

The Late Neurodevelopmental History Questionnaire (LNHQ): a new tool to capture neurodevelopmental diversities in individuals with neurodegenerative diseases

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BACKGROUND AND AIMS

Neurodegenerative dementias display striking clinical heterogeneity that cannot be fully explained by pathological differences alone. Even within the same pathological entity, individuals may differ in symptom profile, disease trajectory, and timing of clinical manifestation. Emerging evidence suggests that disease phenotypes reflects the interaction between pathogenic mechanisms and the intrinsic organization of large-scale brain networks. Emerging evidence suggested that neurodevelopmental diversity (NDDs), lifelong expressions of atypical brain network architecture, may predispose to selective vulnerability of specific brain networks to neurodegeneration later in life (Table 1, Fig. 1, Frijo et al. in preparation). However, no validated instruments exist for the retrospective assessment of neurodevelopmental history in older adults to date, and current approaches largely rely on medical or educational records, thereby limiting systematic research in this area. In this study we aim to: 1) develop and validate the LNHQ in neurodegenerative disorders; 2) determine whether specific NDDs increase vulnerability to specific variants of Alzheimer's disease (AD), Frontotemporal Dementia (FTD) or other neurodegenerative dementias.

Table 1	Primary cognitive domain	Neurodegenerative syndrome	Main evidence
Developmental Dyslexia	Reading, phonology, language	Primary Progressive Aphasia (particularly logopenic variant)	Increased prevalence of personal and familial Dyslexia history among PPA patients; earlier disease onset; overlapping perisylvian neuroanatomical substrates
Developmental Language Disorder (DLD)	Spoken language	Primary Progressive Aphasia	Higher frequency of language-development difficulties reported in some PPA cohorts; overlap in left-hemisphere language regions
Developmental Dyscalculia	Numerical and visuospatial processing	Posterior Cortical Atrophy	Increased prevalence of mathematical learning disabilities in PCA compared with typical Alzheimer's disease
Developmental Dysgraphia	Writing and visuomotor integration	Posterior Cortical Atrophy	Increased prevalence of writing-related learning disabilities in PCA
Attention-Deficit/Hyperactivity Disorder (ADHD)	Attention and executive functions	Alzheimer's Disease and Lewy Body Disease	Longitudinal studies report increased dementia risk in adults with ADHD; LBD particularly overrepresented in some cohorts
Autism Spectrum Disorder (ASD)	Social cognition and behaviour	Frontotemporal Dementia spectrum (particularly behavioural presentations)	Epidemiological evidence of increased dementia risk; overlap with phenocopy syndromes resembling behavioral variant FTD
Congenital amusia	Musical and socio-emotional processing	Potential association with frontotemporal phenotypes	Indirect evidence from studies linking musicality, social cognition, and dementia-related behavioral symptoms
Atypical hemispheric lateralization / left-handedness	Brain network organization	Variants of Primary Progressive Aphasia	Genetic and neurodevelopmental studies suggest associations between cortical asymmetry and agrammatic PPA

Table 1. Evidence of association between neurodiversity and neurodegenerative pathologies (Frijo et al. in preparation)

METHODS

Questionnaire development

- We conducted multidisciplinary meetings involving neuropsychologists, speech and language therapists, and neurologists with expertise in both neurodevelopmental conditions and neurodegenerative diseases
- Questionnaire items were generated based on a synthesis of existing literature, clinical questions derived from standardized diagnostic manuals, routinely used paediatric anamnestic questionnaires, and established assessment instruments previously employed in clinical practice.

Validation

- To validate the questionnaire, it will be administered to a cohort of individuals with confirmed neurodevelopmental conditions and to a comparison cohort without such conditions.
- The questionnaire will then be administered to individuals diagnosed with neurodegenerative dementias.

Neuropsychological assessment

- All participants will undergo an extended neuropsychological assessment in conjunction with the administration of the proposed questionnaire.

