

The Influence of Mixed Neuropathology on the Presence and Severity of Neuropsychiatric Symptoms in Dementia

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Mixed neuropathology associated with increased prevalence of neuropsychiatric symptoms across all symptom domains, with limited effects on symptom severity.

BACKGROUND

Mixed neuropathology is highly prevalent dementia and old age, with many individuals exhibiting combinations of Alzheimer’s disease, Lewy body disease, vascular pathology, and other co-pathologies, such as limbic TDP-43, at postmortem examination.

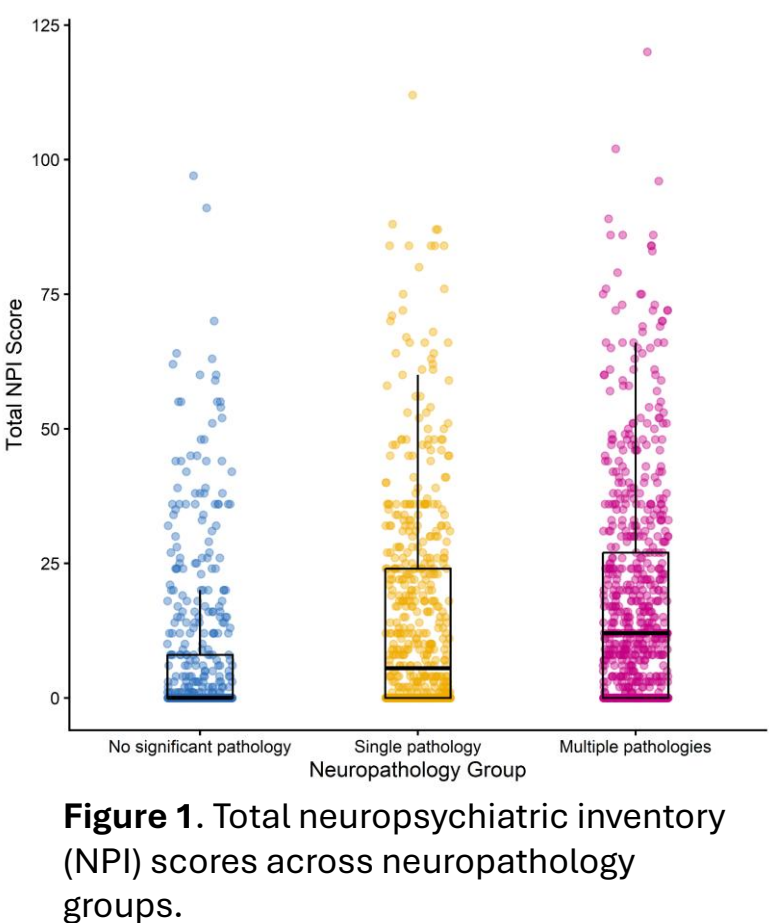
Neuropsychiatric symptoms significantly impact quality of life, contributing to patient distress, caregiver burden, and functional decline. It remains unclear whether mixed pathology influences whether symptoms occur and how severe symptoms become once present^{1,2}.

Aim: Investigate the association between mixed pathology and the presence and severity of neuropsychiatric symptoms to clarify how underlying pathology burden shapes behaviour.

METHODS

Participants were classified as having no significant pathology, single pathology, or multiple pathologies. Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI)³.

Hurdle models accounted for excess zeros by separately modelling symptom presence (logistic regression) and severity (truncated negative binomial regression)⁴. Models were adjusted for time-to-death, age at death, and sex, with participant included as a random effect.



