

BACKGROUND

Frontotemporal dementia (FTD) is an umbrella term that encompasses several clinical syndromes with impaired behavioral, language, and motor functions. These syndromes show considerable overlap in clinical features and imaging patterns. Therefore, there is a need to investigate the syndromic heterogeneity in FTD using unbiased data-driven approaches.

OBJECTIVES

To determine whether structural magnetic resonance imaging (MRI) based clusters would capture the FTD clinical syndromes and determine how these clusters relate to clinical characteristics.

METHODS

- ❖ We used data-driven clustering analysis of structural MRI data on **400 patients with clinical FTD diagnoses** (behavioral variant of frontotemporal dementia (**bvFTD**), semantic variant of primary progressive aphasia (**svPPA**), right temporal variant of frontotemporal dementia (**rtvFTD**), apraxia of speech with agrammatic aphasia (**AOS-PAA**), primary progressive apraxia of speech (**PPAOS**), progressive supranuclear palsy (**PSP**), corticobasal syndrome (**CBS**) and primary progressive aphasia who did not fit into the other diagnostic categories (**PPA-other**)).
- ❖ MR images were w-scored relative to cognitively unimpaired individuals, and principal component analysis was performed.
- ❖ A clustering ensemble approach, including hierarchical algorithms, was applied to the MR-based principal components, and imaging and clinical characteristics of the clusters were investigated. Various numbers of clusters (K=2, 3, or 4) were evaluated.

