

Neuroticism is linked to cognitive decline and increased risk of Alzheimer’s disease through dysregulation of excitatory neurons

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Background

- Neuroticism, a personality trait characterized by sensitivity to stress, is associated with an increased risk of developing Alzheimer’s disease (AD).
- The molecular mechanisms underlying this association remain largely unknown.

What molecular mechanisms mediate the association between neuroticism and AD?

Methods

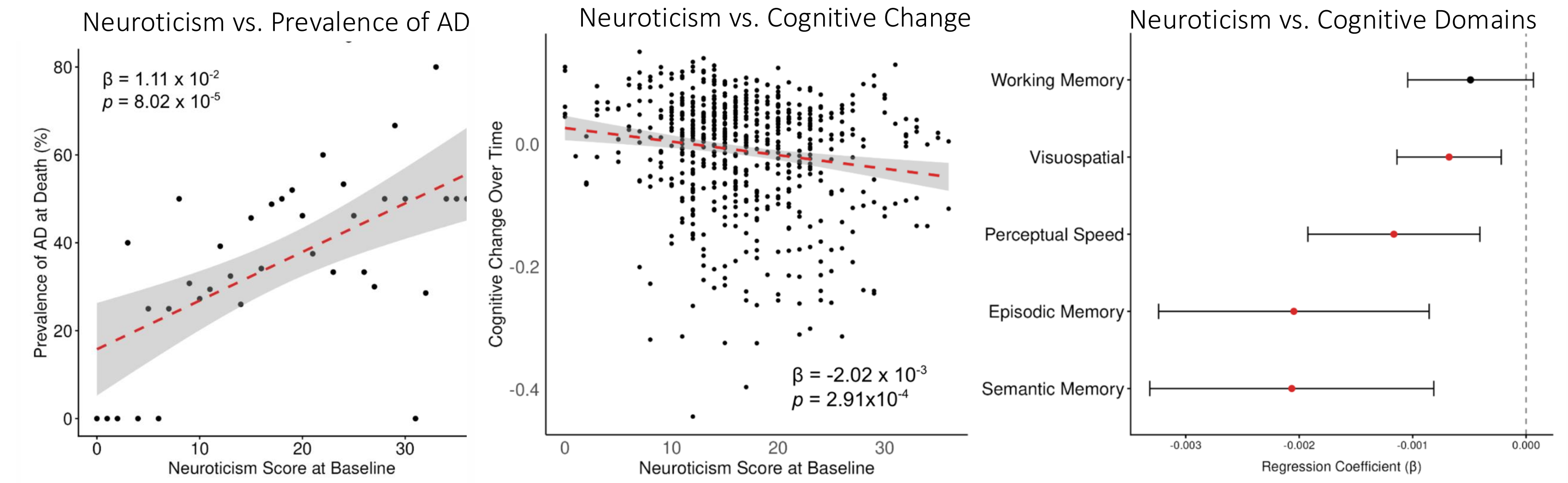
- Data were sourced from ROSMAP: a longitudinal cohort study of cognitive aging.
- Single-nucleus RNA-sequencing data derived from the dorsolateral prefrontal cortex (three subgroups, total n = 655) were analyzed to identify differentially expressed genes in neuroticism.
- A two-stage analysis was conducted to capture genes reproducibly associated with neuroticism across subgroups.
- Mediation modeling was done to assess the influence of transcriptomic changes on the relationship between neuroticism and AD.

Table 1. ROSMAP Participant Characteristics			
Characteristic	CUIMC1 N = 371 ¹	CUIMC2 N = 172 ¹	MIT N = 112 ¹
Neuroticism Score	16 (7)	17 (6)	17 (6)
Cognitive Diagnosis			
No/Mild CI	225 (61%)	94 (55%)	73 (65%)
AD	135 (36%)	76 (44%)	39 (35%)
Non-AD Dementia	11 (3.0%)	2 (1.2%)	0 (0%)
TAU pathology ²	2.12 (1.30)	2.28 (1.17)	1.92 (1.45)
Aβ pathology ²	1.70 (1.19)	1.81 (1.05)	1.29 (1.22)
Race			
Black	0 (0%)	0 (0%)	2 (1.8%)
White	371 (100%)	172 (100%)	110 (98%)
Sex			
Female	255 (69%)	105 (61%)	56 (50%)
Male	116 (31%)	67 (39%)	56 (50%)
Education (years)	16.6 (3.4)	16.9 (3.6)	17.5 (3.6)
Age at Death (years)	89 (7)	90 (7)	86 (6)
PMI (hours)	7.7 (5.2)	8.4 (5.5)	8.3 (8.9)