INCREASE IN SYMPTOM PREVALENCE OBSERVED FROM NO PATHOLOGY TO MULTIPLE PATHOLOGIES

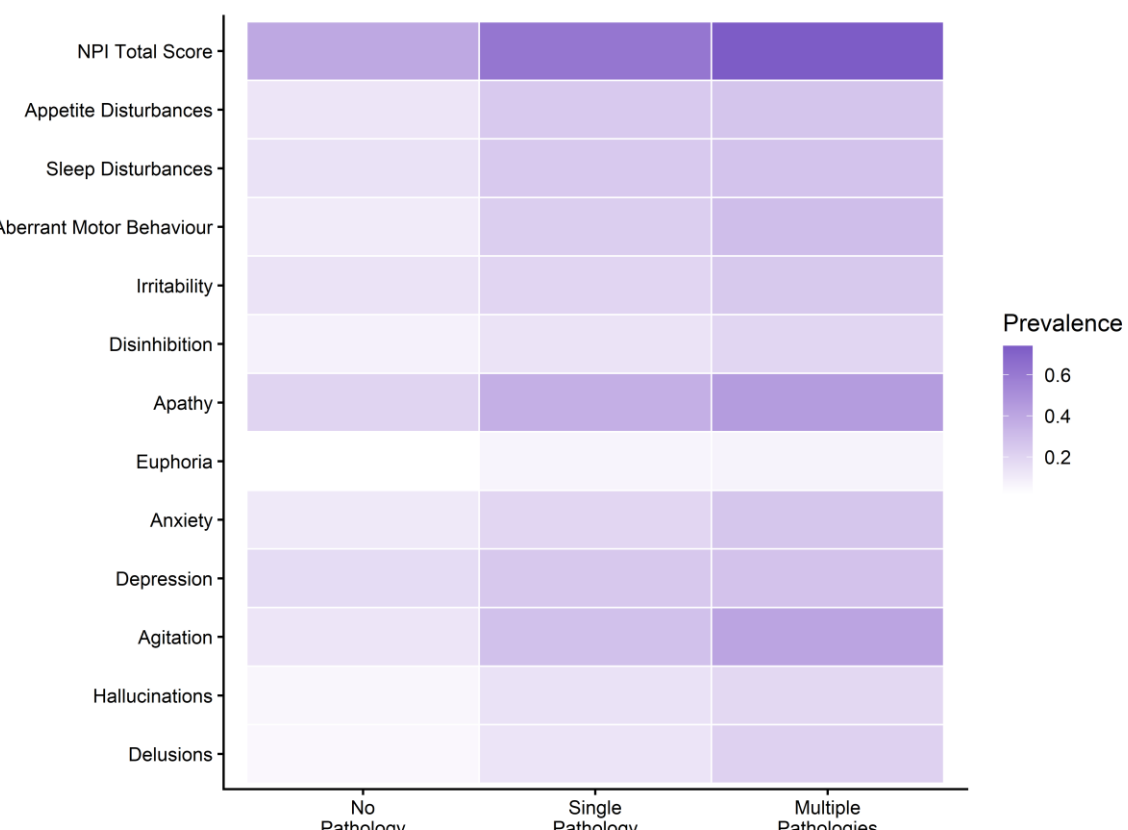


Figure 2. Heatmap showing the prevalence of total and domain specific NPI symptoms by neuropathology group. Darker colours indicate higher symptom prevalence

