

Multidomain Neuropsychological Profiles Reveal Cognitive-Functional Subtypes of Long-COVID by PCA and Cluster Analysis

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TAKE HOME-MESSAGE: Higher educational attainment may protect against severe cognitive-functional impairment in Long-COVID, supporting the role of cognitive reserve.

Introduction

Cognitive dysfunction is a frequent and disabling sequela of Long-COVID, affecting memory, executive functions, and daily functioning. Cognitive reserve, indexed by educational attainment, may modulate vulnerability and resilience to post-infectious brain dysfunction. However, the multidomain organization of cognitive, functional, and affective alterations and their clustering into clinically meaningful subtypes remain poorly characterized. Using data-driven multivariate methods, we applied principal component analysis (PCA) and unsupervised clustering to identify latent neuropsychological dimensions and clinical subtypes of Long-COVID and to examine the role of education as a proxy of cognitive reserve.

Methods

We studied 114 individuals aged ≥ 50 years from Porto Alegre, Brazil: Long-COVID with high education ($n = 30$), Long-COVID with low education ($n = 30$), controls with high education ($n = 27$), and controls with low education ($n = 27$). Participants underwent neuropsychological assessment of global cognition (MMSE), episodic and logical memory (RAVLT; WMS-R), executive and visuospatial functions (TMT-B; Clock Drawing), functional status (CDR; CDR-Sum of Boxes), and affective symptoms (PHQ-9; GAD-7). Measures were entered at the subtest and trial level, z-standardized, and submitted to PCA; component scores were used in k-means clustering.

Conclusions

Long-COVID in later adulthood is characterized by multidomain neuropsychological subtypes, ranging from preserved profiles associated with higher educational attainment to severe cognitive-functional impairment in individuals with lower education, with an intermediate affective-executive modulation subtype. These findings highlight the role of cognitive reserve in shaping post-COVID cognitive trajectories.

Results

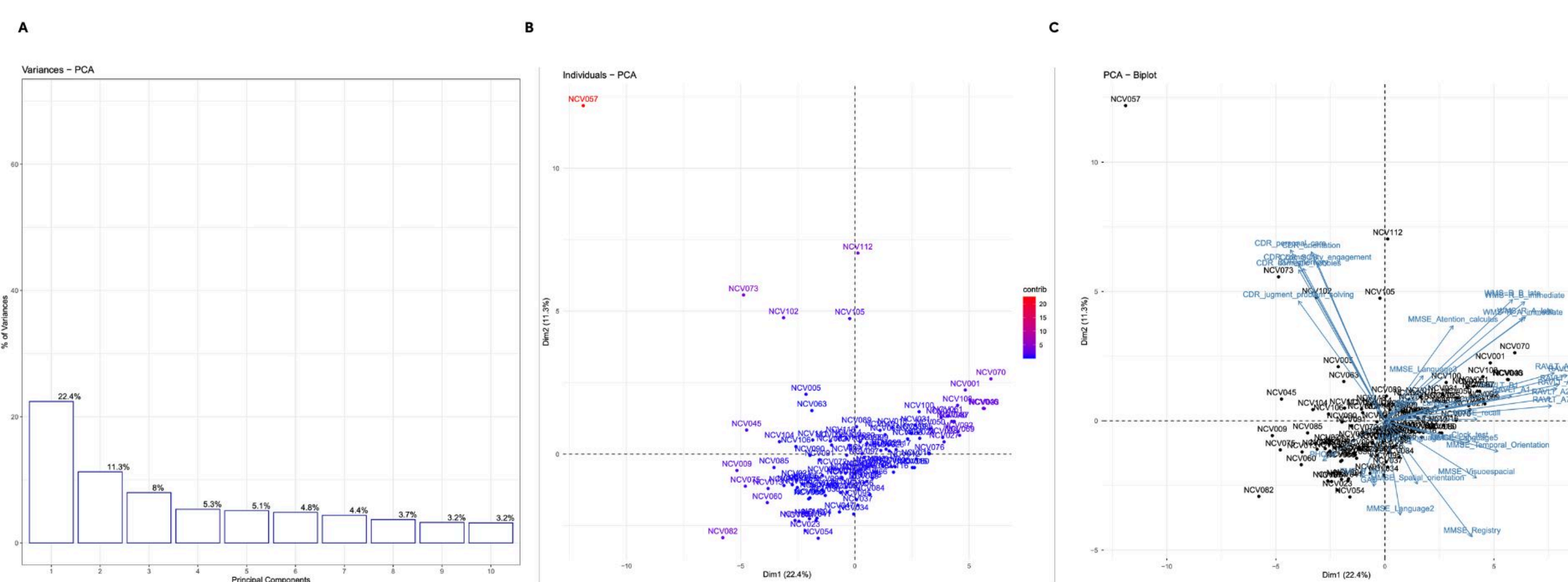


Figure 1. Latent multidomain structure of cognitive and functional measures derived from principal component analysis

(A) Scree plot showing the proportion of variance explained by each principal component.
(B) PCA individual factor map (PC1 x PC2) illustrating the distribution of participants in the cognitive-functional space.
(C) PCA variable factor map (PC1 x PC2) showing the loadings of neuropsychological measures, with PC1 reflecting overall cognitive efficiency (episodic memory, global cognition, executive-visuospatial functions) and PC2 reflecting functional integrity (CDR domains and CDR-Sum of Boxes).

