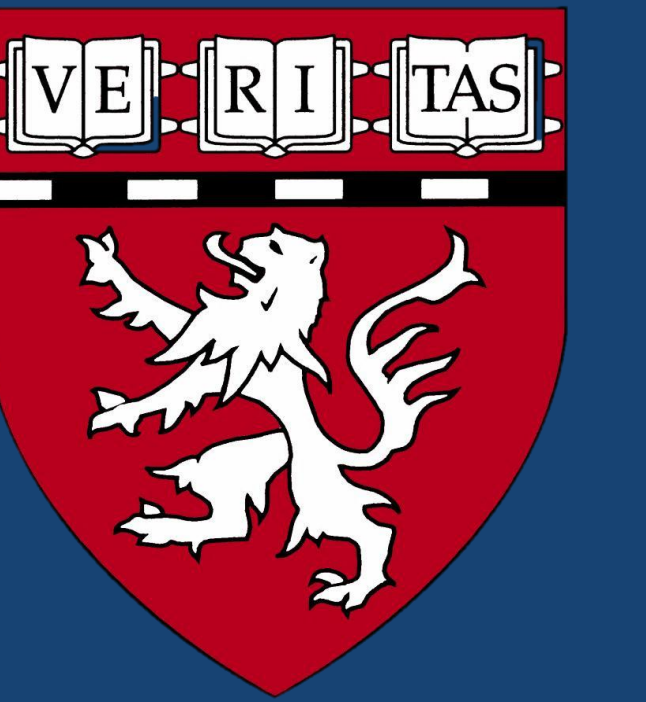




# Mechanical Ventilation Increases Brain Tau-PT217 Levels via the Lung-Vagus Nerve-Brain Axis in Aged Mice



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## BACKGROUND

Postoperative delirium is a common complication in the elderly following anesthesia and surgery, leading to significant healthcare costs and adverse outcomes, including a high risk of development Alzheimer's disease<sup>1</sup>.

Previous clinical studies have demonstrated an association between mechanical ventilation and Postoperative delirium in patients<sup>2</sup>. Our previous research indicates that Tau-PT217 can be detected in the lungs shortly after anesthesia and surgery, with potential transmission to the brain, leading to Postoperative delirium-like behaviors in aged mice<sup>3,4</sup>. However, the underlying mechanism by which mechanical ventilation induces Tau phosphorylation and Tau trafficking remains undermined.

We hypothesize that mechanical ventilation elevates Tau-PT217 levels in the lungs and vagus nerve, subsequently increasing the levels of Tau-PT217 in the brain of aged mice.

## METHODS

In this study, we used 18-month-old wild-type C57BL/6J female mice and performed mechanical ventilation under general anesthesia. The mice were ventilated for one hour at an airway pressure of 15 cm H<sub>2</sub>O and a respiratory rate of 100 breaths per minute, under 1.4% isoflurane anesthesia.

Tau-PT217 levels in the lungs, vagus nerve, nucleus tractus solitarius (NTS) and cortex were measured using Western blotting and immunofluorescence.

## RESULTS

Figure 1. Mechanical ventilation, rather than inhaled anesthetics, increased Tau-PT217 levels in the cortex of aged mice under general anesthesia.

