ADNI Parallel Process Models

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## Purpose of study

The purpose of this study is to examine if changes in neuropsychiatric symptoms co-occur with changes in cognition and beta amyloid. This will add to the field by giving us a better understanding of if/how these symptoms co-occur which may help improve understanding of disease trajectories. Prior work has examined relationship between the presence of NPS and cognitive impairment, but few if any studies have examined if and how these symptoms co-occur. Further, many studies that examine the relationship between NPS and cognition do so by examining a) cognitive status (e.g., Geda et al., 2014) or b) cognitive measures that are insensitive to early cognitive change (e.g., MMSE; Verhey et al., 2018). Through our use of a robust cognitive battery available in ADNI, we will gain an understanding of how different cognitive domains may be associated with cognition and amyloid changes through the use of the ADNI cognitive domain variables. Recent cross-sectional work has examined the relationship between NPS and beta amyloid (e.g., Miao et al., 2023, Krell-Roesch et al., 2023), however, there are currently very few longitudinal examinations of this association.

## Description of cohort

In the current study, we limited our analyses to the ADNI-2 and ADNI-3 cohorts between baseline to 48 month follow-up. Both of these cohorts used the neuropsychiatric inventory (NPI), given yearly. The cognitive battery using to make the ADNI summary scores (ADNI-MEM, ADNI-EF2, ADNI-LAN, and ADNI-VS) were also given yearly. Amyloid data were gathered every other year.

Table 1 shows the sample characteristics, stratified by baseline cognitive status. The sample was predominantly non-Hispanic White, with an average age of 71 and evenly split by gender. A majortiy of the smaple was married and not an APoE4 carrier.

### Table 1: Sample characteristics

| **Characteristic** | **Overall**, N = 1,247 | **CN**, N = 313 | **MCI**, N = 580 | **SMC**, N = 354 |
| --- | --- | --- | --- | --- |
| AGE | 71 (7) | 71 (7) | 72 (7) | 71 (7) |
| Unknown | 4 | 1 | 3 | 0 |
| PTGENDER |  |  |  |  |
| Female | 657 (53%) | 177 (57%) | 259 (45%) | 221 (62%) |
| Male | 590 (47%) | 136 (43%) | 321 (55%) | 133 (38%) |
| PTEDUCAT | 16.48 (2.47) | 16.67 (2.40) | 16.25 (2.57) | 16.69 (2.33) |
| PTETHCAT |  |  |  |  |
| Unknown | 4 (0.3%) | 1 (0.3%) | 1 (0.2%) | 2 (0.6%) |
| Not Hisp/Latino | 1,165 (93%) | 288 (92%) | 553 (95%) | 324 (92%) |
| Hisp/Latino | 78 (6.3%) | 24 (7.7%) | 26 (4.5%) | 28 (7.9%) |
| PTRACCAT |  |  |  |  |
| Am Indian/Alaskan | 3 (0.2%) | 2 (0.6%) | 1 (0.2%) | 0 (0%) |
| Asian | 35 (2.8%) | 10 (3.2%) | 9 (1.6%) | 16 (4.5%) |
| Hawaiian/Other PI | 2 (0.2%) | 0 (0%) | 2 (0.3%) | 0 (0%) |
| Black | 121 (9.7%) | 31 (9.9%) | 39 (6.7%) | 51 (14%) |
| White | 1,056 (85%) | 267 (85%) | 517 (89%) | 272 (77%) |
| More than one | 20 (1.6%) | 2 (0.6%) | 6 (1.0%) | 12 (3.4%) |
| Unknown | 10 (0.8%) | 1 (0.3%) | 6 (1.0%) | 3 (0.8%) |
| PTMARRY |  |  |  |  |
| Divorced | 153 (12%) | 41 (13%) | 64 (11%) | 48 (14%) |
| Married | 898 (72%) | 214 (68%) | 439 (76%) | 245 (69%) |
| Never married | 62 (5.0%) | 18 (5.8%) | 24 (4.1%) | 20 (5.6%) |
| Unknown | 4 (0.3%) | 0 (0%) | 2 (0.3%) | 2 (0.6%) |
| Widowed | 129 (10%) | 40 (13%) | 50 (8.6%) | 39 (11%) |
| Unknown | 1 | 0 | 1 | 0 |
| APOE4 |  |  |  |  |
| 0 | 639 (60%) | 204 (72%) | 252 (51%) | 183 (64%) |
| 1 | 352 (33%) | 72 (25%) | 185 (38%) | 95 (33%) |
| 2 | 72 (6.8%) | 9 (3.2%) | 55 (11%) | 8 (2.8%) |
| Unknown | 184 | 28 | 88 | 68 |

