Parvalbumin interneuron vulnerability in dementia with Lewy bodies

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1. Introduction

Lewy Body dementia (LBD) is a collection of diseases consisting of dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) and is the second most common form of neurodegenerative dementia[1,2]. These diseases are neuropathologically characterised by the aggregation of α-synuclein into intracellular aggregates called Lewy bodies which are thought to play an important role in the pathogenesis of DLB. Symptoms of DLB can vary over time, including visual hallucinations, motor disorders (parkinsonian symptoms) and cognitive fluctuations [1,2,3].

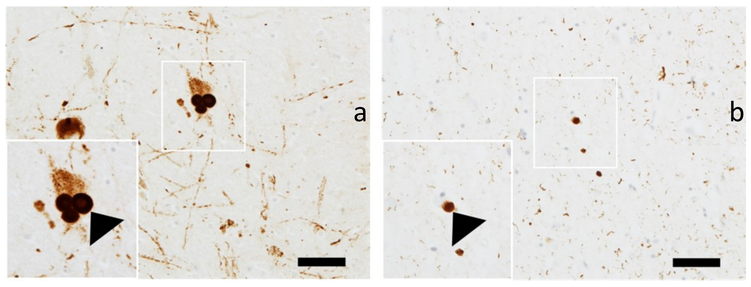

Figure 1: α-synuclein antibody in DLB cases highlighting the formation of Lewy bodies in midbrain (a) and cortex (b).

Lewy bodies in the cortex are thought to underlie cognitive symptoms of DLB. The cortex consists of two major types of neuron: pyramidal neurons that project between brain regions, and interneurons that regulate the firing of pyramidal neurons into the rhythms that underlie cognition. Although pyramidal neurons are the only cells affected by Lewy bodies in the cortex, interneuron dysfunction has been implicated in transcriptomic studies and the transient nature of DLB symptoms is more consistent with dysregulation than degeneration.

This study is amidst the first of it's kind and is aimed to quantify the numbers of pyramidal and inter-neurons in the prefrontal cortex in DLB. Prefrontal cortex was evaluated due to its role in attention, a faculty suggested to be impaired in DLB leading to fluctuating cognition, a core symptom of DLB. DLB cases were compared to aged control cases and Alzheimer's disease (AD) cases as disease controls.

2. Methods

Human post-mortem tissue was obtained by a convenience sample from the Newcastle Brain Tissue Resource, a UK Human Tissue Authority approved tissue repository. Three groups of cases were included in the present study: 12 DLB cases, 12 AD cases, and 12 clinically and pathologically confirmed aged comparison cases. The region of interest (ROI) was the prefrontal cortex (Brodmann area 9, superior frontal gyrus) which was dewaxed and rehydrated. Immunohistochemistry methods were used following EDTA pH8 antigen retrieval in a histology de-cloaker, antisera were parvalbumin (PARV-19, Sigma Aldrich, 1:2,000) and SMI-32 (Merck Millipore, 1:1,000).

Samples were incubated with primary antibody for 30 minutes before being washed with wash buffer. Menarini Menapath kits were used to visualise the stain in accordance with manufacturers instructions. Tissue was mounted using DPX mounting medium.

ROI was traced with Stereologer software at 2.5x magnification across all cortical layers to the grey/white matter junction. Dissector frames were placed in a uniform, random arrangement to calculate the density of cells. Neuronal counts were performed at 20x magnification, in counting frames of 22,500 um^2. The mean coefficients of error were calculated using the Gundersen-Jensen method and all error values were lower than 0.15[4,5].