RESULTS

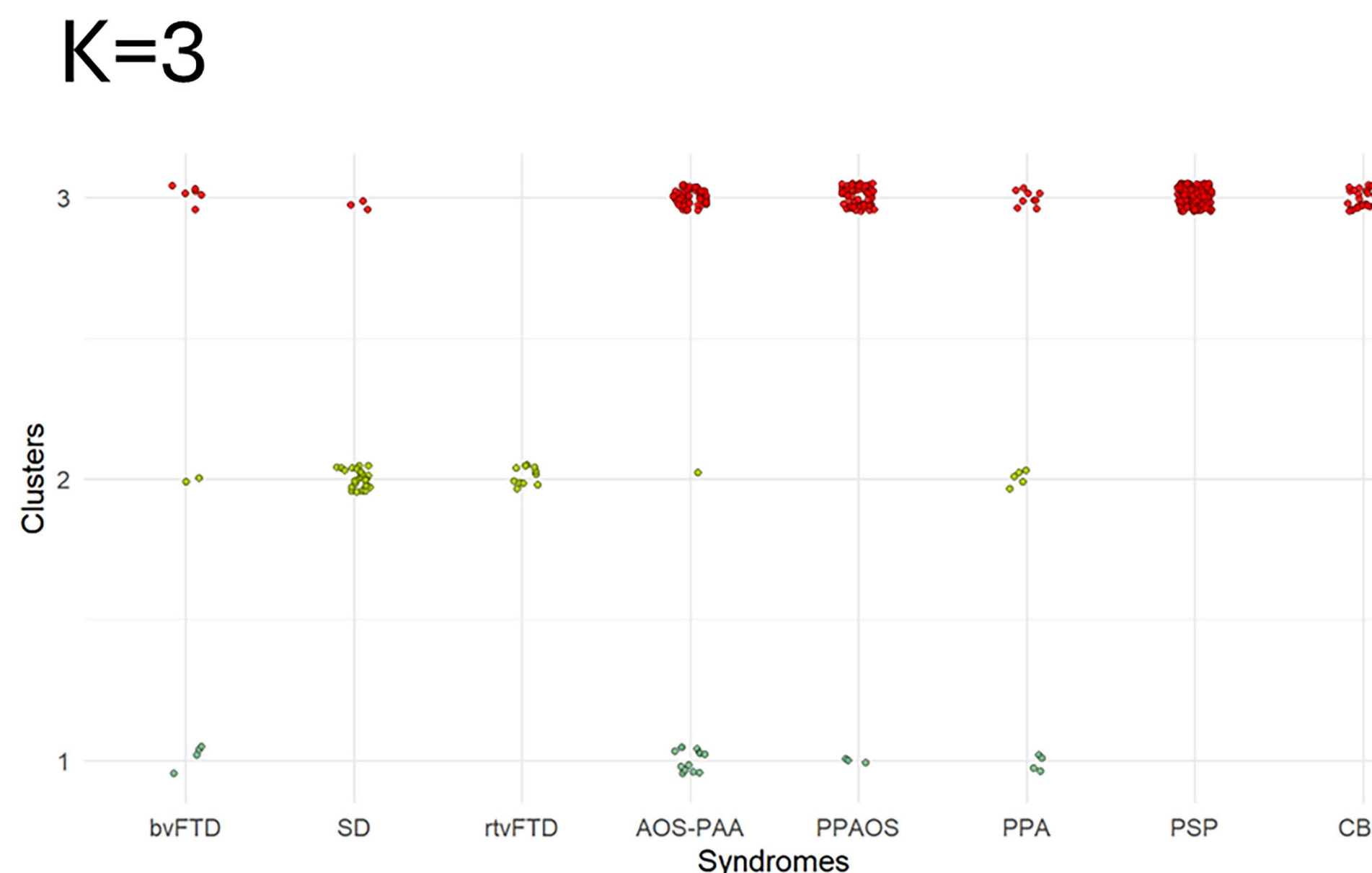


Figure 1: Syndrome distribution within each cluster (K=3). Each one of the 400 patients was assigned to one of the three clusters. Cluster 1 included bvFTD, PPAOS, AOS-PAA and PPA patients. Cluster 2 included bvFTD, SD, rtvFTD, AOS-PAA and PPA patients. Cluster 3 included patients of all syndromes except rtvFTD.