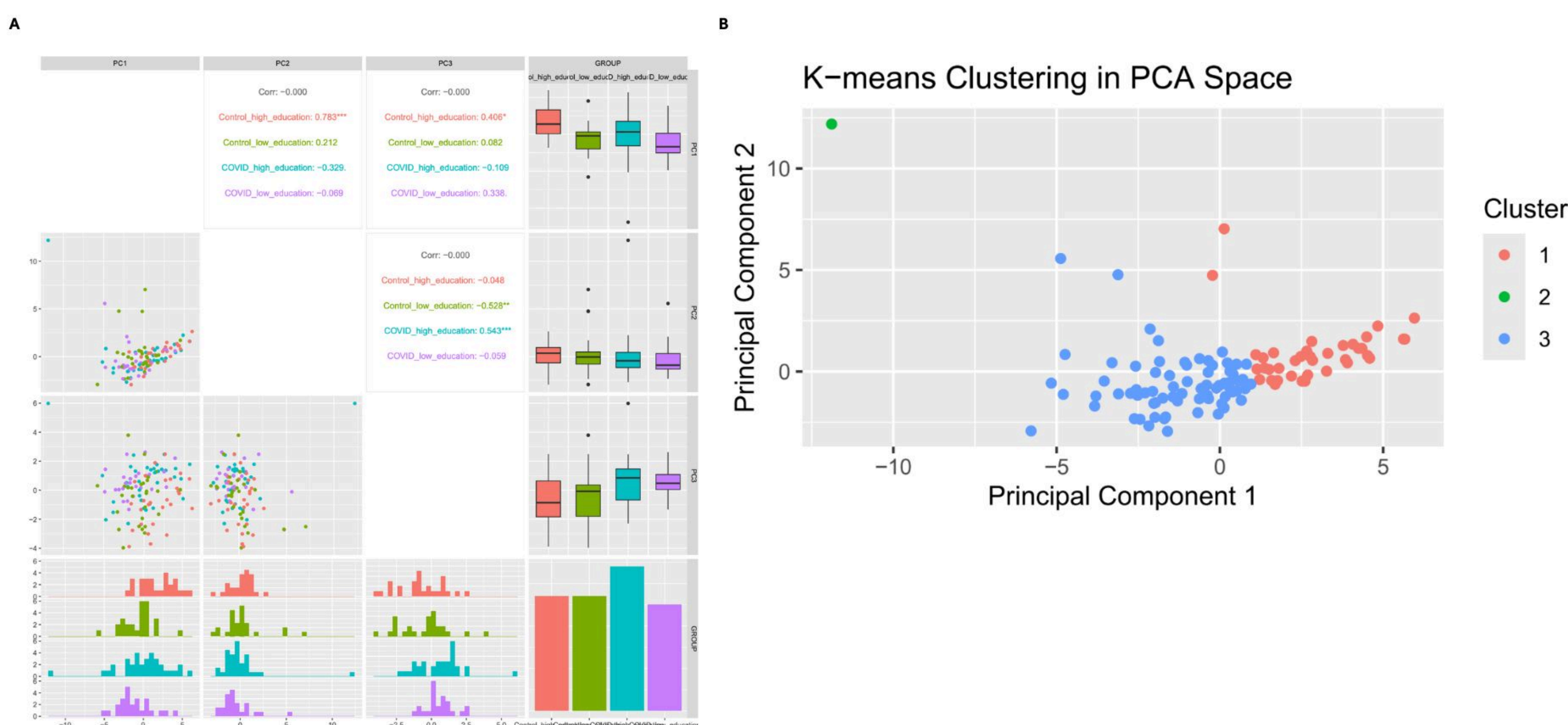


Figure 2. Distribution of participants and clinical subtypes in the PCA space

(A) Projection of individuals according to diagnostic group and educational level, showing a modulatory effect of cognitive reserve.
(B) K-means clustering in the PCA space identifying three neuropsychological subtypes: a preserved cognitive-functional profile, an affective-executive modulation profile, and a multidomain cognitive-functional impairment profile.