Tables 2-5 show the cognitive scores over the five time points for the sample. Cognitive scores were standardized to the baseline mean and standard deviation of the cognitively normal groups. This was done for ease of interpretation, as a score of -2 can be interpreted as 2 standard deviations below the baseline mean of the cognitively normal group.

### Table 2: ADNI-MEM scores over time

| **Characteristic** | **Overall**, N = 1,247 | **CN**, N = 313 | **MCI**, N = 580 | **SMC**, N = 354 |
| --- | --- | --- | --- | --- |
| ADNI-MEM (Baseline) | -0.66 (1.25) | 0.00 (1.00) | -1.36 (1.13) | -0.10 (1.01) |
| (Missing) | 4 | 1 | 2 | 1 |
| ADNI-MEM (Month 12) | -0.87 (1.50) | 0.10 (1.06) | -1.43 (1.44) | -0.06 (1.15) |
| (Missing) | 528 | 117 | 136 | 275 |
| ADNI-MEM (Month 24) | -0.58 (1.57) | 0.26 (1.04) | -1.45 (1.61) | 0.09 (1.10) |
| (Missing) | 513 | 103 | 239 | 171 |
| ADNI-MEM (Month 36) | -1.27 (1.77) | -0.10 (1.14) | -1.51 (1.76) | -0.54 (1.85) |
| (Missing) | 912 | 272 | 308 | 332 |
| ADNI-MEM (Month 48) | -0.61 (1.77) | 0.04 (1.16) | -1.51 (1.87) | 0.11 (1.54) |
| (Missing) | 795 | 167 | 384 | 244 |

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### Table 3: ADNI-EF2 scores over time

| **Characteristic** | **Overall**, N = 1,247 | **CN**, N = 313 | **MCI**, N = 580 | **SMC**, N = 354 |
| --- | --- | --- | --- | --- |
| ADNI-EF2 (Baseline) | -0.40 (1.15) | 0.00 (1.00) | -0.83 (1.15) | -0.03 (1.03) |
| (Missing) | 5 | 1 | 3 | 1 |
| ADNI-EF2 (Month 12) | -0.56 (1.24) | -0.06 (1.01) | -0.85 (1.28) | -0.11 (1.00) |
| (Missing) | 537 | 117 | 140 | 280 |
| ADNI-EF2 (Month 24) | -0.38 (1.29) | 0.05 (1.05) | -0.81 (1.40) | -0.05 (1.04) |
| (Missing) | 544 | 110 | 244 | 190 |
| ADNI-EF2 (Month 36) | -0.82 (1.51) | -0.37 (1.12) | -0.94 (1.54) | -0.03 (1.32) |
| (Missing) | 919 | 275 | 309 | 335 |
| ADNI-EF2 (Month 48) | -0.37 (1.38) | -0.08 (1.04) | -0.80 (1.58) | 0.02 (1.18) |
| (Missing) | 815 | 167 | 390 | 258 |

