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Additive effect of distant Lewy bodies and tau seeds injections on nigral degeneration in macaques

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The influence of Lewy body (LB) and tau co-pathologies is increasingly acknowledged as putatively affecting neurodegeneration and clinical phenotypes. Here, we injected rhesus macaques with LB fractions or/and tau seeds derived from patients brains into distinct brain areas connected to the mesencephalon. Compared to control macaques, we observed increased mesencephalic staining of pathological α -synuclein and tau, as well as nigrostriatal dopaminergic neuronal loss, with a cumulative effect of co-pathology.

Neurodegenerative diseases, such as Parkinson's disease (PD), are characterised by the accumulation of misfolded proteins and the progressive loss of neuronal function¹. While α -synuclein-containing Lewy bodies (LB) are recognised as the main pathological hallmark of PD and dementia with Lewy bodies (DLB), increasing evidence indicates that co-pathologies significantly influence clinical phenotypes and progression². Notably, post-mortem studies have reported tau pathology in the brain of approximately 50% of patients with PD and DLB^{3,4}. Moreover, genome-wide association studies of sporadic PD have identified the *MAPT* gene, which encodes the microtubule-associated protein tau, associated with an increased disease risk⁵. Recently, nigral AT8-positive phosphorylated tau was observed in patients with a mild motor deficit suggestive of early parkinsonism, both with and without the presence of LB pathology⁶. It suggests that nigral tauopathy may mediate nigrostriatal degeneration in early PD. Although these post-mortem correlative studies are fundamental to better understanding the mechanisms involved in the early phase of dopaminergic denervation, direct experimental evidence on relevant models still needs to be provided.

To address this gap, our study aims to elucidate the distinct and combinatorial neuropathological effect of α -synuclein and tau pathologies, using the prion-like properties⁷ of these proteins in a macaque model. First, pathological sarkosyl-insoluble AD tau proteopathic seeds (AD-tau) (Fig. 1A) and enriched fractions of LBs (Fig. 1B) were derived from AD and PD patients' brains and characterised through in vitro and biochemical analyses (see *Methods* and Supplementary Table 1). Filter retardation assays confirmed the absence of detectable amount of phospho-synuclein in the AD-tau mix and the absence of detectable amount of phospho-tau in the LB-mix (Fig. 1C). Then, we injected rhesus macaques with LB ($n = 7$), AD-tau ($n = 4$), or a combination of both extracts ($n = 4$). We also injected tau

extracts from aged-matched healthy brains in three macaques as a control procedure. To study the effect of the independent spreading of these pathologies toward the mesencephalon and not the consequences of local injections, we injected LB and AD-tau seeds into two distinct rostral regions, both connected to the midbrain: LBs were injected into the striatum, and tau seeds into the lateral and posterior thalamus (Fig. 2).

Eighteen months post-injection, the quantitative analyses of phosphorylated α -synuclein at S129 (pSyn), as a surrogate marker of α -syn aggregation^{8,9} in the substantia nigra pars compacta, revealed a significant pSyn accumulation in the two groups injected with LB compared to controls. Interestingly, mesencephalic pSyn was also detected in macaques injected with AD-tau in the thalamus (Fig. 3A, B; Kruskal-Wallis test: $p = 0.020$). We found a positive neuronal AT8-positive staining for phosphorylated-tau in the mesencephalon of both AD-tau and LB+tau macaques, mainly in the zona incerta (Fig. 3C, D; Kruskal-Wallis test: $p < 0.0001$). No tau lesion was detected in LB-injected macaques. Quantification of surface staining with GFAP/S-100 or IBA1 revealed no astrocyte or microglial reactivity in the mesencephalon of macaques injected with LB and/or tau compared to controls (Supplementary Fig. 1).

