document primarily affected cerebellar efferents, but also the dorsal midbrain, lending additional metabolic support to functional imaging data, suggesting changes in the SCol in dystonia. Various lines of evidence ranging from animal studies reporting improvements in lesions, gene expression experiments in monogenic forms, human structural and functional imaging, and eye-blink classical condition experiments point toward an involvement of efferent cerebellar structures in dystonia pathophysiology. Thus far, it proved difficult to conclude regarding how far cerebellar activity in dystonia is causal, contributory, or compensatory. In contrast to increased metabolic activity on cerebellar glucose-positron emission tomography imaging, which can be interpreted as both possibly causative and compensatory, our observation of decreased enzyme activity is compatible with a primary deficit within the cerebellar outflow tract.

The b-GAL results overall argue against a purely GCasemediated effect but more likely general lysosomal activity changes in dystonia. Larger genetic studies are planned to elucidate whether lysosomal dysfunction in dystonia is associated with a specific gene, such as GBA, or broader mechanisms regulating lysosomal function. Mechanistically, endosomal-lysosomal deficiency has recently been reported to be implicated in dystonia due to mutations affecting the homotypic fusion and vacuole protein sorting complex, postulating disrupted cellular processes in motor control networks as a possible mechanism. Similarly, network signaling abnormalities and synaptic dysfunction have been described in the context of lysosomal storage disorders, and future studies should explore if they provide a possible mechanistic relation between lysosomal and network dysfunction in dystonia.

Brain regions in this study were chosen based on their presumed role in dystonia pathophysiology and tissue availability and thus are not representative. We acknowledge the limitations regarding phenomenotypical information and statistical power due to the paucity of dystonia brain donors (Table S1). The presence of signs of pathological aging in some donors, reflecting the age at death, was balanced between groups and unlikely to have affected results. Medication-related bias seems equally unlikely, especially for botulinum toxin injections, the most frequently used medication in our sample.

In summary, our observations provide preliminary evidence for a possible role of lysosomal dysfunction in isolated dystonia. Although the enzyme activity pattern identified points to a primary role of cerebellar output-/brainstem structures, the exact mechanism of how lysosomal dysfunction causes dystonia remains to be established.

Acknowledgment: The Queen Square Brain Bank is supported by the Reta Lila Weston Institute of Neurological Studies, UCL Queen Square Institute of Neurology.

Supporting Data
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

In Vivo Brain Sodium Disequilibrium in ATP1A3-Related Rapid-Onset Dystonia-Parkinsonism

ATP1A3-related neurological disorders display a broad clinical spectrum with three predominant phenotypes, including rapid-onset dystonia-parkinsonism (RDP). The ATP1A3 gene encoding the α-subunit (subtype 3) of the Na+/K+-ATPase enzyme maintains the neuronal electrochemical gradient by removing intracellular sodium in exchange for extracellular...
potassium ions, which is essential for regulating the excitability of neurons, cell volume, and neurotransmission.\textsuperscript{2,3}

This study used \(^{23}\text{Na-MRI}\) (magnetic resonance imaging) employing the nuclear magnetic resonance of sodium, with a combination of total sodium (tNa) and intracellular-weighted sodium imaging (inversion recovery \(^{23}\text{Na-MRI [IR-Na]}\)).\textsuperscript{4} The latter measurement is particularly interesting considering that decreased Na\(^+\)/K\(^+\)-ATPase activity is expected to lead to an accumulation of intracellular sodium, which might serve as a direct measure of the proposed disease mechanisms in \(\text{ATP1A3}\)-related disorders.

A 45-year-old male patient with RDP harboring a heterozygous missense mutation in the \(\text{ATP1A3}\) gene [NM_152296.5 (ATP1A3:c.2788C>T[p.Arg930Trp])] and seven age/sex-matched (45.4 ± 2.4 years) control subjects were enrolled. Neuroimaging was performed on a 3T Siemens MAGNETOM Skyra MRI scanner using a 64-channel head/neck coil (Siemens) and a dual-tuned quadrature head coil \(^{1}\text{H}/^{23}\text{Na}\) (RAPID Biomedical). Preprocessing of sodium images and voxel-based morphometry was done using the SPM12 software package and CAT12 toolbox. Volumes (T1) and the mean voxel intensities (tNa and IR-Na images) for caudate, putamen, pallidum,