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### Table 4: ADNI-LAN scores over time

| **Characteristic** | **Overall**, N = 1,247 | **CN**, N = 313 | **MCI**, N = 580 | **SMC**, N = 354 |
| --- | --- | --- | --- | --- |
| ADNI-LAN (Baseline) | -0.44 (1.08) | 0.00 (1.00) | -0.84 (1.06) | -0.19 (0.96) |
| (Missing) | 4 | 1 | 2 | 1 |
| ADNI-LAN (Month 12) | -0.53 (1.16) | 0.09 (0.99) | -0.87 (1.15) | -0.17 (0.82) |
| (Missing) | 529 | 117 | 136 | 276 |
| ADNI-LAN (Month 24) | -0.45 (1.22) | 0.03 (0.97) | -0.95 (1.29) | -0.09 (0.96) |
| (Missing) | 514 | 103 | 240 | 171 |
| ADNI-LAN (Month 36) | -0.88 (1.38) | -0.24 (1.14) | -1.01 (1.39) | -0.47 (1.35) |
| (Missing) | 915 | 274 | 308 | 333 |
| ADNI-LAN (Month 48) | -0.47 (1.30) | -0.05 (0.99) | -0.95 (1.47) | -0.16 (1.04) |
| (Missing) | 795 | 167 | 384 | 244 |

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### Table 5: ADNI-VIS scores over time

| **Characteristic** | **Overall**, N = 1,247 | **CN**, N = 313 | **MCI**, N = 580 | **SMC**, N = 354 |
| --- | --- | --- | --- | --- |
| ADNI-VIS (Baseline) | -0.21 (1.16) | 0.00 (1.00) | -0.46 (1.25) | 0.03 (1.04) |
| (Missing) | 4 | 1 | 2 | 1 |
| ADNI-VIS (Month 12) | -0.24 (1.17) | -0.02 (0.98) | -0.37 (1.26) | -0.06 (1.00) |
| (Missing) | 529 | 117 | 136 | 276 |
| ADNI-VIS (Month 24) | -0.14 (1.19) | -0.02 (1.08) | -0.33 (1.30) | 0.08 (1.04) |
| (Missing) | 514 | 103 | 240 | 171 |
| ADNI-VIS (Month 36) | -0.37 (1.50) | 0.10 (1.13) | -0.46 (1.54) | -0.06 (1.32) |
| (Missing) | 915 | 274 | 308 | 333 |
| ADNI-VIS (Month 48) | -0.12 (1.28) | -0.01 (1.10) | -0.37 (1.42) | 0.19 (1.14) |
| (Missing) | 795 | 167 | 384 | 244 |

Tables 6 and 7 shows the NPI scores and amyloid data over time. NPI scores were min-max normalized in the long-form data set, based on the total NPI scores. Amyloid data were converted to be on a centiloid scale since both florbetapir (FBP) and florbetaben (FBB) tracers were used in ADNI-2 and ADNI-3. See Royse et al. (2021) for a description of the centiloid conversion method. After the centiloid conversion, amyloid data were also min-max normalized in the long-form data set. The data were min-max normalized in the long-form dataset so that there was a consistent minimum and maximum value used for standardization, and so that change over time could be modeled.

### Table 5: NPI scores over time

| **Characteristic** | **Overall**, N = 1,247 | **CN**, N = 313 | **MCI**, N = 580 | **SMC**, N = 354 |
| --- | --- | --- | --- | --- |
| NPI (Baseline) | 0.04 (0.08) | 0.01 (0.03) | 0.06 (0.10) | 0.02 (0.04) |
| (Missing) | 6 | 2 | 3 | 1 |
| NPI (Month 12) | 0.06 (0.10) | 0.02 (0.07) | 0.08 (0.12) | 0.03 (0.09) |
| (Missing) | 492 | 109 | 126 | 257 |
| NPI (Month 24) | 0.06 (0.11) | 0.02 (0.05) | 0.10 (0.15) | 0.03 (0.06) |
| (Missing) | 484 | 96 | 219 | 169 |
| NPI (Month 36) | 0.08 (0.14) | 0.03 (0.07) | 0.10 (0.14) | 0.04 (0.17) |
| (Missing) | 899 | 272 | 295 | 332 |
| NPI (Month 48) | 0.06 (0.13) | 0.02 (0.08) | 0.10 (0.15) | 0.04 (0.10) |
| (Missing) | 802 | 170 | 380 | 252 |