PCA identified three components explaining 41.7% of the variance (Fig. 1A). PC1 (22.4%) reflected overall cognitive efficiency (episodic memory, global cognition, executive-visuospatial functions), PC2 (11.3%) functional integrity (CDR domains), and PC3 (8.0%) affective modulation of executive performance (Fig. 1B-C). Projection by diagnostic group and educational level showed a modulatory effect of cognitive reserve (Fig. 2A). K-means clustering revealed three neuropsychological subtypes (Fig. 2B): a preserved cognitive-functional profile enriched in highly educated controls and Long-COVID individuals; a subtype characterized by affective modulation of executive performance; and a multidomain cognitive-functional impairment profile composed of low-education Long-COVID participants. Subtype stability is shown in pairwise PCA projections (Fig. 3A), and variable contribution analyses confirmed the meaning of PC1 and PC2 (Fig. 3B).

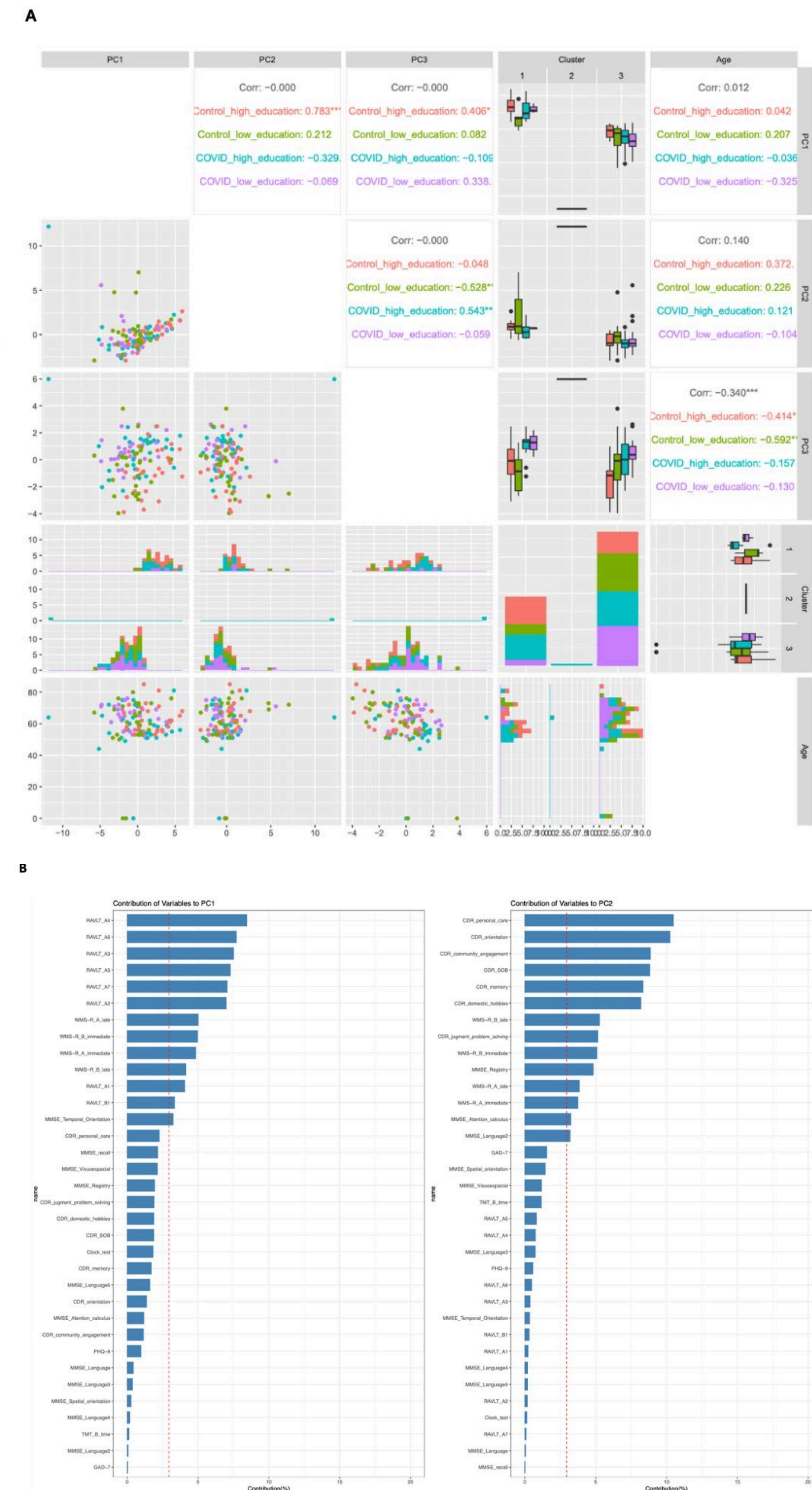


Figure 3. Robustness of neuropsychological subtypes and variable contributions to principal components
(A) Pairwise projections of the first three principal components (PC1 x PC2, PC1 x PC3, and PC2 x PC3) demonstrating the stability and separation of the identified subtypes across multiple component combinations.
(B) Contribution of neuropsychological variables to the principal components, highlighting the dominant role of episodic memory, global cognition, and executive measures in PC1, functional indices (CDR domains and CDR-Sum of Boxes) in PC2, and affective-executive measures in PC3.

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