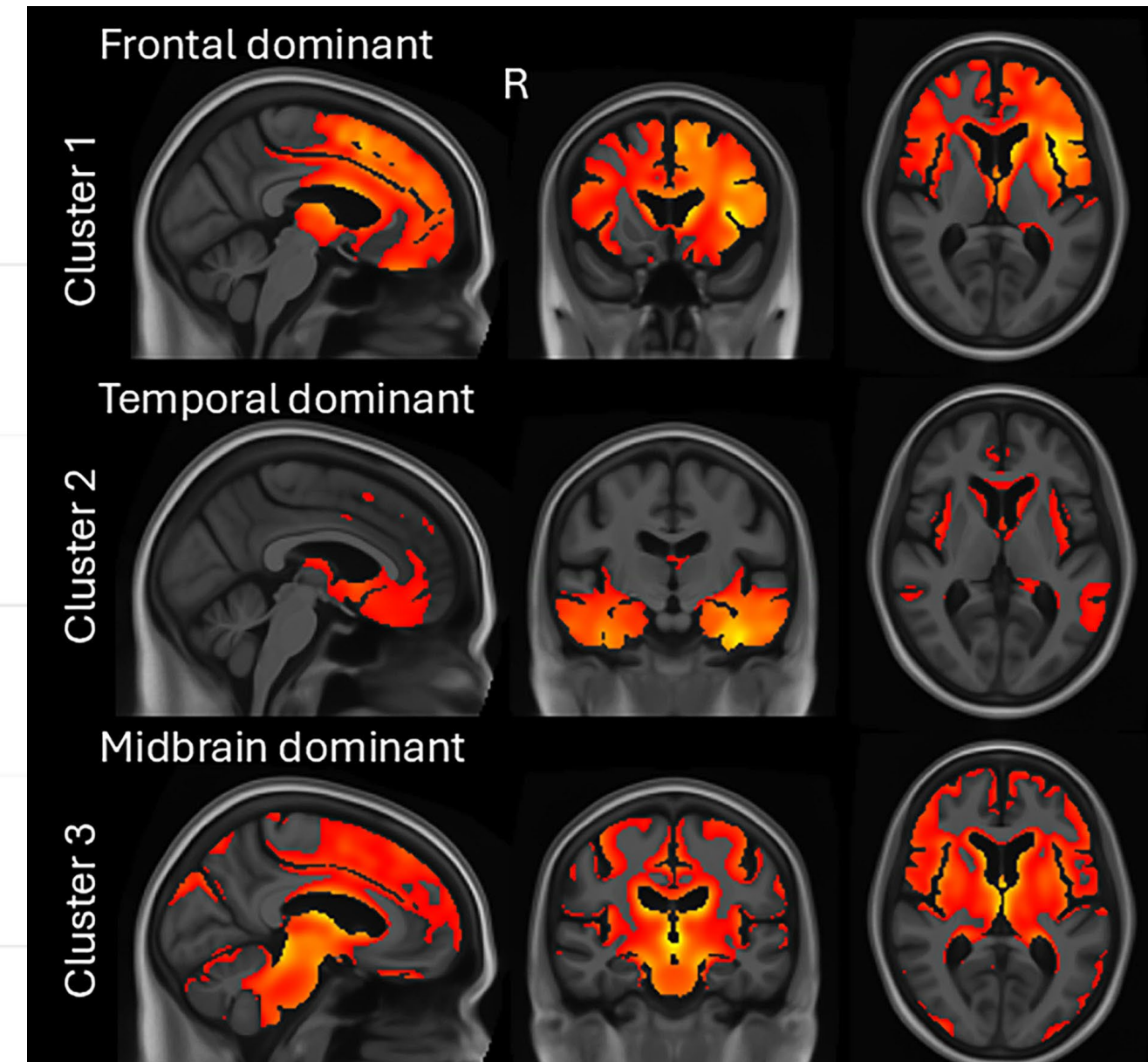


Figure 2: Atrophy patterns in each cluster. SPM maps of atrophy (gray and white matter segmentation) in each cluster relative to cognitively unimpaired individuals, at p<0.05 with FWE correction covarying for age, sex and scanner manufacturer.

The K=3 solution offered the most clinically meaningful separation of FTD syndromes (**Figure 1**). The first cluster captured mostly frontal MRI abnormalities related to the speech, language and behavioral clinical dimensions, including patients with AOS-PAA, PPAOS, PPA-other, and bvFTD (**Figure 2 and 3**). The second cluster captured mostly temporal abnormalities and included mainly patients with svPPA and rtvFTD, but also bvFTD, AOS-PAA and PPA-other (**Figure 2 and 3**). The third cluster captured cortical and subcortical

atrophy, particularly in the midbrain, and included atypical Parkinsonian syndromes, with all PSP and CBS patients captured in this cluster, as well as most PPAOS patients (**Figure 2 and 3**). Considerable overlap of clinical syndromes was noted across these clusters, whereby patients with AOS-PAA, svPPA, PPA-other, and bvFTD were captured in more than one cluster (**Figure 4**).