### Table 7: Amyloid scores over time

| **Characteristic** | **Overall**, N = 1,247 | **CN**, N = 313 | **MCI**, N = 580 | **SMC**, N = 354 |
| --- | --- | --- | --- | --- |
| Amyloid, in centiloids (Baseline) | 0.28 (0.18) | 0.22 (0.13) | 0.35 (0.20) | 0.23 (0.14) |
| (Missing) | 108 | 16 | 50 | 42 |
| Amyloid, in centiloids (Month 24) | 0.30 (0.19) | 0.24 (0.15) | 0.36 (0.20) | 0.26 (0.16) |
| (Missing) | 648 | 135 | 308 | 205 |
| Amyloid, in centiloids (Month 48) | 0.31 (0.20) | 0.27 (0.17) | 0.35 (0.21) | 0.30 (0.21) |
| (Missing) | 986 | 214 | 461 | 311 |

## Univariate Latent Growth Curve Models

The first set of models used univariate latent growth curve models (LGCM). The term univariate is used for convenience, as we are referring to modeling a single variable. The purpose of these LGCMs was to ensure each variable was change as expected over time. We expected to see declines over time in the cognitive variables, and increases over time in NPI and amyloid.

In these models, residual variances were constrained to be equal at each time point. In the cognitive variables, we also added a latent variable modeling practice and retest, known as the “boost effect.” Table 8 shows the model fit indices, latent intercepts and means, and boost effect.

### Table 8: Univariate LGCM Summaries

| Statistic | AB.Estimate | NPI.Estimate | MEM.Estimate | EF2.Estimate | LAN.Estimate | VIS.Estimate |
| --- | --- | --- | --- | --- | --- | --- |
| Chi-sq | 4.117 | 57.9 | 59.550 | 18.8020 | 21.651 | 31.2590 |
| df | 3 | 14 | 13.000 | 13.0000 | 13.000 | 13.0000 |
| p-value | 0.2491 | 0 | 0.000 | 0.1294 | 0.061 | 0.0031 |
| CFI | 0.999 | 0.884 | 0.985 | 0.9970 | 0.995 | 0.9660 |
| RMSEA | 0.018 | 0.05 | 0.054 | 0.0190 | 0.023 | 0.0340 |
| SRMR | 0.006 | 0.098 | 0.027 | 0.0210 | 0.022 | 0.0630 |
| Unstd. Intercept | 0.283 | 0.039 | -0.660 | -0.3960 | -0.444 | -0.2060 |
| Unstd. Slope | 0.031 | 0.032 | -0.358 | -0.3600 | -0.397 | -0.0680 |
| Boost Effect | - | - | 0.180 | 0.0750 | 0.127 | 0.0510 |

The results show that each model showed good fit to the data, with exception of the NPI model. Both the amyloid and NPI models showed increase over time based on the slope, whereas each cognitive measure showed decline over time. The boost effect was significant for ADNI-MEM, EF2, and LAN but not for ADNI-VIS.

## Bivariate Latent Growth Curve Models

The second set of models used bivariate LGCMs. The term bivariate is used for convenience, as we are referring to modeling cognition and NPI together. The purpose of these LGCMs was to ensure each variable was change as expected over time. We again expected to see declines over time in the cognitive variables and increases over time in NPI. We also hypothesized a negative correlation between the NPI and cognitive slopes, as the NPI values should be increasing while the cognitive values should be decreasing.

In these models, residual variances were constrained to be equal at each time point. In the cognitive variables, we also added a latent variable modeling practice and retest, known as the “boost effect.” Table 9 shows the model fit indices, latent intercepts and means, and boost effect.