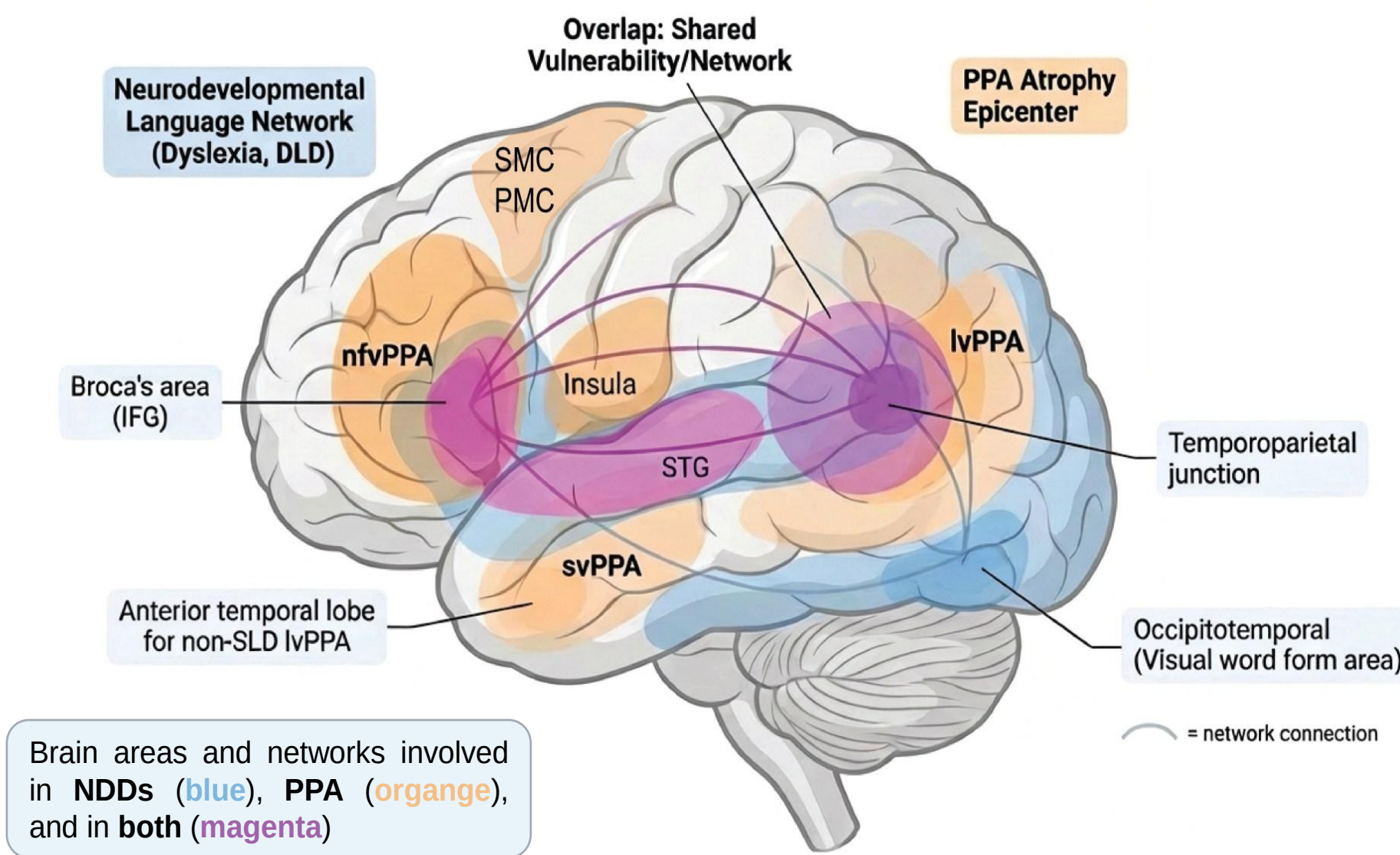


Figure 1. Representation of the overlap between neurodevelopmental language networks and PPA atrophy patterns, suggesting that pre-existing neurodevelopmental differences may contribute to disease-specific imaging phenotypes. Frijo et al. in preparation

CONCLUSIONS

The LNHQ could provide a novel framework for retrospectively examining neurodevelopmentally mediated vulnerability to neurodegeneration. Elucidating how early developmental diversity interacts with lifelong brain organization may offer new insights into disease mechanisms and inform preventive or resilience-oriented strategies aimed at supporting vulnerable neural networks across the lifespan.

