and clinical symptoms being responsive to L-dopa and appearing stable across time. However, the general concept of disease progression is probably too heterogeneous to assume that a 5-year period of 10 patients using our clinical and TMS paradigms is sufficient to allow firm conclusions. Therefore, a follow-up multimodal examination is planned in another 5 years.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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.

Focal Subthalamic Atrophy after Long-Term Deep Brain Stimulation in Parkinson's Disease

Deep brain stimulation (DBS) is a surgical procedure that is increasingly being applied to selected patients with movement disorders, and other conditions. In Parkinson's disease (PD), DBS is particularly effective against disabling and pharmacotherapy-resistant motor symptoms.[1] DBS has been effectively applied to the nucleus ventralis intermedius of the thalamus, the subthalamic nucleus (STN),[2] or the internal globus pallidus.[3,4] We previously reported that DBS induces no significant brain damage between 3 and 70 months (nearly 3 years; mean 33 months) of electrode implantation, with the exception of a mild chronic tissue reaction around the lead track.[4]

Here we present postmortem neuropathological findings of four additional patients who underwent long-term DBS for a period of up to 16 years (96−192 months) nd compared them with nine additional PD patients that did not undergo DBS. Neurosurgical procedures and neuropathological workup are detailed in Supplementary file S1 and results are summarized in Table S1.

In all cases, we observed a mild to moderate gliofibrillar capsule around the track of the electrode, mild surrounding gliosis with occasional distortion of axonal profiles (Fig. 1B1–B4), reactive microglia and occasional (hemosiderin) pigment. In patient 3 we found several foreign body multinucleated giant cells (Fig. 1C2, arrow) around the tip of the electrode. In all cases, the tip of the electrode was located within or beside the STN (Fig. 1). In two patients (patient 1, patient 4) there was a distortion of the medial part of the nucleus with moderate shrinkage of its volume (Fig. 1A1–A4). Compared to the lateral part of the STN and to the STN of nine non-DBS treated PD patients, there was a moderate astrogliosis, microglial

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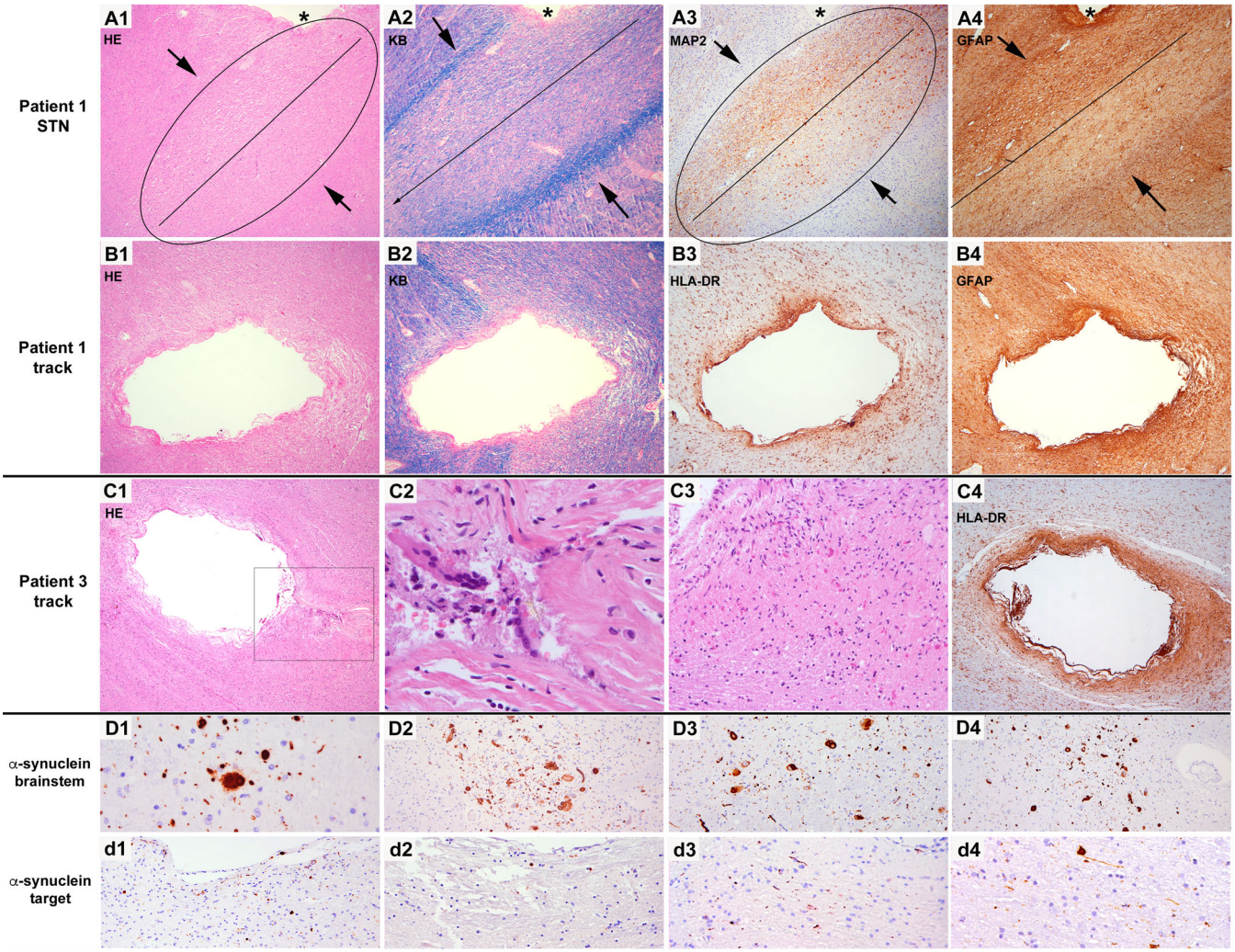