BEHAVIOURAL AND AFFECTIVE SYMPTOMS EXHIBITED THE GREATEST CO-OCCURRENCE ACROSS NPI DOMAINS

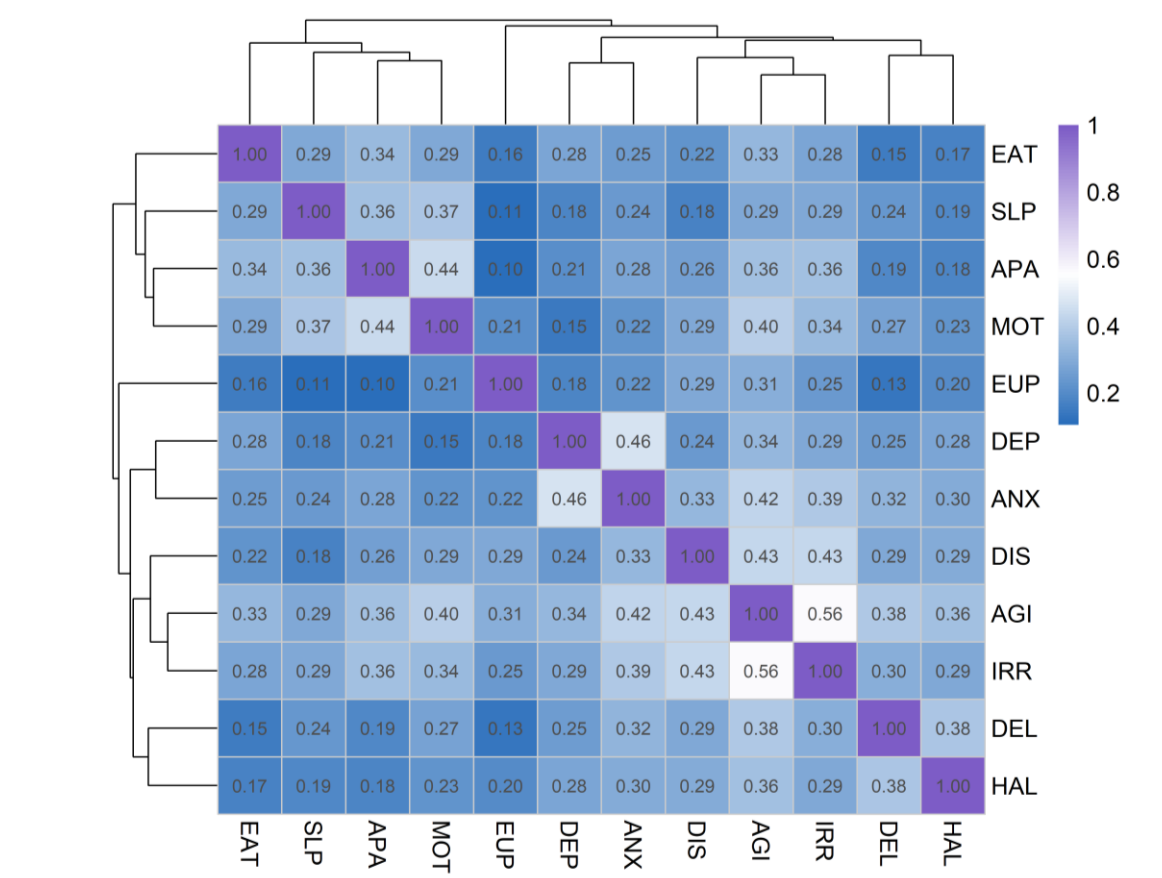


Figure 3. Spearman correlation matrix of NPI domains. Higher values indicate greater symptom co-occurrence. Hierarchical clustering groups symptoms with similar co-occurrence patterns.