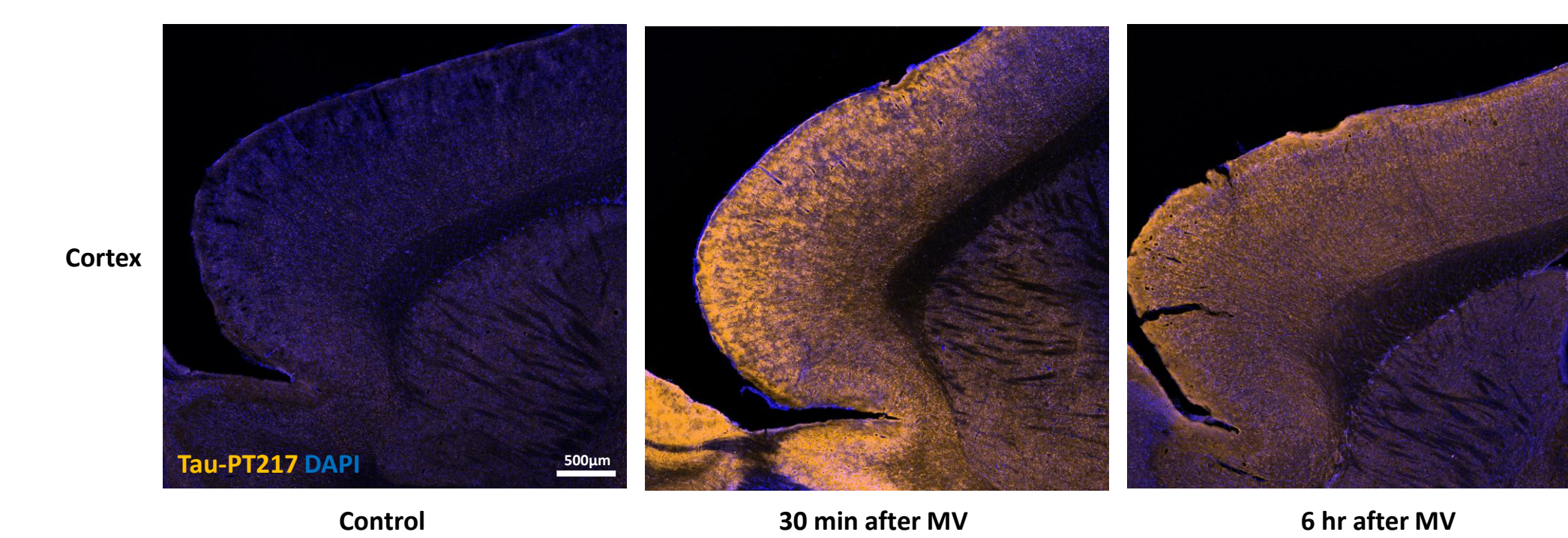
