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# Disentangling Heterogeneity in Grey Matter Alterations in Multiple Sclerosis Using Generative Normative Modelling


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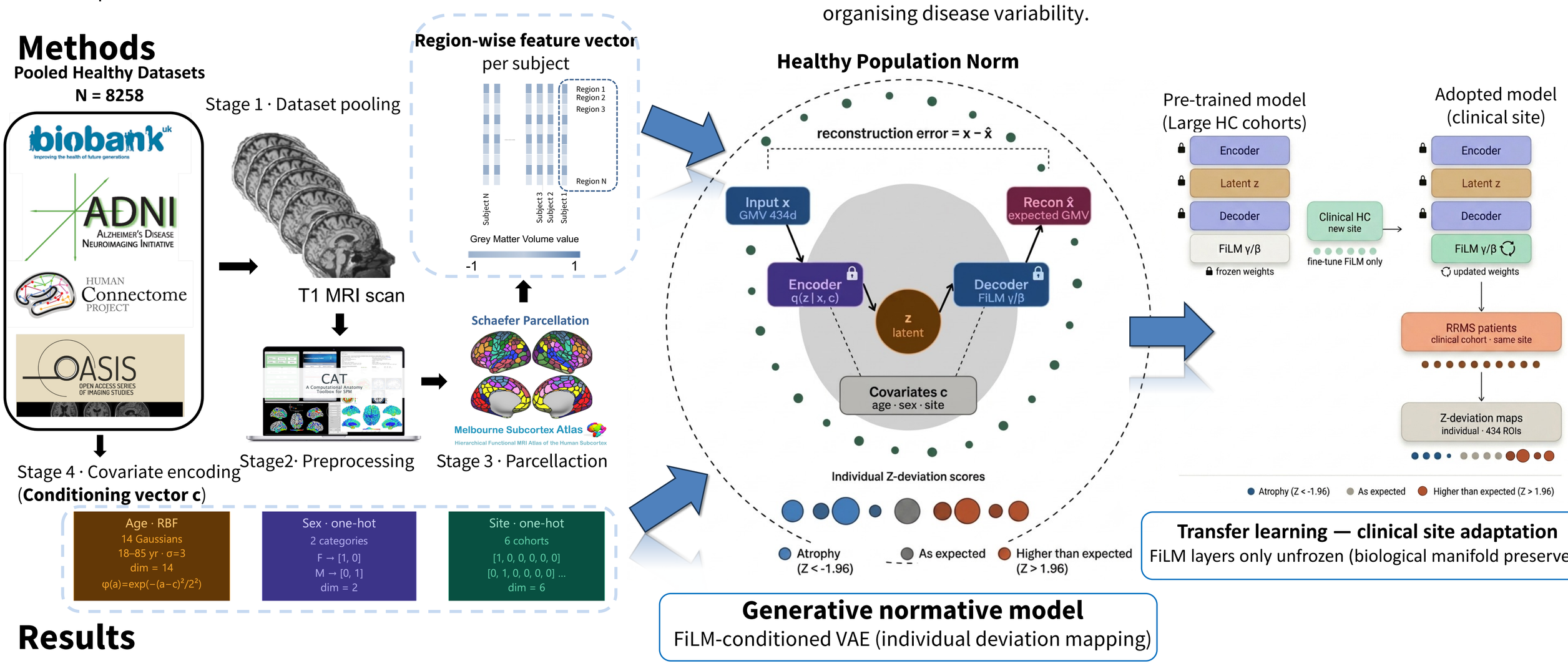
## Introduction

