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Regional levels of physiological  $\alpha$ -synuclein are directly associated with Lewy body pathology

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Lewy body (LB) pathology has been described as progressing through the brain in a stereotyped sequence suggesting it may spread in a trans-synaptic manner similar to prion protein [1]. A recent report demonstrated  $\alpha$ -synuclein pathology in the deep cerebellar nuclei of LB disease cases [4]. However, the cerebellar cortex is strongly connected with early predilection sites in the brainstem yet had virtually no  $\alpha$ -synuclein pathology, indicating anatomical connectivity is not the sole determinant of vulnerability and cell- or region- autonomous factors may influence its development [5]. A previous study in wild-type mice suggested an association between regional expression levels of physiological  $\alpha$ -synuclein and vulnerability to LB pathology [6]. However, no study has yet compared the expression of physiological  $\alpha$ -synuclein across human brain regions and evaluated its relationship to  $\alpha$ -synuclein pathology. Therefore, we sought to quantify regional expression levels of physiological  $\alpha$ -synuclein under normal conditions to evaluate its association with the topography of pathology in LB disease.

We obtained fixed human brain tissue from ten cases with neocortical LB disease to evaluate the typical topography of LB pathology across the cortex and cerebellum (Supplementary Table 1). Quantitative image analysis demonstrated a consistent hierarchy of LB pathology severity with temporal and cingulate regions most severely affected, intermediate pathology in prefrontal and parietal regions, very low deposition in the primary visual cortex and a complete absence of LB pathology in the cerebellar cortex (Figure 1a).

We next obtained frozen tissue corresponding to the same brain regions from the brains of eight aged cognitively normal control cases without LB disease to evaluate the expression of physiological  $\alpha$ -synuclein (Supplementary Table 2). Using western blot analysis (Supplementary Protocol 2) we quantified  $\alpha$ -synuclein levels across regions within cases. Amongst regions that typically develop LB pathology we did not find higher levels in regions which typically manifested the most severe LB pathology (Figure 1b and 1c). However, physiological  $\alpha$ -synuclein was consistently virtually absent from the primary visual cortex and cerebellar cortex, regions not prone to  $\alpha$ -synuclein pathology (Figure 1b, Supplementary data 2). We directly compared the expression of physiological  $\alpha$ -synuclein at 16 kDa in the anterior cingulate, temporal cortex, primary visual cortex and cerebellum as they manifested the highest and lowest burdens of LB pathology (Figure 1a). We found a significant main effect on  $\alpha$ -

synuclein levels (K-W  $\chi^2=19.8$ ,  $df=3$ ,  $p<0.001$ ) and post-hoc Wilcoxon tests revealed significantly lower expression of  $\alpha$ -synuclein in the primary visual cortex and cerebellum compared to the anterior cingulate and temporal cortex (all  $p<0.05$ ).

These results indicate physiological  $\alpha$ -synuclein has strikingly lower expression in brain regions not prone to LB pathology. The recruitment of endogenous protein into aggregates is crucial for pathological 'prion-like' propagation [1] and  $\alpha$ -synuclein pathology does not propagate in knockout mice [2]. Therefore, we speculate the cerebellum and primary visual cortex do not develop high levels of pathology in LB disease because propagation is significantly slowed by relatively low levels of physiological  $\alpha$ -synuclein. However, as regions with the greatest proclivity to LB pathology did not have highest levels of physiological  $\alpha$ -synuclein, we suggest physiological expression levels are not the sole determinant of vulnerability. One may speculate that vulnerability to LB pathology is the product of anatomical connectivity and region-autonomous factors, with a baseline level of physiological  $\alpha$ -synuclein expression necessary for pathology to develop. Our report of low expression levels of physiological  $\alpha$ -synuclein in brain regions which do not typically develop LB is particularly important as down-regulation of physiological  $\alpha$ -synuclein expression has recently been shown to exert neuroprotective qualities against LB diseases [3].

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## Conflict of interest

The authors declare they have no conflict of interest.

## Declaration

Ethical approval was granted by Newcastle University Ethics Board and the Joint Ethics Committee of Newcastle and North Tyneside Health Authority (ref: 08/H0906/136).

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Figure 1: A consistent hierarchy of LB pathology was observed amongst cases with neocortical LB disease (a). Representative western blot membrane demonstrating low expression of physiological  $\alpha$ -synuclein in the primary visual cortex (V1) and cerebellum in an aged control case (b). In controls, physiological  $\alpha$ -synuclein was expressed across regions which typically develop LB but was remarkably lower in the primary visual cortex (V1) and cerebellum (CB; c). Western blot sample order: prefrontal cortex (PFC), anterior cingulate (AC), temporal cortex (TC), mid-cingulate (MC), posterior cingulate (PC), lateral parietal (LP), primary visual cortex (V1) and cerebellum (CB).