FIG. 1. Histological features at the subthalamic nucleus (STN) and track (for more detailed features see Figure S2). **(A1–A4)** STN (encircled) of patient 1 with an adjacent hole caused by the tip of the electrode, seen at the upper part of the figure (asterisk). The medial part of the STN (upper arrow left) shows oedematous change with small vacuoles (**A1, A2**: Klüver Barrera [KB] stain, the blue colour represents myelin sheaths). **A3**: There is a reduction of neuronal density in MAP2 immunohistochemistry with smaller residual neurons and condensed neuronal processes on the left side. **A4**: This medial area of the STN also shows an increase in microglia and a moderate chronic fibrillary astrocytic gliosis (**A4**). **(B1–B4)** In all cases, a mild tissue reaction was observed around the lead track with formation of a gliofibrillar capsule already visible on hematoxylin eosin (HE)-stained sections (patient 1 as representative for all cases) with reduction of myelin sheaths (**B2**, Klüver-Barrera), increase of reactive, ameboid shaped microglia (**B3**) and mild-to-moderate chronic fibrillar gliosis (**B4**). **(C1–C4)** In patient 3 there was also an accumulation of multinucleated giant cells at the tip of the electrode (**C1** box and **C2** in higher magnification) associated with a proliferation of Rosenthal fibres around the hole (**C3**). There was also more prominent immunoreaction for human leukocyte antigen-DR isotype (HLA-DR) (**C4**). **(D1–D4)** Abundant alpha-synuclein immunoreactive Lewy bodies and Lewy neurites were detected in several brainstem nuclei of all cases (**D1** substantia nigra/patient 1; **D2** dorsal motor nucleus of the vagal nerve/patient 2; **D3** locus coeruleus/patient 3; and **D4** dorsal motor nucleus of the vagal nerve/patient 4) confirming the diagnosis of Parkinson's disease. **(d1–d4)**: Mild-to-moderate amount of alpha-synuclein immunoreactive cell processes around the track/tip of the electrode (**d1** to **d4** correspond to patients 1 to 4, respectively). Original magnifications: A1, A2, A3, A4, B1, B2, B3, B4, C1, C4: x40; D1, D2, D3, D4, d1-d2: x100; C2, C3, D1, d4: x200. [Color figure can be viewed at wileyonlinelibrary.com]

activation, coarsening of neuronal processes, and a change of neuronal shape, size, and density (Fig. S2). These changes were consistent with a moderate degeneration, particularly of the medial aspect – limbic part – of the STN. This was also observed to a milder degree in patient 2, while in patient 3 only tiny and gliotic fragments of the STN were identified. These changes did not seem to be related to the implantation site, the disease duration, or the intensity of stimulation.

In summary, our observations show that in contrast to short-duration DBS, chronic DBS may elicit moderate degeneration of the stimulated target neuronal tissue, here the STN, after up to 16 years of stimulation. It remains unclear whether these changes are related to chronic depolarization block or due to an alteration of the synaptic conduction or other causes including the mere physical proximity of a foreign body, and is a matter of speculation. However, there are descriptions of positive effects of DBS on synaptic function and neurogenesis.[5,6] In contrast, along the lead track, we found no major changes besides a gliofibrotic capsule, as described previously,[4,7] and occasional foreign body reaction

at the tip of the electrode. Mild to moderate alpha-synuclein aggregates were also identified within neuronal processes in the immediate surroundings of the canal and the tip of the electrode. Although not very prominent, these findings might suggest that chronic noxae may increase alpha-synuclein aggregation.[8]

Our findings are important particularly because the application of DBS for different diseases is being increasingly performed on younger patients.[1] DBS is, however, a stable and effective long-term therapy.

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Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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Supporting Data

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