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{\textsuperscript{23}Na-magnetic resonance imaging of our index patient with reference to the control group. (A) The coregistered tNa images of our index patient are shown. (B) The respective coregistered IR-Na images are highlighted. Here, the suppression of the extracellular \(^{23}\text{Na-signal}\) by our inversion recovery sequence (IR-Na) can be easily visualized on cerebrospinal fluid-signal suppression (ie, by the dark-appearing lateral ventricles). However, the IR-Na sequence has a decreased signal-to-noise ratio because of the selective tissue suppression (as shown by the lower mean voxel intensity \(z\) scores compared with tNa-derived values). The results from the TIV-normalized region of interest (ROI)-labeled mean voxel intensities are shown in (C) (for the tNa analyses) and (D) (for the IR-Na analyses). The control ROI (the occipital lobe) is hatched. The TIV-standardized ROI-voxel intensities of the reference group (bars) are compared with our index patient (lines with respective \(z\) scores). The control ROI (the occipital lobe) is hatched. Arb. units, arbitrary units; IR-Na, intracellular-weighted sodium imaging; OccL, occipital lobe; PostC, postcentral gyrus; PrecG, precentral gyrus; SMA, supplementary motor area; TIV, total intracranial volume; tNa, total sodium. [Color figure can be viewed at wileyonlinelibrary.com]}
\end{figure}
thalamus, supplementary motor area (SMA), precentral gyrus (PrecG), postcentral gyrus (PostcG), and the cerebellum were extracted using the Neurorhymnphemetics brain atlas. We selected the side-averaged regions of interest (ROIs) based on their involvement in the development of dystonia. In addition, the occipital lobe (OccL) served as a control ROI because it is not implicated in the pathophysiology of dystonia. Extracted ROI values were scaled to the total intracranial volume (TIV) and z-transformed. More details on the methods and the case description can be found in the Supporting Information Methods and Video S1.

The volumetry values of our index patient were within the reference range of the control group (Supporting Information Fig. S1D). The assessment of tNa content demonstrated marked differences for most of the earlier-mentioned ROIs contrary to the control ROI (Fig. 1C). The cerebellum showed the highest tNa z-score (6.29) and also the highest IR-Na z-score (2.79) (Fig. 1D).

Our study provides the first in-vivo evidence that sodium predominantly accumulates in the cerebellum of patients with RDP, which appears to be driven by intracellular accumulation. The measurement of a sodium disequilibrium is supported by previous reports showing pathophysiological involvement of the cerebellum in the development of ATPLA3-related disorders and other forms of dystonia. In rodent models, cerebellar injection of ouabain (a pharmacological inhibitor of the Na+/K+ -ATPase enzyme) or an ATPLA3-directed small hairpin RNA leads to the development of dystonia-like phenotypes. In addition, cerebellar pathologies either caused by structural lesions or consequent to inherited ataxias can result in dystonia in humans. Overall, these results indicate that tNa and IR-Na imaging may be suitable for studying ATPLA3-related disorders and should be applied once it becomes broadly available to future clinical trials. Future studies in patients with other forms of dystonia or parkinsonism are needed to evaluate the pathophysiological specificity of 23Na-MRI in ATPLA3-related neurologic disorders.

Acknowledgments: J.P. received funding from the Parkinson’s Foundation, the Deutsche Parkinsongesellschaft, and the Deutsche Forschungsgemeinschaft via the Clinician Scientist School Lübeck (DFG-GEPRIS 413353489). N.B. received funding from the Deutsche Forschungs-Gemeinschaft (BR4328/2-1 [FOR2488], GRK1957). Open Access funding enabled and organized by Projekt DEAL. Open access funding enabled and organized by Projekt DEAL.

Data Availability Statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to containing information that could compromise the privacy of research participants.

Jannik Prasuhn, MD, Martin Göttlich, PhD, Sinja S. Gasser, MD, Katharina Reuther, MD, Britt Ebeling, MS, Alexander Münchau, MD, Armin M. Nagel, PhD, and Norbert Brüggemann, MD

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Extreme Clinical Variability Among Carriers of Pathogenic Variant in SSBP1

Optic atrophy 13 with retinal and foveal abnormalities (OPA13, OMIM #165510) is an autosomal dominant optic atrophy caused by pathogenic variants in SSBP1. This is a nuclear gene that encodes tetrameric mitochondrial single-stranded DNA binding protein (mtSSB), an essential protein for mitochondrial replication and maintenance. Mutations in nuclear genes associated with mitochondrial DNA (mtDNA) replication can lead to damage to mtDNA and variable degrees of disturbances in oxidative phosphorylation and, as a