Stereological counting of TH-positive neurons revealed a significant dopaminergic neuronal loss in the three groups of macaques injected with LB and/or AD-tau (Fig. 3E, F; Kruskal-Wallis test: $p = 0.021$). Compared with control macaques, LB-injected macaques exhibited denervation estimated at 26.5%, and AD-tau-injected macaques at 38.4%. Interestingly, the denervation was more pronounced in the co-injected group (53.5%), as shown in the estimation plots (Fig. 3F). We also assessed the integrity of striatal dopaminergic fibers by measuring TH intensity in the caudate of macaques (Fig. 3G). Although there was no significant difference when analyzing the overall

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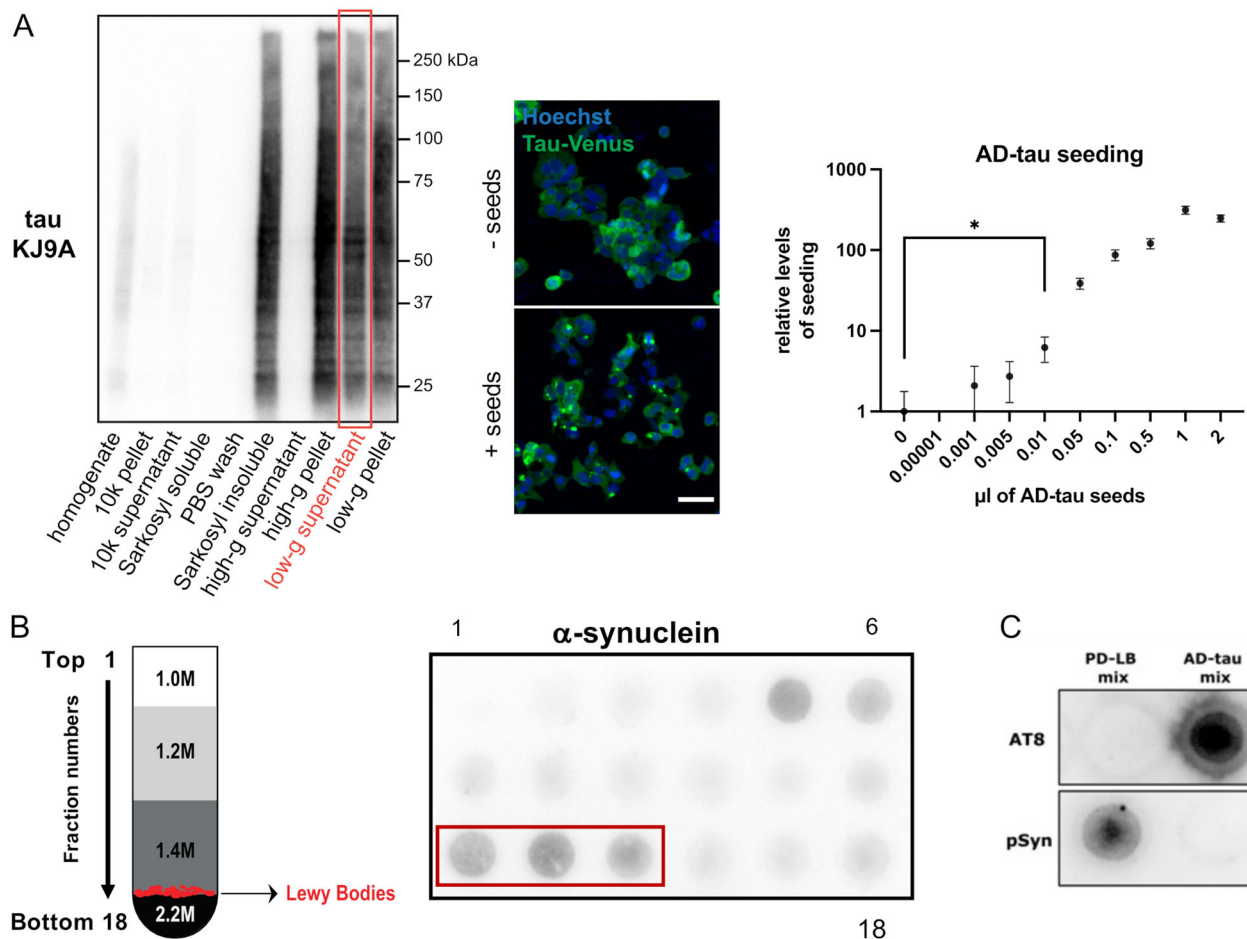