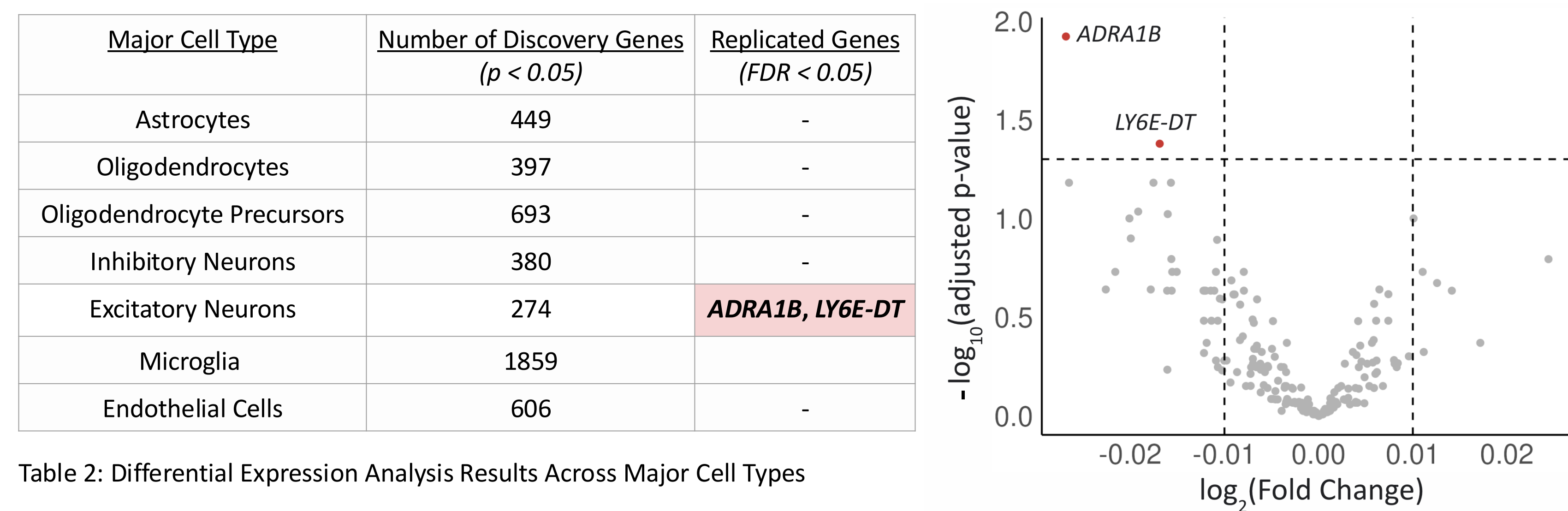
¹ Mean (SD); n (%)
² Square-root transformed