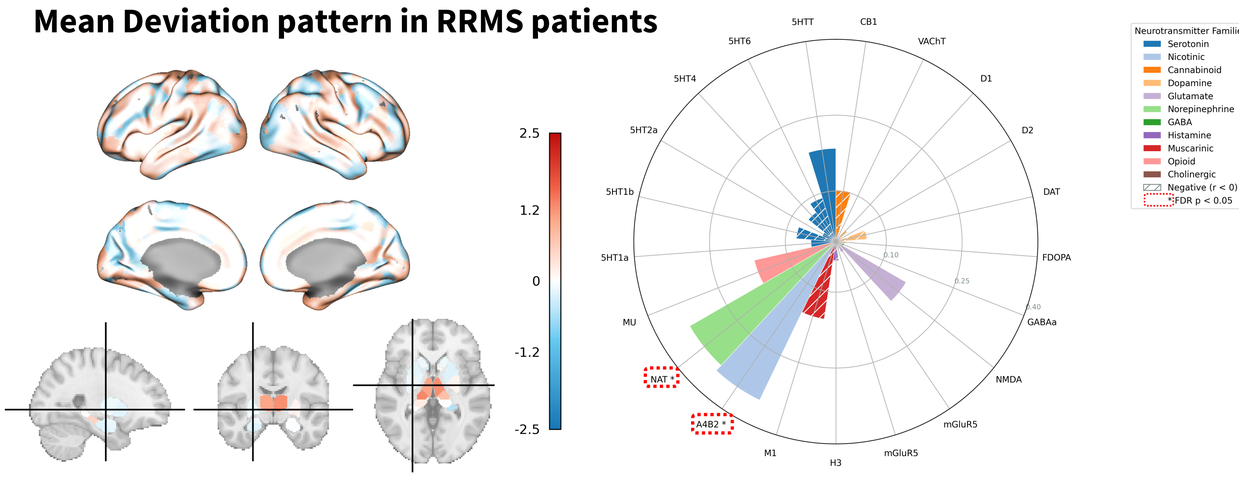
- Relapsing-remitting MS (RRMS) patients sharing the same diagnosis differ substantially in disability, cognition, and patterns of brain alterations— yet the biological basis of this heterogeneity remains poorly understood.
- By providing a brain alteration pattern at the individual level, normative modelling enables new insight into the spectrum of brain heterogeneity among RRMS patients.
- Axes of heterogeneity can be further characterized by diffusion embedding decomposition.
- Here, we derived individual Grey matter volume (GMV) deviation maps across 434 regions in 200 RRMS patients using a **Feature-wise Linear Modulation (FiLM)-conditioned Variational Autoencoder (VAE)**, applied diffusion embedding to recover continuous axes of neuroanatomical heterogeneity, and anchored these axes in neurotransmitter receptor maps to reveal the neurochemical systems organising disease variability.

## Methods

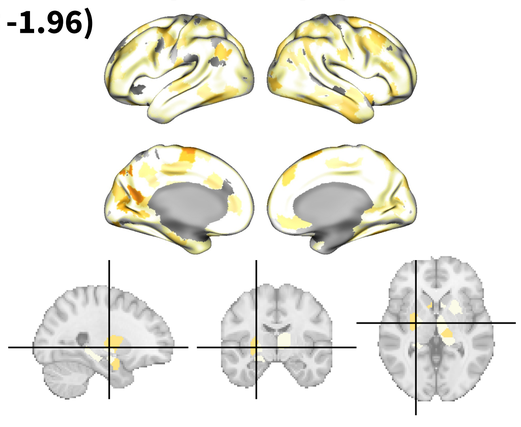



## Results

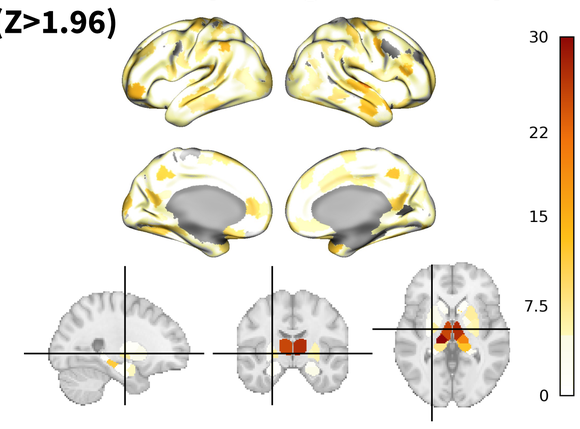
### Mean Deviation pattern in RRMS patients




### Prevelance map of atrophy (Z< -1.96)



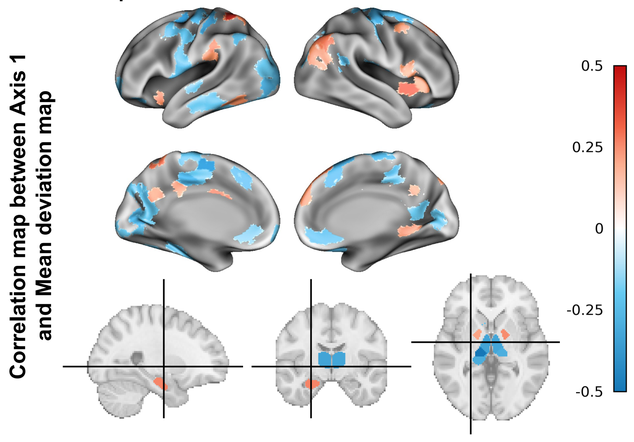
### Prevelance map of higher than expected (Z>1.96)