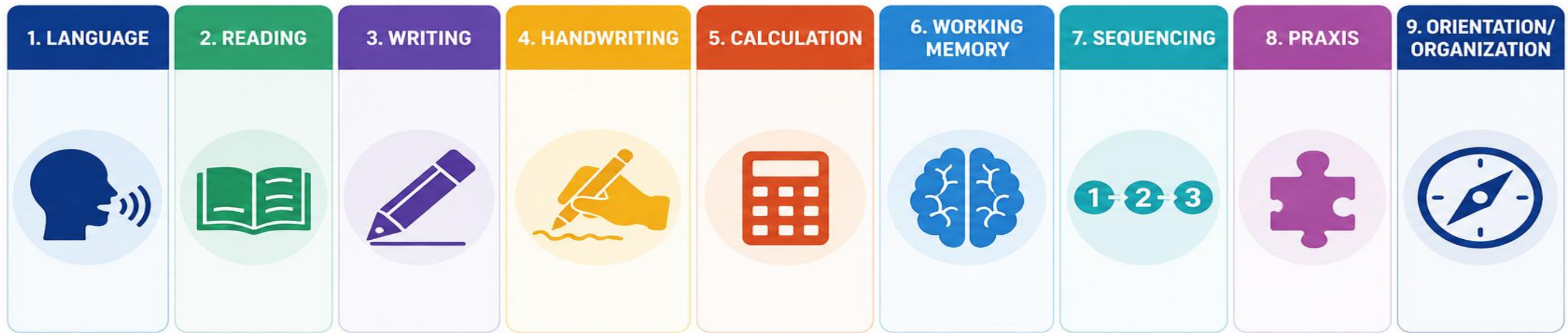
RESULTS

THE LATE NEURODEVELOPMENTAL HISTORY QUESTIONNAIRE

- We introduce the Late Neurodevelopmental History Questionnaire (LNHQ), a 60-item instrument organized across three age bands (preschool, school age, and adulthood).
- It investigates 9 domains of neurodevelopmental and neurocognitive functioning (Fig.2).
- For each item, the questionnaire reports the area evaluated and, in some cases, provides brief examples to support comprehension.
- The LNHQ can be administered by a clinician or self-administered.
- To enhance accessibility for individuals with Primary Progressive Aphasia (PPA), each item includes visual stimuli that support comprehension and response selection.

Figure 2

LNHQ – 9 DOMAINS



Examples of items:

Childhood

- Did you have difficulty learning how to tie your shoelaces? (Dyspraxia, Fig .3.A)
- Did you get confused during games involving numbers or quantities? (Calculation Fig .3.B)

School age

- When you were at school, did you lose your place, skip words, or skip lines while reading? (Reading, fig. Fig .3.C)
- When you were at school, did you sometimes write letters backwards (such as b/d or p/q)? (Handwriting, Fig .3.D)