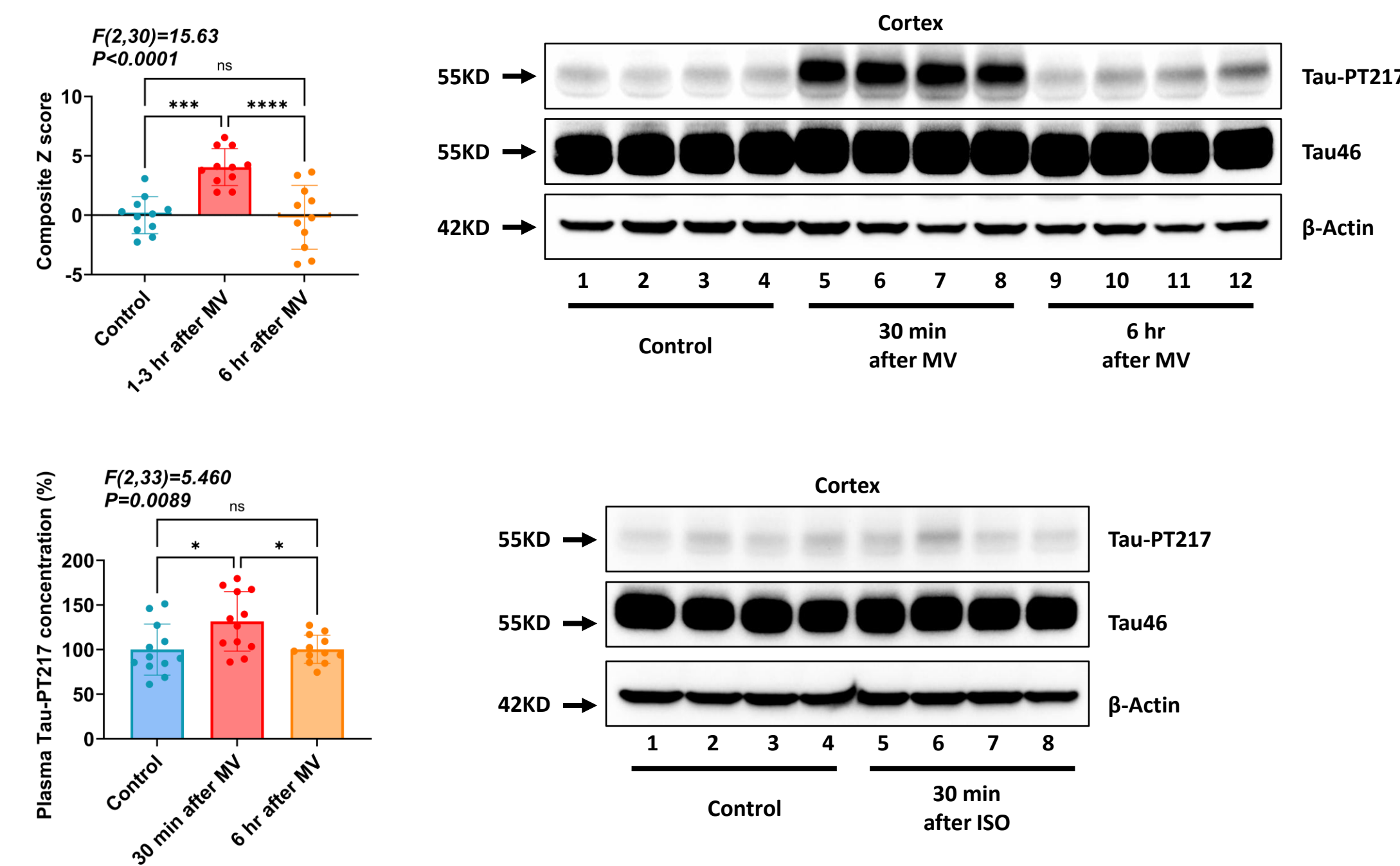