RESULTS

MIXED NEUROPATHOLOGY ASSOCIATED WITH BOTH INCREASED LIKELIHOOD OF NEUROPSYCHIATRIC SYMPTOMS AND GREATER SYMPTOM SEVERITY

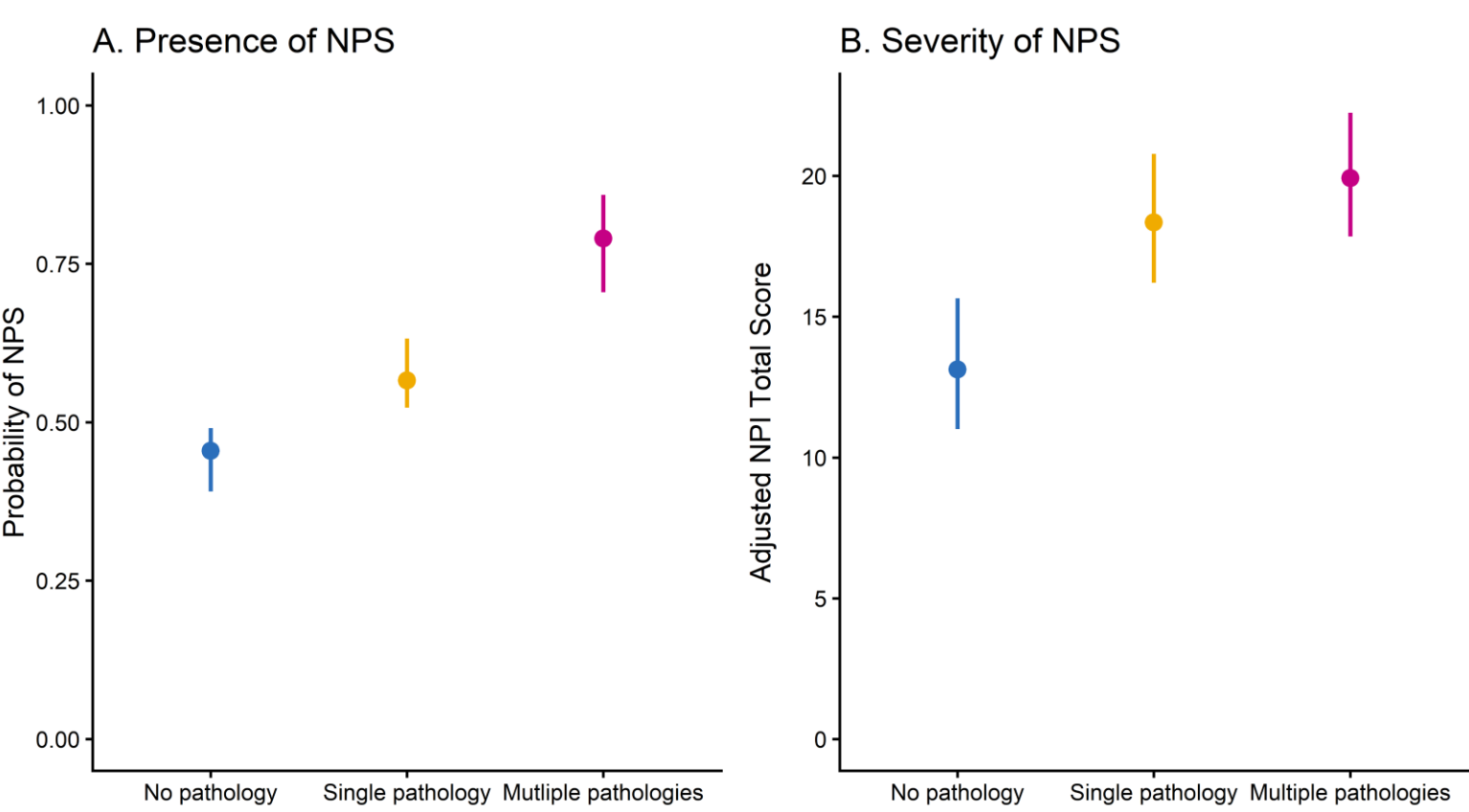


Figure 4. Hurdle model estimates of neuropsychiatric symptom (NPS) presence (A) and severity (B) by neuropathology group. Points represent adjusted model estimates and error bars indicate 95% confidence intervals. Models were adjusted for time-to-death, age at death, and sex.

PREVALENCE OF NPS INCREASED WITH PROXIMITY TO DEATH WITH PERSISTENT DIFFERENCES IN SYMPTOM BURDEN ACROSS NEUROPATHOLOGY GROUPS