Fig. 1 | Characterisation of AD-tau seeds and LB fractions. **A** Extraction of AD-tau seeds and in vitro demonstration of their seeding efficiency. Left: The fractions from the AD-tau sarkosyl extraction (see methods) were probed with a pan-tau KJ9A antibody. The red box indicates the fraction corresponding to the final AD-tau seeds. Middle: Representative immunofluorescence images from unseeded and seeded tau P301S-Venus cells with 0.1 µl of AD-tau seeds. Fixed cells were imaged using Venus fluorescence (green) for the imaging of total tau, and Hoechst (blue) was used to imaging the nuclei. Scale bar, 50 µm. The cell seeding experiments were performed as described previously in McEwan et al., *PNAS*, 2017. Right: Tau P301S-Venus cells were seeded with increasing amounts of sarkosyl-insoluble AD-tau seeds. The number of detected seeds was quantified, normalised to the number of cells, and compared to the mock-treated cells ($n \geq 2700$ cells/condition analysed). The plotted data represent mean values $\pm$ SD. The statistical analysis is based on a one-way ANOVA test combined with Tukey's post hoc test ($*p < 0.05$). **B** Extraction of LB

fractions. After homogenisation, LB were extracted, purified and characterised using a sucrose gradient, as previously reported in Bourdenx et al., *Sci Adv* 2020. Left: schematic representation of the sucrose gradient fractionation procedure used to purify LB fractions from freshly frozen postmortem nigral brain tissue of 4 sporadic patients with PD. Right: Example of a filter retardation assay probed with a human α -syn antibody (i.e., syn211) to assess the presence of α -syn aggregates in the different fractions obtained by sucrose gradient fractionation from patients PD#3 (see Suppl. Table). The red square indicates LB-containing fractions selected to prepare the injection mix. The fractions containing LBs from 4 patients with PD were revealed by this alpha-synuclein filter retardation assay and pooled to obtain the LBs mix injected into the animals. **C** Filter Retardation Assays probed with AT8 and pSyn antibodies to assess the presence of pathological phosphorylated tau (Ser202/Thr205) and phosphorylated alpha-synuclein at Ser 129 in PD-LB mix and AD-tau mix samples.

variance across groups (Kruskal-Wallis test, $p = 0.226$, Fig. 3H), the estimation plots showed significant fiber loss in the LB+tau group compared to controls (-12% of TH terminal optical densitometry, with the 95% confidence interval of the mean difference not overlapping control value, Fig. 3H). We ran a multiple linear regression model with TH neuronal counting as a dependent variable and α -synuclein and tau pathologies as explanatory variables ($R^2 = 0.39$, $p = 0.023$). In this model, dopaminergic nigral neuronal loss was independently associated with AT8-phosphorylated tau staining ($F = 7.83$, $p = 0.014$) but not with pSyn ($F = 3.01$, $p = 0.10$).

We used in this study our innovative approach consisting of injecting patient-derived proteopathic aggregates into macaques' brains^{10–15}, to address the issue of a putative contribution of tau versus α -synuclein pathologies to the survival of dopaminergic mesencephalic neurons. Thanks to these aggregates' prion-like properties, we induced specific lesions in the mesencephalon, caudally from the injection sites. First, we confirmed that the striatal injections of PD patient-derived LB induce pSyn accumulation in the substantia nigra, as well as dopaminergic denervation in the nigrostriatal

pathway, in the same proportion as was previously described in rodents, macaques and baboons^{10,12,14,15} ($\sim 30\%$ of TH neuronal loss). Second, we confirmed that brain injections of AD patients-derived tau proteopathic seeds could trigger the seeding and spreading of AT8-positive neuronal inclusions^{11,13,16}. It corroborates our previous findings in macaques, showing that AD-tau injections in the entorhinal cortex can induce local seeding and distant spreading in the hippocampus and the cingulate cortex¹³. Third, we reported for the first time the cooperation between LB and tau pathologies in this experimental context. We found that the injection of AD-tau could induce distant pSyn, whereas we did not observe the reverse phenomenon; the injection of LB did not induce distant AT8-positive tau phosphorylation. Although not sufficient to induce tau lesions on its own, the injection of LB could modulate tau spreading, as suggested by a slightly more pronounced effect size in our AD-tau+LB group and as indicated by previous work in mice co-injected with AD-tau and α -synuclein preformed fibrils¹⁷.