Results

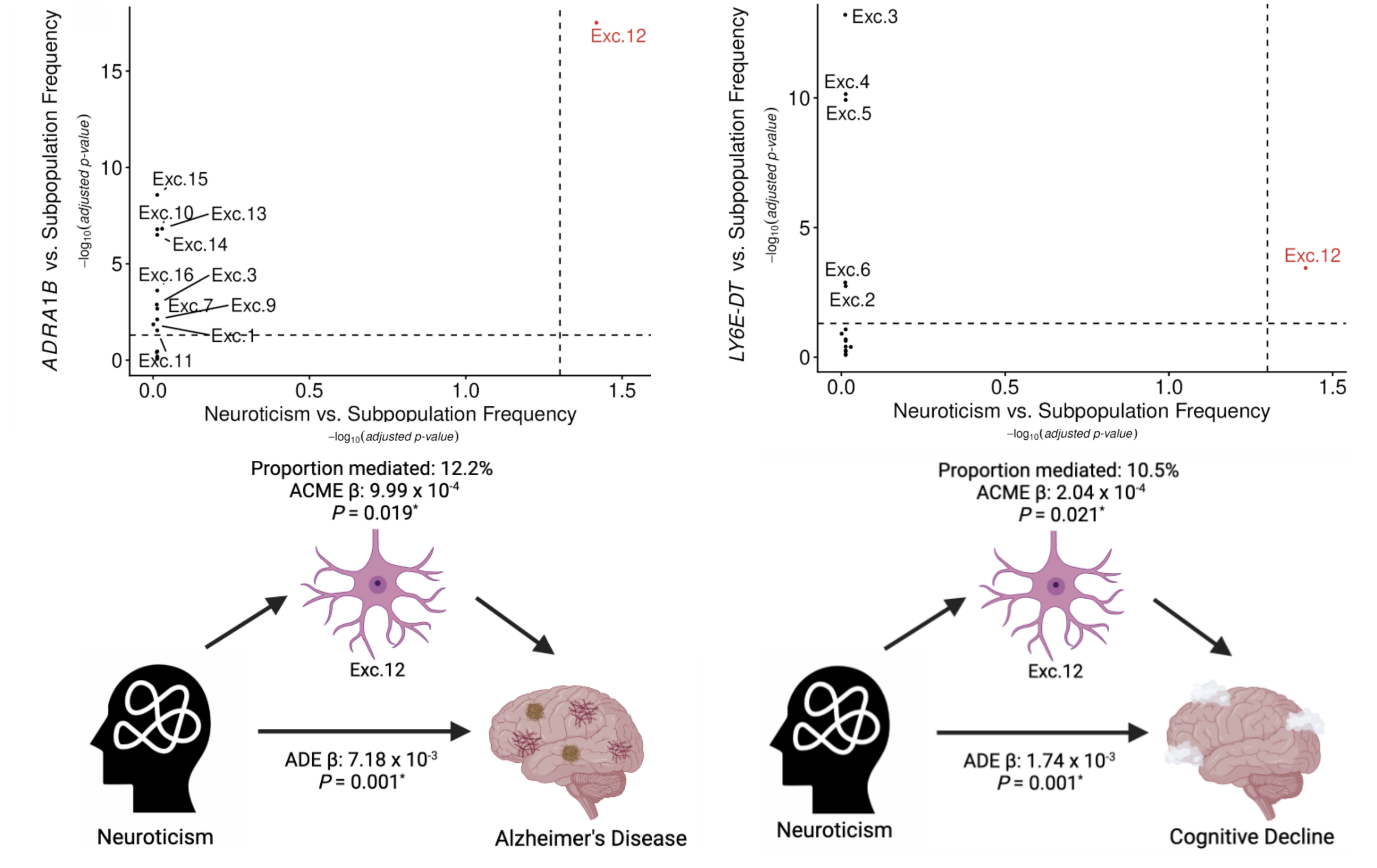
Neuroticism is significantly associated with cognitive decline and AD, independent of amyloid or tau pathology



