmyelinated fiber populations [48]. Likewise, diffusion-weighted spectroscopy measuring the diffusion of metabolites that are specific to certain cell types could boost specificity and could, in combination with advanced diffusion-encoding schemes, resolve glial and neuronal morphologies in the cerebellum as recently demonstrated in human and rodent cerebrum [49,50].

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

HL is an inventor on patents owned by Random Walk Imaging AB, Lund, Sweden, related to diffusion encoding with free gradient waveforms.

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