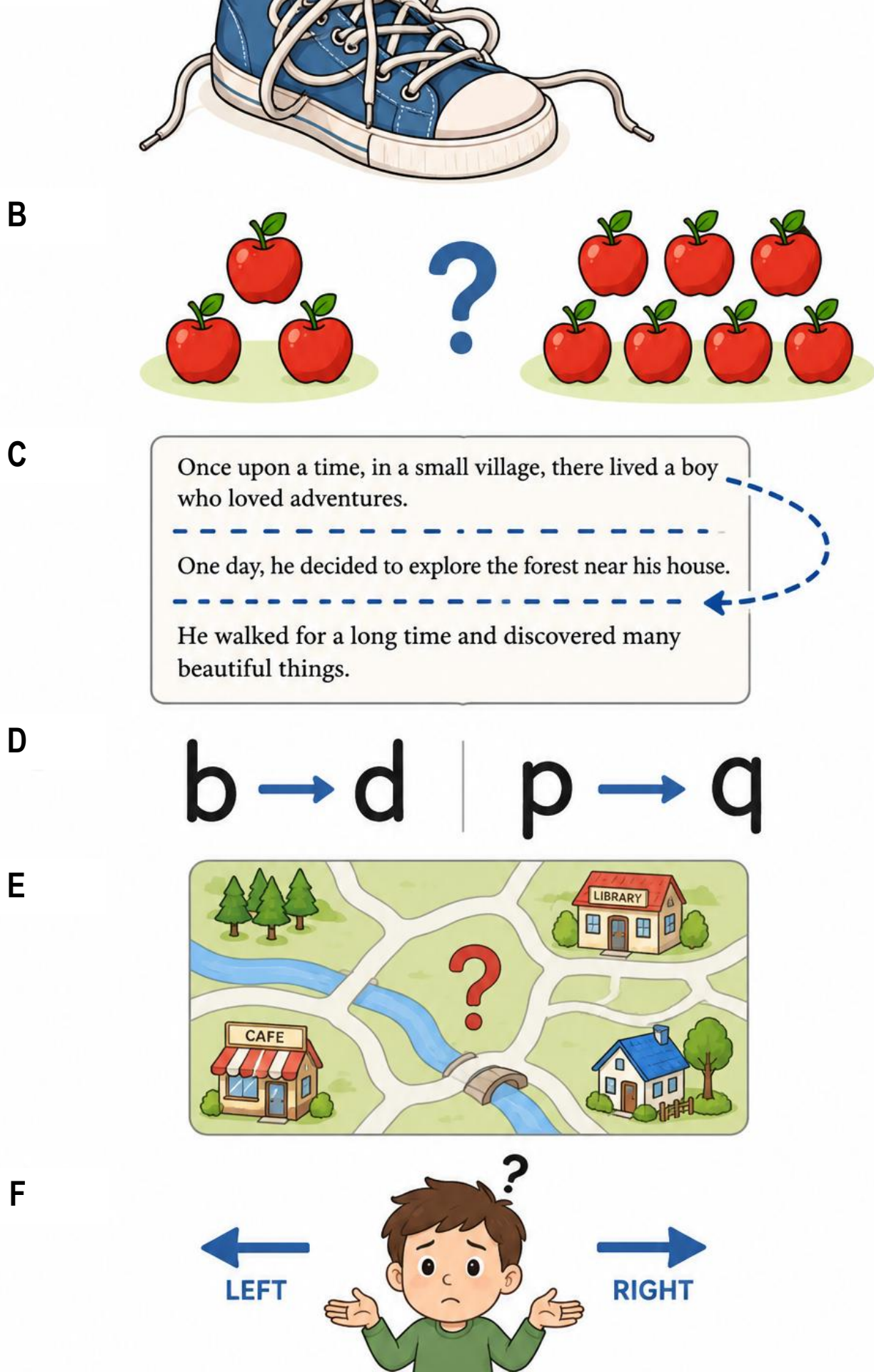
Adulthood

- When you were younger, did you get confused with maps, directions, or spatial locations? (Working Memory, Fig .3.F)
- When you were younger, did you often confuse left and right? (Orientation, Fig .3.F)

EXPECTED OUTCOMES

- Among participants with neurodegenerative conditions, we anticipate that individuals with PPA will report a higher prevalence of childhood- or adolescence-onset differences in language-related domains compared with individuals with other variants of AD and FTD.
- Within the PPA group, we further expect distinct patterns of early-life differences across PPA variants.

Figure 3



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ACKNOWLEDGMENTS