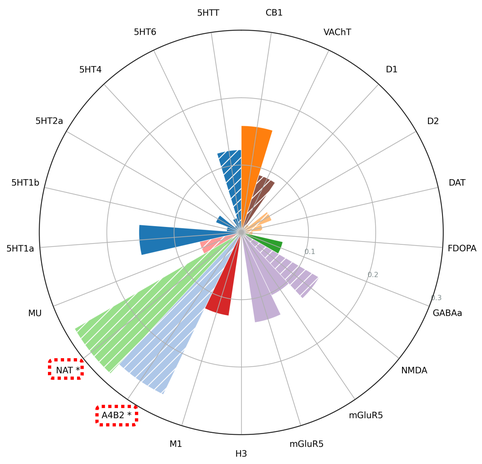



**Diffusion embedding** reveals the main axes of neuroanatomical heterogeneity underlying the **continuous disease manifold.**

### First Axis: Disease Severity Gradient

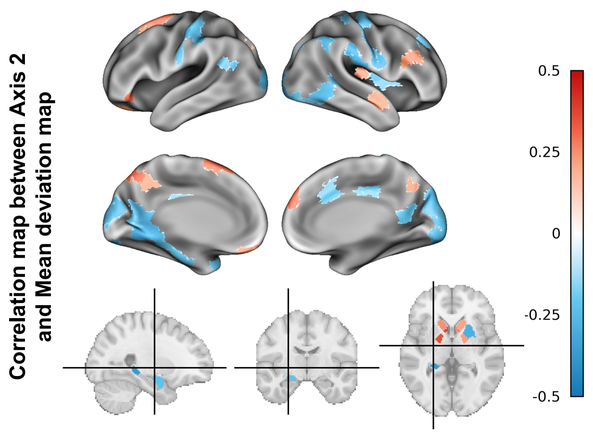
Axis 1 negatively correlates with both disease severity (EDSS) & duration in RRMS patients.

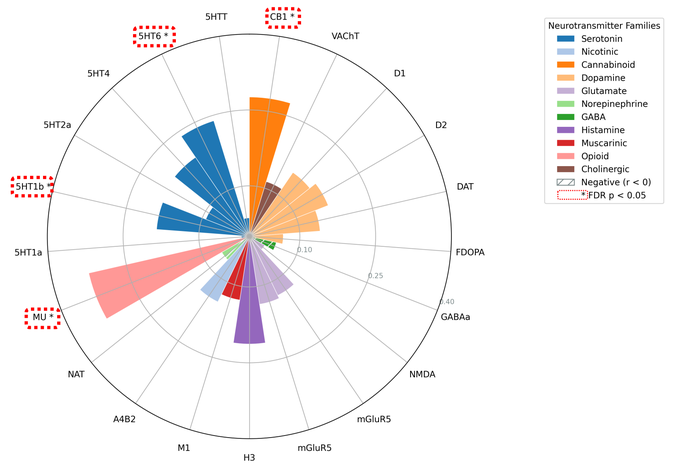



### Second Axis: Severity-Independent Individual Differences

In contrast, Axis 2 is orthogonal to both disease severity (EDSS) and duration.




## Main Findings & Discussion

- Generative normative modelling reveals heterogeneity in RRMS patients beyond typical thalamic atrophy.
- Although thalamic atrophy can be observed in many patients, normative modelling further shows higher than expected thalamic volume in a substantial number of patients.
- While a first axis of heterogeneity is characterized by alterations in thalamo-sensorimotor regions associated with disease severity and duration, a second axis of heterogeneity is characterized by alterations in limbic regions engaging mood and pain modulation systems.
- Future studies should further investigate thalamic alterations beyond typical atrophic patterns in RRMS and can capitalize on generative normative modelling to better understand clinical variability for the development of personalized approaches.




**Reference:** [1] Reich, Lucchinetti & Calabresi, 2018, NEJM, [2] Thompson et al., 2018, The Lancet, [3] Lublin, 2014, Neurology, [4] Bethlehem et al., 2022, Nature, [5] Coifman & Lafon, 2006.



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