The main finding of our study concerns the impact of α -synuclein, tau, and co-pathology on the integrity of the nigrostriatal pathway, which is

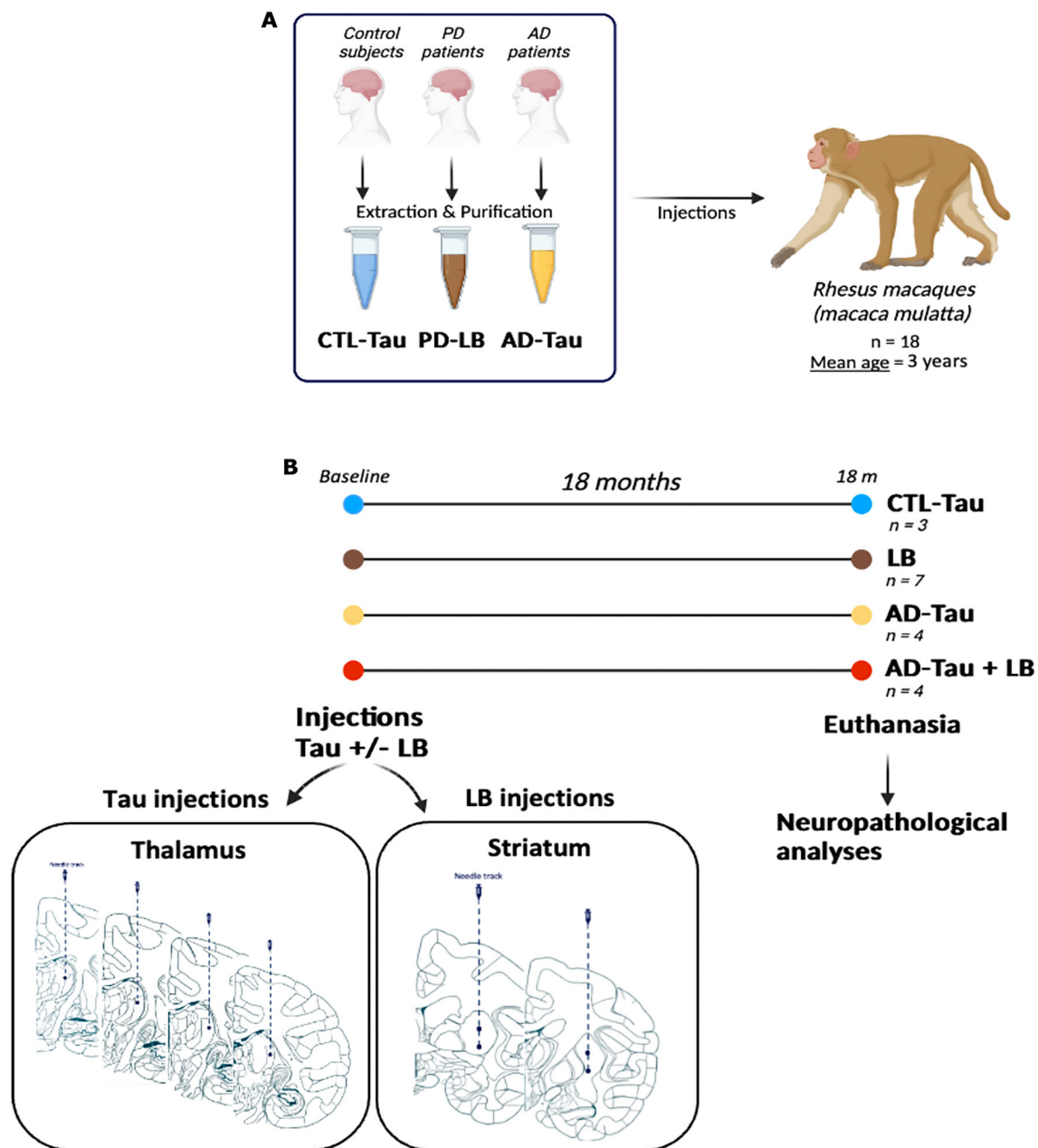


Fig. 2 | Experimental design. A LB fractions were derived and purified from sporadic PD midbrains, tau proteopathic seeds were extracted from a single AD brain. As a control procedure, we used tau extracts from aged-matched healthy brains. B To study the effect of the independent spreading of these pathologies toward the mesencephalon and not the consequences of local injections, we injected LB fractions and AD-tau seeds into two distinct rostral regions, both connected to

the midbrain: LB were injected into the striatum, and AD-tau seeds (or CTL-tau) into the lateral and posterior thalamus. A group of macaques received a co-injection of LB and AD-tau. Animals were euthanised 18 months after injections. Brain images were adapted from *The Rhesus Monkey Brain In stereotaxic coordinates*, G. Paxinos, 2008; the other images were created in bioRender.com.