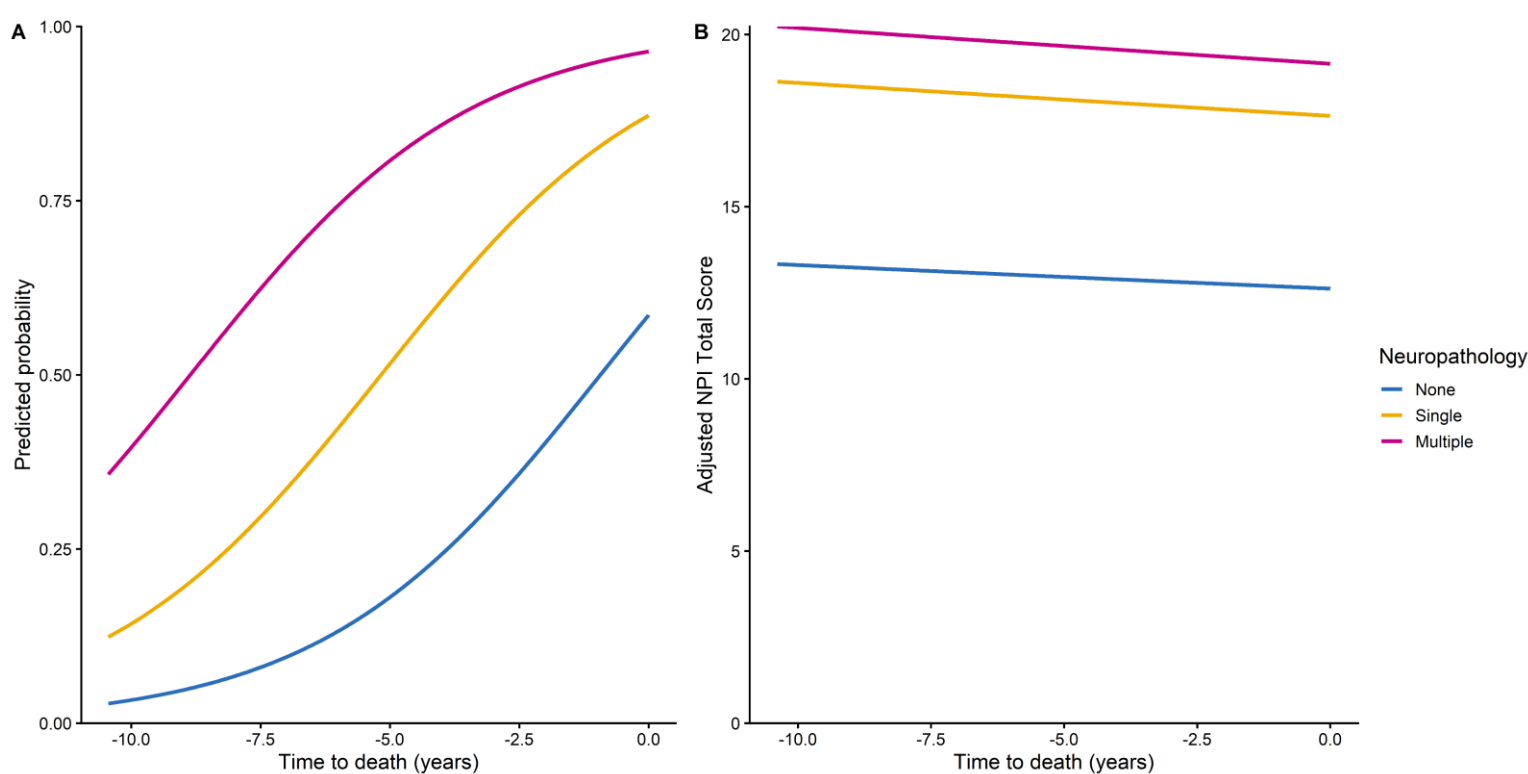


Figure 5. Hurdle model predictions of NPS presence (A) and severity (B) by neuropathology group across the 10 years preceding death, Estimates were adjusted for age at death and sex.