### Table 9: Bivariate LGCM Summaries

| Statistic | MEM.Estimate | EF2.Estimate | LAN.Estimate | VIS.Estimate |
| --- | --- | --- | --- | --- |
| Chi-sq | 164.956 | 128.985 | 135.614 | 138.241 |
| df | 48.000 | 48.000 | 48.000 | 48.000 |
| p-value | 0.000 | 0.000 | 0.000 | 0.000 |
| CFI | 0.966 | 0.965 | 0.962 | 0.924 |
| RMSEA | 0.044 | 0.037 | 0.038 | 0.039 |
| SRMR | 0.059 | 0.059 | 0.060 | 0.067 |
| Unstd. Intercept (Cognition) | -0.659 | -0.396 | -0.444 | -0.206 |
| Unstd. Slope (Cognition) | -0.366 | -0.369 | -0.407 | -0.087 |
| Boost Effect | 0.184 | 0.081 | 0.134 | 0.062 |
| Unstd. Intercept (NPI) | 0.039 | 0.039 | 0.039 | 0.039 |
| Unstd. Slope (NPI) | 0.032 | 0.035 | 0.033 | 0.033 |
| Correlation among slopes (STDY) | -0.648 | -0.581 | -0.601 | -0.515 |

The results show that each model showed good fit to the data. The NPI models showed increase over time based on the slope, whereas each cognitive measure showed decline over time. The boost effect was significant for ADNI-MEM, EF2, and LAN but not for ADNI-VIS. The ADNI-VIS slope also suggested no significant change over time. There was a negative correlation among slopes in each model.

## Trivariate Latent Growth Curve Models

The third set of models used trivariate LGCMs. The term trivariate is used for convenience, as we are referring to modeling amyloid, cognition, and NPI together. The purpose of these LGCMs was to ensure each variable was changing as expected over time. We again expected to see declines over time in the cognitive variables and increases over time in NPI and amyloid. We also hypothesized a negative correlation between the NPI and cognitive slopes, as the NPI values should be increasing while the cognitive values should be decreasing. We hypothesized there would be a positive correlation between amyloid and NPI as both values should be increasing over time. Finally, we hypothesized a negative correlation between amyloid and cognition based on the AT(N) framework.

### Modeling Note

The trivariate models did not initially converge, and there was a Mplus warning of: “THE COVARIANCE COVERAGE FALLS BELOW THE SPECIFIED LIMIT.” This was resolved by changing the covariance coverage default of 0.10 to 0.095. The ADNI-LAN model had a non-positive definite matrix that needed debugging, and was resolved by omitting the constrained residual error variances on ADNI-LAN and NPI.

### Table 10: Trivariate LGCM Summaries

| Statistic | MEM.Estimate | EF2.Estimate | LAN.Estimate | VIS.Estimate |
| --- | --- | --- | --- | --- |
| Chi-sq | 205.107 | 169.867 | 86.928 | 177.542 |
| df | 73.000 | 73.000 | 65.000 | 73.000 |
| p-value | 0.000 | 0.000 | 0.036 | 0.000 |
| CFI | 0.978 | 0.979 | 0.995 | 0.968 |
| RMSEA | 0.038 | 0.033 | 0.016 | 0.034 |
| SRMR | 0.048 | 0.048 | 0.027 | 0.054 |
| Unstd. Intercept (Cognition) | -0.659 | -0.396 | -0.444 | -0.206 |
| Unstd. Slope (Cognition) | -0.349 | -0.343 | -0.394 | -0.082 |
| Boost Effect | 0.184 | 0.081 | 0.137 | 0.068 |
| Unstd. Intercept (NPI) | 0.039 | 0.039 | 0.038 | 0.039 |
| Unstd. Slope (NPI) | 0.031 | 0.033 | 0.034 | 0.031 |
| Unstd. Intercept (Amyloid) | 0.282 | 0.284 | 0.283 | 0.283 |
| Unstd. Slope (Amyloid) | 0.031 | 0.030 | 0.031 | 0.031 |
| Correlation among cognition and NPI (STDY) | -0.645 | -0.576 | -0.511 | -0.513 |
| Correlation among cognition and amyloid (STDY) | -0.111 | 0.005 | -0.103 | -0.018 |
| Correlation among amyloid and NPI (STDY) | 0.031 | 0.026 | -0.024 | 0.028 |

The results in Table 10 showed each model had good fit to the data. In the MEM, EF2, and VIS models, there was no association between the amyloid slope or the cognition and NPI slopes. However, the negative correlation between NPI and cognition was found as hypothesized. All models showed slopes in the expected directions.