closely related to the onset of PD and parkinsonism. We found that the distant injection of LB or AD-tau induced nigral TH neuronal loss of 26.5% and 38.4%, respectively. Notably, the co-injection of these aggregates into distinct but anatomically connected regions to the mesencephalon resulted in an additive effect with 53.5% neuronal loss, impacting also distant striatal dopaminergic fibers. Such observation further supports a bridge across these diseases and accounts for mixed α -syn/tau pathophysiological mechanisms. The impact of this co-pathology seems clinically relevant because the threshold of nigrostriatal dopaminergic denervation necessary for the appearance of overt parkinsonism in non-human primates is known to be 45%, as seen in MPTP-macaques^{18,19}. Interestingly, LB and tau co-pathology seems to differ from A β and tau interaction, which is known to be synergistic rather than additive, as it outstrips what would be expected from the

combined effect of A β and tau²⁰. Taken together, our findings align with the growing body of literature indicating that co-pathologies can significantly influence the severity and progression of neurodegenerative diseases^{4,5,21,22}.

Our results highlight the vulnerability of dopaminergic neurons in the substantia nigra to both synucleinopathy (as seen in PD, DLB, or multiple system atrophy) and tauopathy (as seen in progressive supranuclear palsy (PSP), corticobasal degeneration, or FTLT-parkinsonism)²³. Recent studies suggest that the initiation of nigrostriatal dopaminergic neurodegeneration may occur independently of α -synuclein aggregation and could be tau-mediated⁶. The induction of α -synuclein phosphorylation by distant tau seeds injection, contemporaneously with dopaminergic denervation, is consistent with this hypothesis. Furthermore, in this context of co-pathology, our multivariate analysis showed that the quantification of TH-positive