MULTIPLE PATHOLOGY ASSOCIATED WITH GREATER LIKELIHOOD OF SYMPTOMS THAN SINGLE PATHOLOGY ACROSS ALL NPI SUBDOMAINS

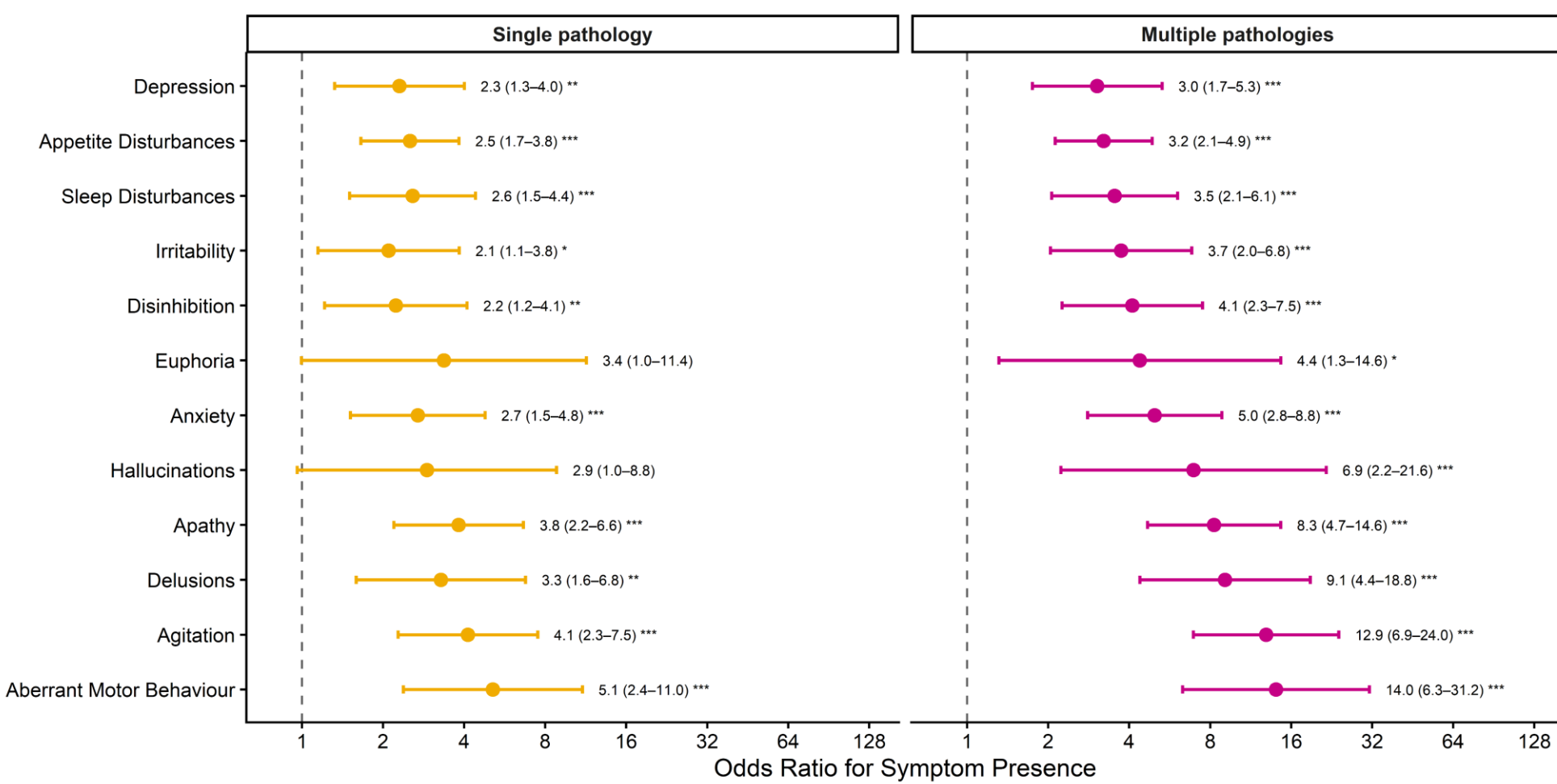


Figure 6. Odds ratios (ORs) and 95% confidence intervals for neuropsychiatric symptom presence from adjusted hurdle models. Estimates compare single or multiple pathologies relative to no significant neuropathologies (comparison group). * P < 0.05, ** P < 0.01, *** P < 0.001. Pathology group had no significant effect on symptom severity in any NPI subdomain (figure not included).

CONCLUSIONS

- Mixed neuropathology increases likelihood of neuropsychiatric symptoms - effects were observed across all NPI domains
- Mixed pathology had stronger effects on symptom presence than severity
- Findings suggest that mixed pathology contributes to the development of neuropsychiatric symptoms
- Symptom severity may be associated with specific pathology combinations
- Future work will identify latent neuropsychiatric symptom profiles and examine their neuropathological correlates