Figure 2. Mechanical ventilation increased Tau-PT217 levels and decreased Tau levels in lungs, vagus nerve and NTS of

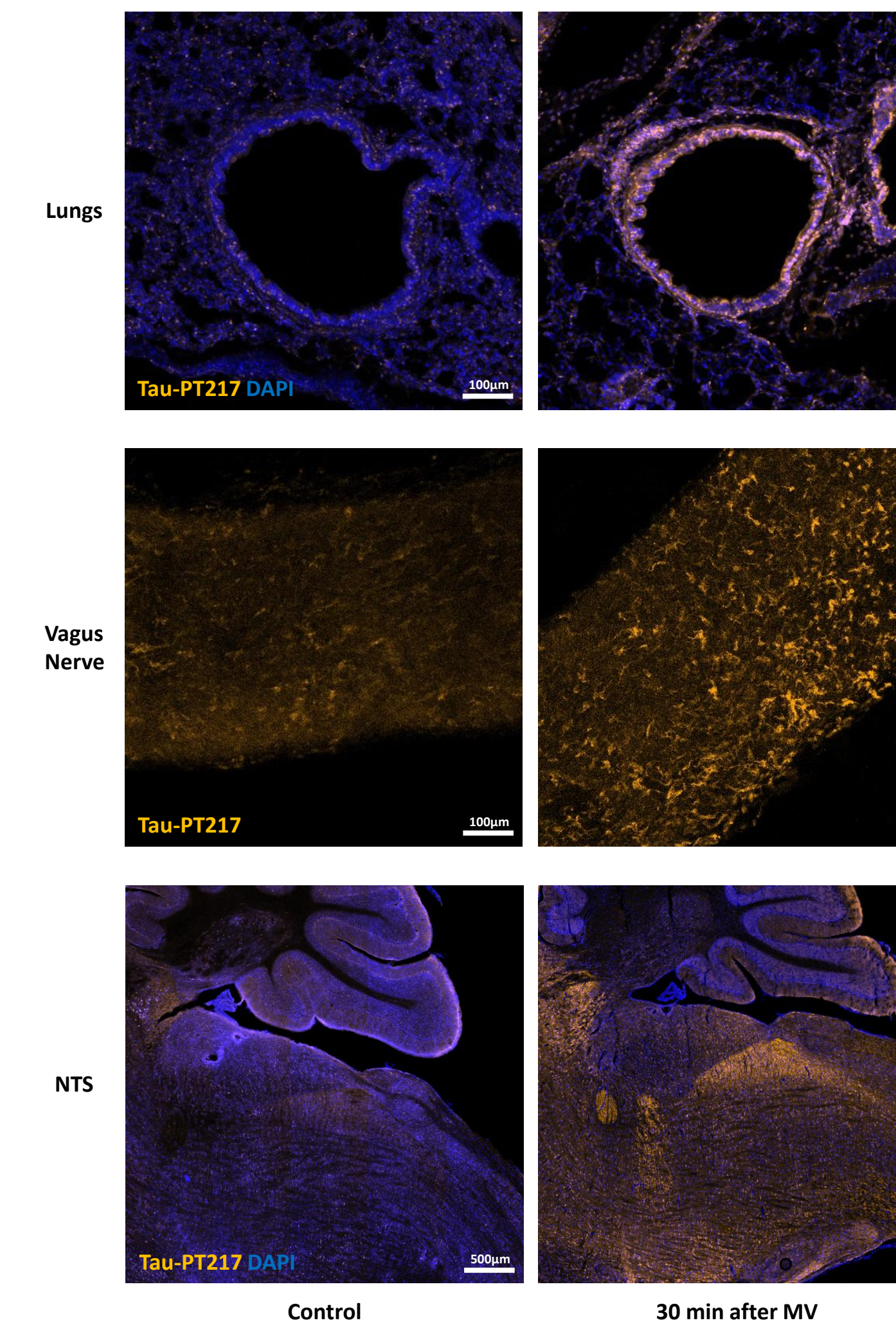
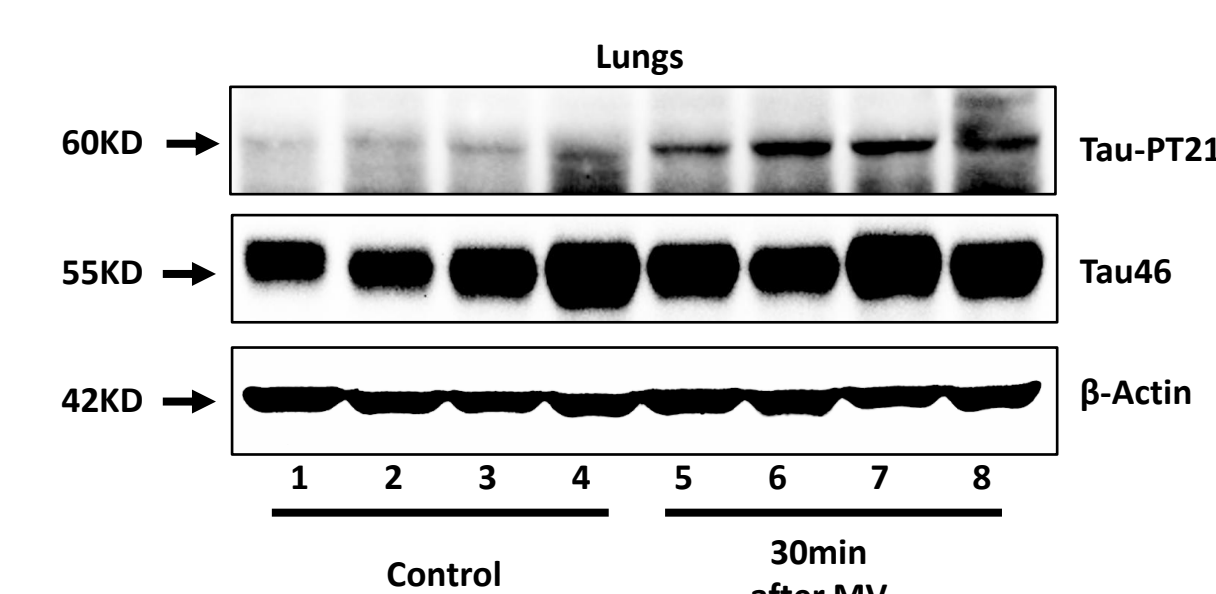


Figure 3. Bilateral vagotomy at the neck reduced the increase of Tau-PT217 levels in cortex but not in lungs induced by mechanical ventilation in aged mice.