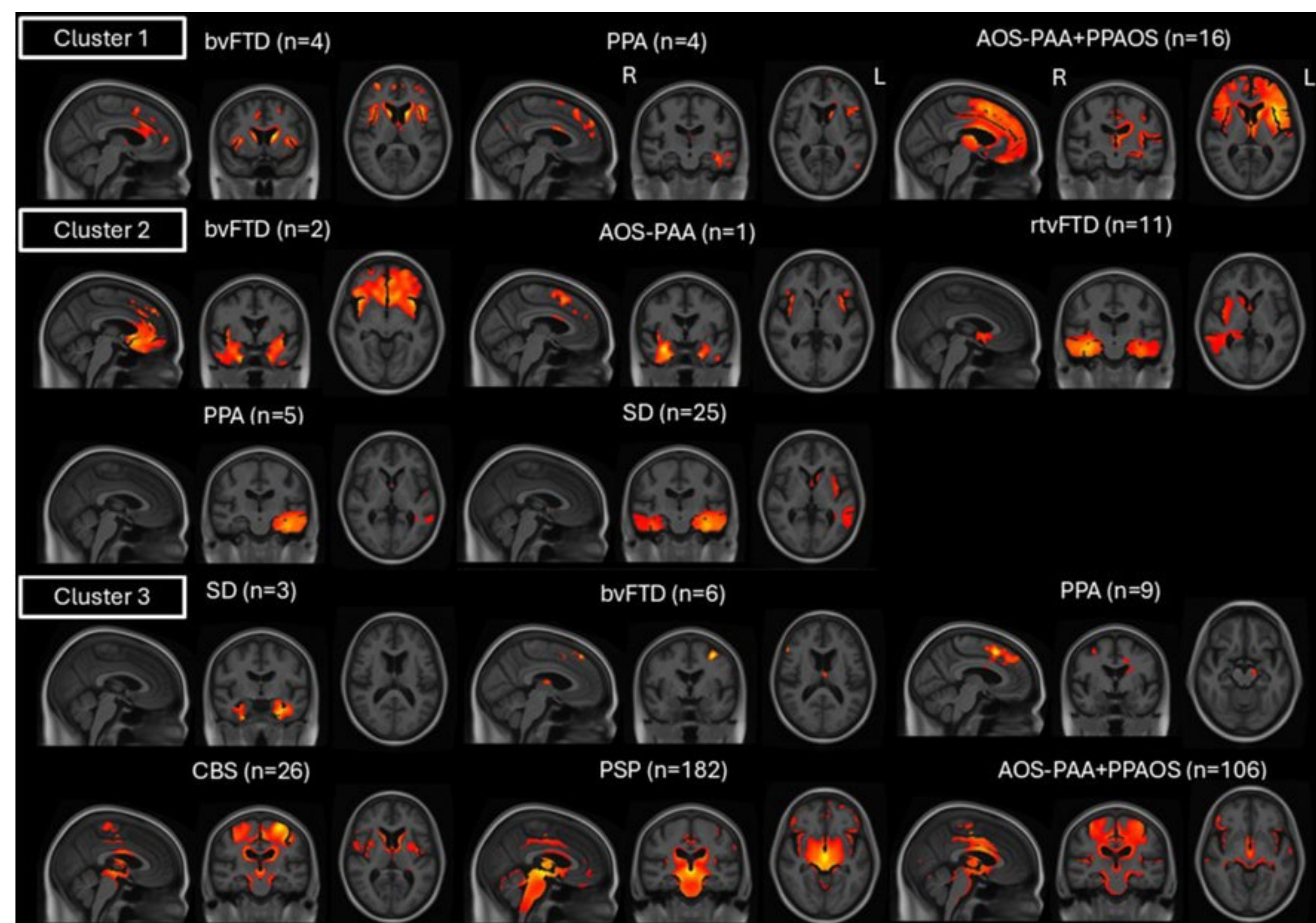


Figure 3: Atrophy patterns of each syndrome within a cluster. SPM maps of atrophy (gray and white matter segmentation) in each syndrome in cluster 1 (A), cluster 2 (B), and cluster 3 (C) relative to cognitively unimpaired individuals, at p<0.05 with FWE correction covarying for age, sex and scanner manufacturer. AOS-PAA and PPAOS were combined in the same group.