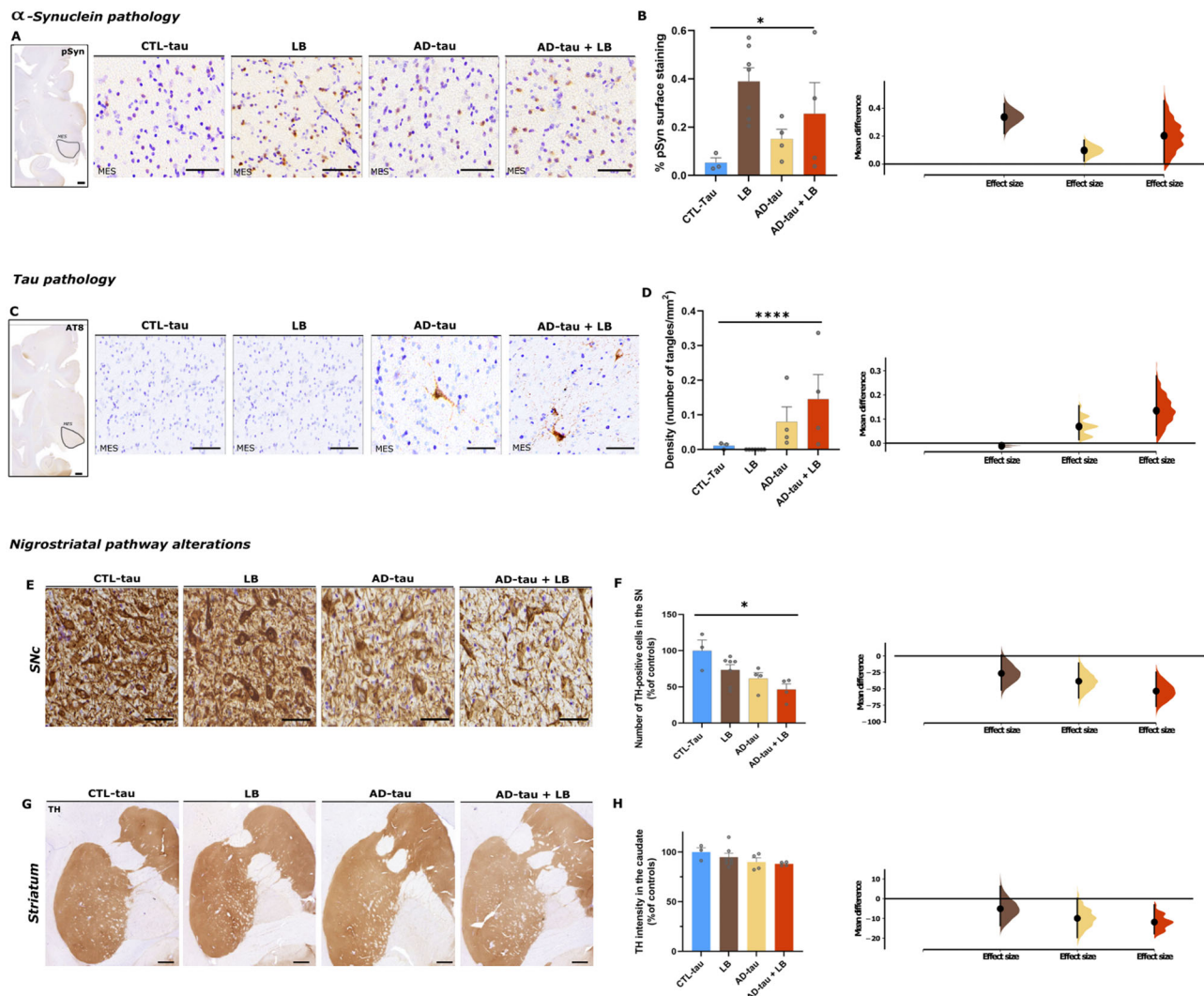


Fig. 3 | Neuropathological effects in the mesencephalon of α-synuclein-containing LB and tau proteopathic seeds injections in rostral connected brain regions. Representative images of S129 phosphorylated α-synuclein staining (A) and AT8 phosphorylated tau staining (C) in a whole hemisphere (left) and in the mesencephalon (MES – right) of injected macaques. Scale bar: 5 mm (left) and 20 μm (right). Illustrative images of the tyrosine-hydroxylase (TH)-staining in the substantia nigra pars compacta (E) and in the anterior striatum (G) of macaques. Scale bar: 20 μm. Quantitative analyses (B, D, F, H) are represented using bar and dot

plots (left) and estimation plots reporting effect sizes (right) (CTL-tau: $n = 3$; LB: $n = 7$; AD-tau: $n = 4$; AD-tau + LB: $n = 4$). Stars represent the results of the Kruskal-Wallis test (* $p < 0.05$; **** $p < 0.0001$). Estimation plots represent the difference distribution between groups using resampled distributions of observed data (colour curves). Horizontally aligned with the mean of the CTL-tau group, the mean difference is indicated with the black circle. The black vertical line illustrates the 95% CI of the mean difference.

neurons in the substantia nigra was independently associated with tauopathy but not with synucleinopathy (this independent association, however, was not far from being significant in the context of limited statistical power).

The main limitation of our study is the need for further biochemical and histological investigations and a comprehensive behavioural assessment that would provide a complete understanding of the functional impact of our findings. In future studies, we can envision assessing the kinematic features of the macaques, as we previously reported parkinsonism in a small group of macaques injected with patient-derived PSP-tau seeds¹¹. Another limitation of the study, affecting the comparison between the neuropathological consequences of LB and/or AD-tau injections, is that we did not inject these proteins at the same concentrations. Indeed, there was 1000 times less total synuclein in the LB fractions than total tau in the AD-tau extracts. However, we replicated our previous mono-injection design protocols to assess inter-study reproducibility. Furthermore, as these concentrations are high compared to physiological values, it is reasonable to assume that there is no longer an apparent dose-response effect. Additionally, we cannot exclude that unidentified proteins present in our AD-tau and/or LB fractions may have played

a role in the development of the observed pathology. However, we confirmed that there were no remarkable amounts of phospho-synuclein in the AD-tau extracts nor phospho-tau in the LB-enriched fractions. Furthermore, to account for the potential impact of injecting a “protein cocktail” into the macaque brain, our control group was not injected with a vehicle but with a tau extract from the brain of an age-matched patient without AD.

In conclusion, our study offers important experimental insights into the impact of LB and tau pathologies on neurodegeneration, highlighting their combined influence on disease progression²⁴. These findings pave the way for future research focused on developing targeted therapies that address the complex nature of neurodegenerative diseases.