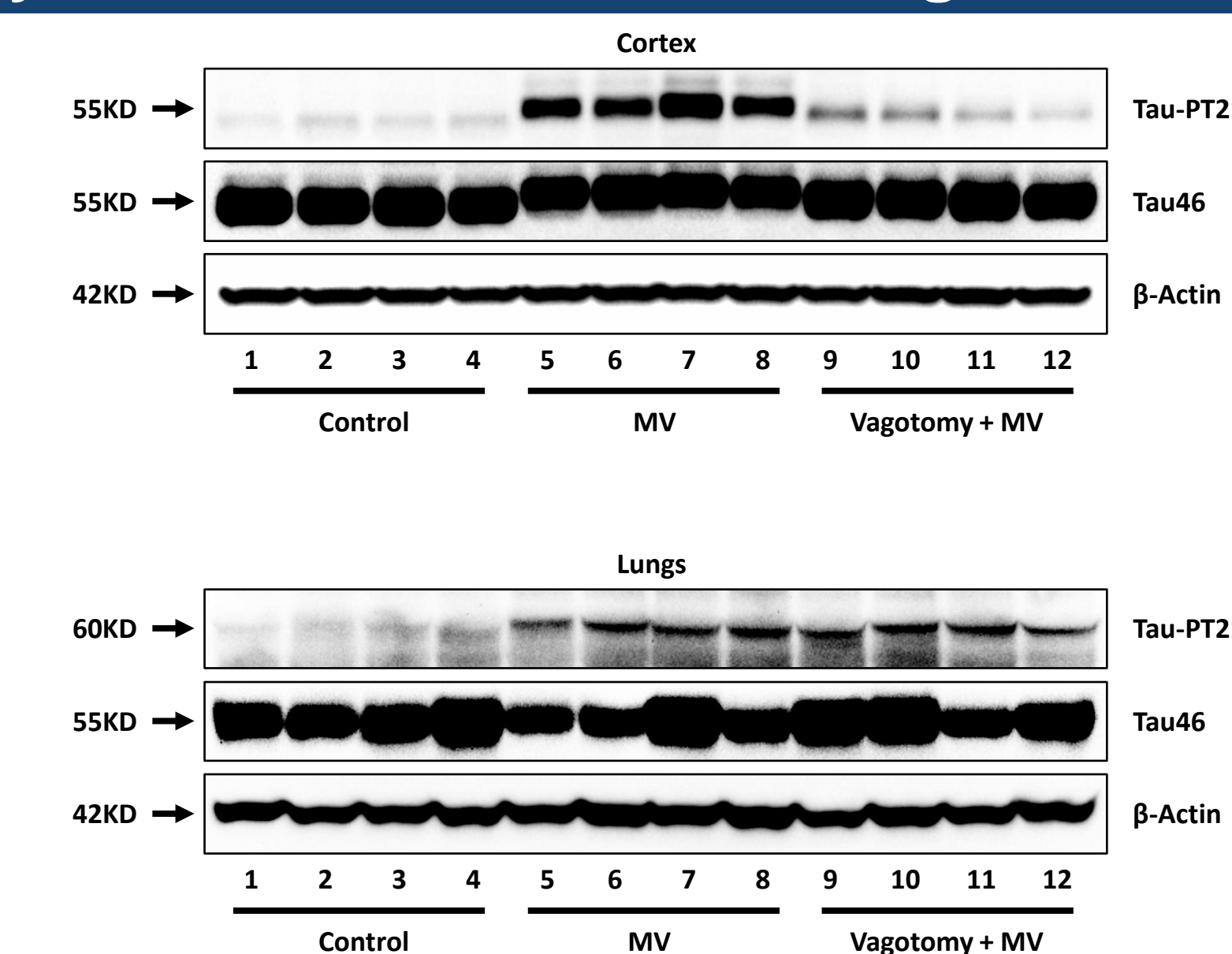
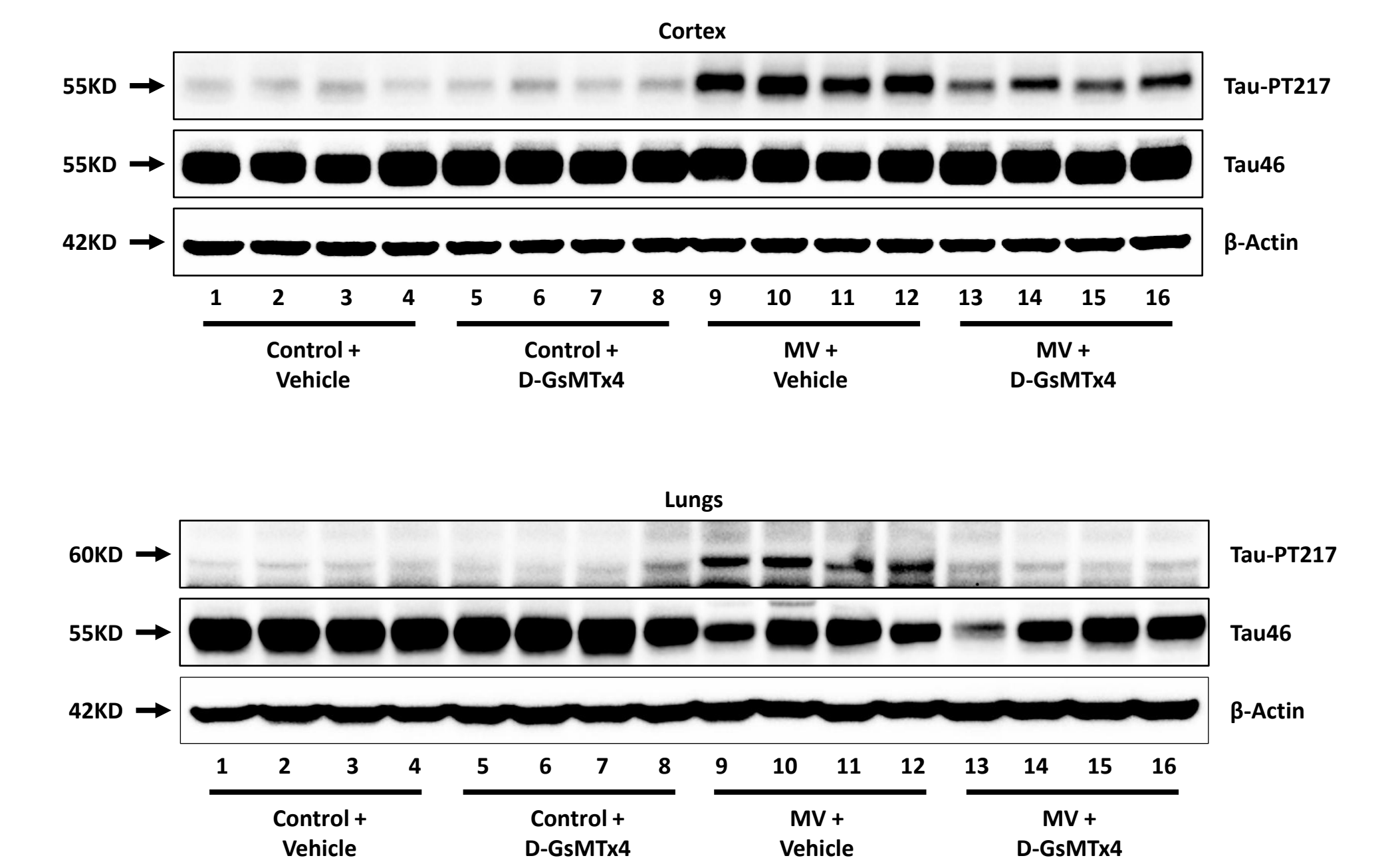


Figure 4. Intratracheal injection of Piezo2 receptor inhibitors can reduce the increase of Tau-PT217 levels in both cortex and lungs induced by mechanical ventilation in aged mice.



## SUMMARY/CONCLUSIONS

Mechanical ventilation increases Tau-PT217 levels in the lungs, vagus nerve, NTS and cortex of aged mice compared to the sham control condition.

The findings suggest a potential lung-vagus nerve-brain axis mediating the increase in cortical Tau-PT217.

Future studies will explore the molecular mechanisms behind the elevation of Tau-PT217 in the lungs due to mechanical ventilation and its transmission to the cortex, aiming to identify strategies to reduce postoperative delirium by targeting Tau-PT217 in the lungs.

## REFERENCES

1. Witlox J, et al. JAMA. 2010.
2. Bassi TG, et al. Crit Care. 2021.
3. Lu J, et al. Alzheimers Dement. 2023.
4. Liufu N, et al. Aging (Albany NY). 2020