3. Results

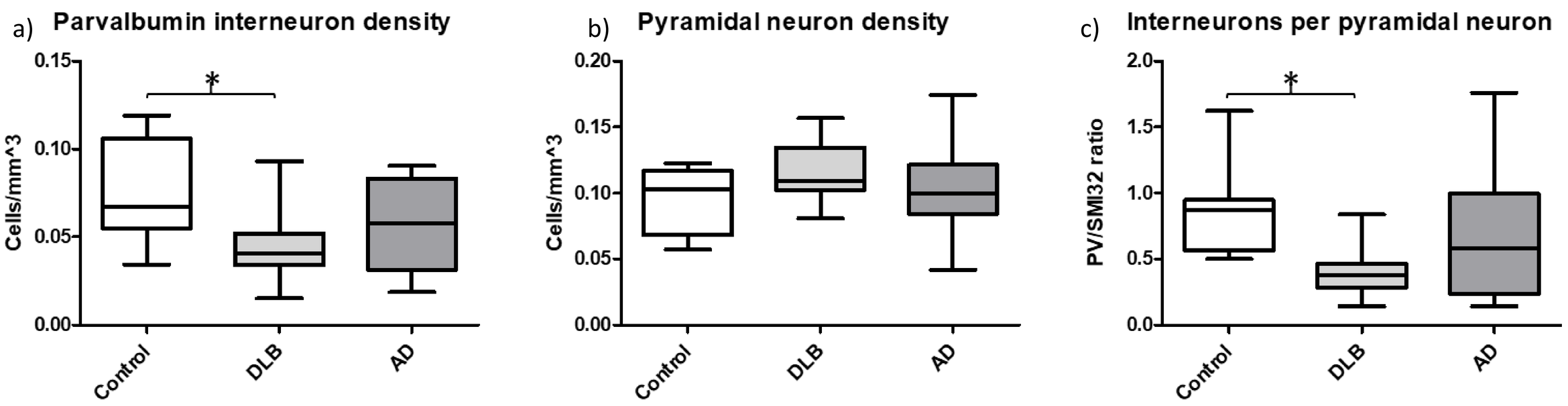

*Figure 2: Data from an ANOVA test indicates a significant reduction of PV interneurons in DLB compared to the control (p=0.018), but no significant difference between AD and control. * = p<0.05*

There was a significant decrease in the density of PV interneurons in the DLB cases compared to the control ($p<0.05$), from an average density of 0.06 cells/mm^3 to <0.05 cells/mm^3 (figure 2a). The inverse of this was recorded for pyramidal neuron density, where the density of these neurons was higher in DLB neurons than in the control cases (figure 2b).

Pyramidal neurons (labelled by SMI32) were not different across all groups. The ratio of interneurons per pyramidal neurons was also altered in DLB ($p=0.026$), suggesting a loss of the number of interneurons compared to pyramidal neurons, meaning that DLB cases have a lower number of interneurons compared to pyramidal neurons (figure 2c).

These changes may lead to altered brain activity in DLB, which can lead to the transient symptoms, including fluctuating cognition, where DLB patients change in their ability to pay attention over time then spontaneously improve.

The region analysed was the PFC which is involved with attention and when affected by DLB causes the loss of interneurons and therefore the transient changes in consciousness. The findings of this study highlight the significant loss in regions of PFC in cases of patients suffering with DLB.

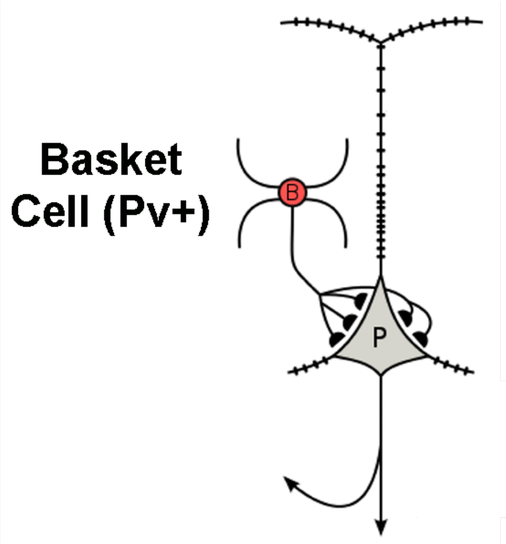

Figure 3: A simple diagram to show the basic structure and connections between a pyramidal neuron and PV interneuron (basket cell) in the PFC.

4. Conclusions

This study demonstrates that there is a significant reduction in interneurons (parvalbumin) in DLB, when compared to the unaffected (control) samples, but no effect on interneurons in Alzheimer's (AD) cases when compared to unaffected (control) samples. There was no significant difference between the pyramidal cells in any of the cases, however a loss of interneurons was noted, which could lead to a altered brain activity, giving the trademark symptoms of inconsistent cognition, where the pre-frontal cortex is key in attention-based activity creating difficulties in co-ordination and poor focus.

5. References

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6. Acknowledgements

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