Appendix e-1: Derivation of cognitive domain scores via confirmatory factor analysis

We used confirmatory factor analysis (CFA) to derive cognitive domain scores based on the neuropsychological information of the DELCODE-NP (see the method section of main manuscript for the tests included in the DECLODE-NP). CFA was performed in Mplus7 [1] using robust maximum likelihood (MLR) estimation. Variance and mean of the latent factors were fixed to one and zero, respectively. Assignment of indicator variables to latent factors was guided by previous CFAs on similar test batteries of two cohort studies with a focus on preclinical and prodromal AD, namely, the ADNI [2] and WRAP studies [3]. Based on this, we tested a 5-factor structure with intercorrelated factors of learning & memory (MEM), language ability (LANG), executive functions and mental processing speed (EXEC), working memory (WM) and visuo-spatial abilities (VIS). A graphical representation of the proposed model including indicator variables for the different factors is shown in figure e-1. To take into account the close methodological relatedness of some indicators, we specified residual correlations as follows: (1) between the immediate word list learning trials; (2) between TMT-A and TMT-B; (3) between logical memory parts 1 and 2; (4) between digit span forward and backward; (5) between verbal fluency, animal and grocery version; and (6) between free recall and cue efficiency in the FSCRT.

Factor score estimates of the latent variables were extracted using the regression method [4]. We computed factor determinacy coefficients to determine whether factor scores represented the latent factors adequately. Factor determinacy coefficients >0.90 indicate a reasonable representation whereas scores <0.80 point to an insufficient concordance of factor score estimates and latent variables [4]. In addition, we calculated a global cognitive domain score by averaging the performance across all five extracted domain scores.

One hundred four (15%) participants had missing values on at least one neuropsychological variable. Three (n=1 MCI, n=2 SCD) of these subjects were excluded from the model estimation due to missing data on all neuropsychological variables. Subjects without missing data were younger (*M*=69.9, *SD*=5.65) and had less years of education (M=13.5, SD=3.25) than subjects with at least one missing value (age: *M*=72.6, *SD*=6.44; education: M=14.7, SD=2.92). In addition, the FCSRT and the two computer-based tests were more often excluded due to overtaxing in cognitively impaired (MCI/AD dementia) vs. unimpaired (HC, SCD, AD relatives) participants (FCSRT: *26.7% vs. 1%*; Flanker task: *27.6% vs. 4.5%*; Face Name Associative Recognition Test: *15.2% vs. 3.%*). Thus, a missing completely at random (MCAR) data pattern was violated [5]. Rather, we assumed a missing at random data (MAR) pattern. Assuming an MAR pattern, missing data in single indicators were associated with and could thus be estimated by the other observed cognitive variables [5]. We addressed this appropriately with the Full Information Maximum Likelihood (FIML) approach implemented in Mplus7.

The proposed five-factor model achieved a good model fit (RMSEA = 0.047, 95%CI: 0.043 - 0.052, $p_{(RMSEA \leq 0.05)}$=0.842; CFI = 0.948; TLI = 0.940; SRMR = 0.043). Factor determinacy scores >0.90 could be achieved for MEM, LANG, and EXEC, >0.80 for WM and VIS, supporting the use of factor score estimates in subsequent analyses [4]. Intercorrelations between the factors (range of ≈0.5-0.8; estimation based on the complete clinical sample including MCI and AD dementia patients) are shown in figure e-1.

References

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