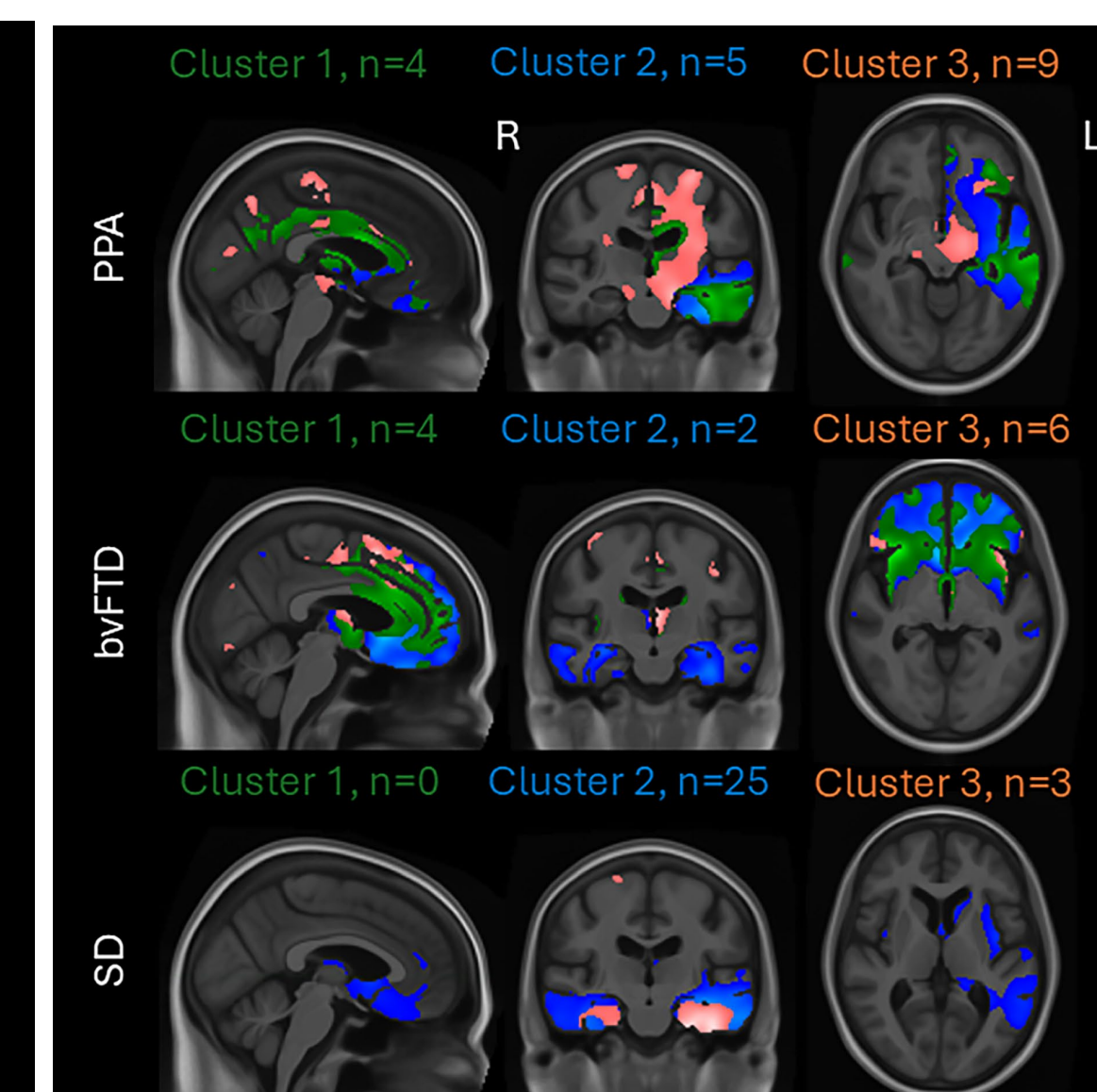


Figure 4: Atrophy patterns of PPA, SD and bvFTD assigned to multiple clusters. SPM maps of atrophy (gray and white matter segmentation) in PPA (top row), bvFTD (middle row), and SD (bottom row) relative to cognitively unimpaired individuals shown at p<0.001 without correcting for multiple comparisons, covarying for age, sex and scanner manufacturer. For each clinical diagnosis, the SPM maps of the patients in cluster 1, 2 and 3 are in green, blue and pink, respectively. The use of a more relaxed threshold helps capture the different atrophic patterns of patients with the same clinical diagnosis but assigned to different clusters.

CONCLUSIONS

Our findings highlight heterogeneity in FTD, which mainly exists along three axes: speech, language and behavioral deficits reflecting frontal atrophy, language deficits reflecting temporal atrophy, and motor and motor speech deficits reflecting mostly midbrain and subcortical atrophy, with cortical involvement.