Methods

Extraction and purification of tau seeds and LB from AD and PD brains

Pathological sarkosyl-insoluble AD tau proteopathic seeds (AD-tau) were provided by the IMPriND consortium (<https://www.imprind.org/>), following a protocol adapted from Guo et al.¹⁶ and using a single AD case

(Oxford Brain Bank) (Supplementary Table 1). Comparable fractions were extracted from aged-matched healthy brains (CTL-tau) using the same protocol. Frozen brain tissue was homogenised in 9x v/w of PHF Extraction buffer (800 mM NaCl, 10 mM Tris-HCl pH 7.4, 1 mM EDTA, 10% sucrose, 1x cOmplete™, EDTA-free protease inhibitor cocktail (Merck, #11873580001), 1x PhosSTOP™ phosphatase inhibitor cocktail (Merck, #4906845001), 0.1% w/v sarkosyl, and 2 mM DTT), using the FastPrep-24 homogeniser (4 m/s, Quickprep, 30 s). A sample was kept for western blot analysis (Fig. 1A) and the homogenate was transferred to clean tubes and centrifuged at 10,000 for 10 min at 4 °C. The supernatant was then filtered through a 70 µm cell strainer and the pellet was re-homogenised under the same conditions in 5x v/w of PHF Extraction buffer. This second homogenate was centrifuged again at 10,000 for 10 min and the supernatants were combined. The pellet was re-homogenised in 3x v/w of PHF Extraction buffer, a sample was kept for western blot analysis (“10k pellet”) and the rest was discarded. The clarified supernatants were brought to a final concentration of 1% w/v Sarkosyl and mixed for 1 h at RT. At the end of the incubation, a sample was kept for western blot analysis (“10k supernatant”) and homogenates were centrifuged at 150,000 g for 75 min at 4 °C. The supernatant (“Sarkosyl soluble”) was separated from the pellet, which was washed with 30 ml PBS and centrifuged at 250,000 g for 30 min at 4 °C. At the end of the spin, the supernatant (“PBS wash”) was removed and the pellet was resuspended in 0.1 ml/gr PBS and incubated overnight at RT on a rocking platform. The next day the sample (“Sarkosyl insoluble”) was sonicated using the UP200St with VialTweeter (Hielscher Ultrasonics) using standard conditions (A = 100%, C = 50%, Total Ws = 200) and it was centrifuged at 100,000 g for 30 min at 4 °C. The supernatant (“high-g supernatant”) was separated and the pellet (“high-g pellet”) was resuspended in PBS (50 µl/gr of initial tissue) and sonicated again under the same conditions. The sample was then centrifuged at 10,000 g for 30 min at 4 °C and the supernatant (“low-g supernatant”) corresponding to the final seeds were aliquoted and stored at –80 °C. The pellet was resuspended in the same volume of PBS (50 µl/gr of initial tissue), a sample was kept for western blot analysis (“low-g pellet”) and the rest was discarded.

The seeding efficiency of the AD-tau extract was confirmed *in vitro* on tau P301S-Venus human embryonic kidney 293 (HEK293) cells (Fig. 1A). Total tau concentrations were 100 ng/µL in AD-tau extracts and <5 ng/µL in CTL-tau extracts, as measured with quantitative filter retardation assay with HT7 antibody¹³.

Enriched fractions of LB were derived from midbrain samples of 4 patients with sporadic PD exhibiting conspicuous LB pathology on neuropathological examination (Supplementary Table 1), obtained from the French Brain Bank GIE NeuroCEB (Pitié-Salpêtrière Hospital, Paris). After homogenisation, LBs were extracted and purified using a sucrose gradient, as previously reported^{10,12} (Fig. 1B). Quantification by ELISA indicated that the final LB mix contained ~16 pg/µL of α-synuclein.

PD-LB mix and AD-tau mix were further analysed for the presence of phosphorylated α-synuclein at Ser 129 (pSyn (pS129, EP1536Y, Abcam, 1:2000, rabbit) and phosphorylated tau (Ser202/Thr205) (AT8, Fischer Scientific, 1:500, mouse) by filter retardation assay on nitrocellulose membranes, as previously described^{10,12} (Fig. 1C).

Animals

Experiments were performed following the European Union Directive (2010/63/UE) on protecting animal use for scientific purposes in the Institute of Laboratory Animal Science (ILAS) and the Motac facilities in Beijing, accredited by AAALAC (Association for Assessment And Accreditation of Laboratory Animal Care). Experimental procedures were performed following study design acceptance by two independent ethics committees in France (CEEA 50, #12286) and China (Chinese Academy of Medical Science, Beijing, approval number: IACUC-QC18008 and QC19025).