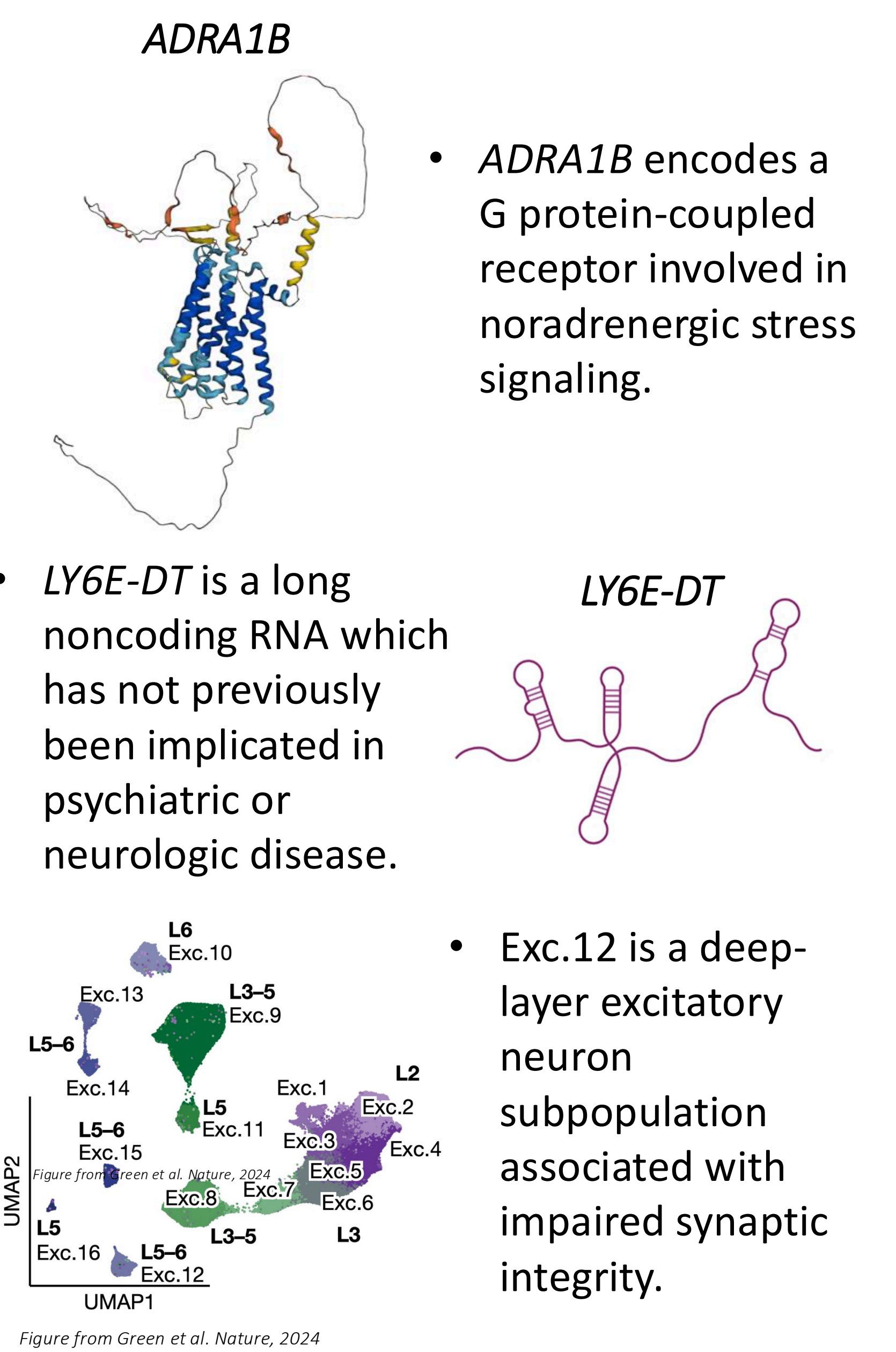
ADRA1B and LY6E-DT expression is downregulated in excitatory neurons of individuals with elevated neuroticism



The Exc.12 excitatory neuron subpopulation mediates the association between neuroticism and AD



ADRA1B, LY6E-DT, & Exc.12



Conclusion

- Neuroticism is linked to cognitive decline and an increased risk of AD, even after adjusting for the effect of Aβ and tau proteinopathy.
- Neuroticism is associated with the downregulation of two genes, ADRA1B and LY6E-DT, in excitatory neurons.
- Neuroticism is correlated with enrichment of a specific subpopulation of excitatory neurons: Exc.12.
- Exc.12 is a deep-layer excitatory neuron subpopulation found to mediate 12.2% of the association between neuroticism and AD.

Acknowledgements

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