Eighteen male rhesus macaques (*Macaca mulatta*, Xiexin, Beijing, China) were randomly selected to receive 100 µL/hemisphere of LB fractions ($n = 7$; mean age = 2.5 years, ± 0.2 SD), AD-tau seeds ($n = 4$; mean

age = 3.6 years, ± 0.6 SD), LB+tau ($n = 4$, mean age = 3.3 years, ± 0.7 SD) or CTL-tau solutions ($n = 3$, mean age = 3.3 years, ± 0.9 SD) into 4 injection sites. LB were injected bilaterally into the striatum according to the previously reported stereotactic procedure¹⁵. AD-tau seeds were injected bilaterally into the lateral thalamus and the pulvinar (Track 1: anterior commissure (AC) = -8, length (L) = 6, depth (D) = +3; Track 2: AC = -10, L = 8.5, D = +2; Track 3: AC = -12, L = 8.5, D = +1 and Track 4: AC = -13, L = 7, D = +0).

Eighteen months post-injections, macaques were euthanised as the European Veterinary Medical Association guidelines recommended. The right cerebral hemisphere of each macaque was fixed in 4% PFA for a week, cryo-protected in sucrose PBS until sunk, frozen in snap-frost isopentane bath at –50 °C and stored immediately at –80 °C until sectioning for histological analyses¹³.

Histological analysis

Immunohistochemical staining for phosphorylated α-synuclein at Ser 129 (pS129, EP1536Y, Abcam, 1:2000, rabbit), phosphorylated tau (Ser202/Thr205) (AT8, Fischer Scientific, 1:500, mouse), dopaminergic neuron (Tyrosine hydroxylase (TH), EP1532Y, Abcam, 1:5000, rabbit), microglia (Iba1, ab5076, Abcam, 1:1000, goat) and astrocytes (mix of GFAP and S-100, MAB 3402 GA5, Sigma, 1:2000 and PAP 11341, Abcam, 1:1000, mouse) were performed on free-floating coronal slices (50 µm thickness), as previously described^{11,13}. TH-positive cells were counted by stereology in the substantia nigra of each macaque, using a Leica DM6000B motorised microscope coupled with the Mercator software (ExploraNova) and the optical fractionator method, blinded of the experimental conditions, as in our previous reports¹¹. TH intensity in the striatum was quantified using optical densitometry with a threshold detection macro on Visiopharm, applied to a mask of 2 delineated caudate slices from each macaque. All quantitative analyses were performed blinded to the experimental conditions.

Statistical analysis

Comparisons among experimental groups were first performed using Kruskal-Wallis tests. We further analyzed our data using estimation graphics called ‘Gardner–Altman plots’ emphasising the effect size and comparing LB, AD-tau, and LB+tau groups to the CTL-tau group, as previously reported^{11,13,15}. We also performed linear regressions to assess associations between dopaminergic neuronal loss, phosphorylated α-synuclein, and AT8 staining.

Our proposal to base part of our conclusions on effect sizes and estimation graphics rather than p-values is now well-documented in the literature²⁵. The size of the experimental groups was set between $n = 3$ and $n = 7$ due to the now well-established statistical power of using three monkeys in such studies²⁶. No animal initially injected was excluded from the final analyses.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

E.B. and V.P. designed the experiments and supervised the overall study. M.X., B.D., E.B., and V.P. obtained funding. B.D. extracted patient-derived LB fractions. T.K. and W.A.M. provided tau seeds. E.B., B.D., and V.P. performed macaques surgeries. Q.L. supervised macaques experiments. M.D., V.K., and M.L.A. performed histological experiments. M.D. and V.P. wrote the first draft of the manuscript. All authors discussed the results, participated in manuscript editing and approved the final manuscript.

Competing interests

E.B. is a director and shareholder of Motac Neuroscience Ltd. During the past 3 years, V.P. was a local unpaid investigator or sub-investigator for clinical trials granted by Novo Nordisk, Biogen, Janssen, and Alektor. V.P. served as a consultant for Motac Neuroscience Ltd, outside the submitted work. Other authors declare no competing interests.

Additional information

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