

**Title:**

Changes in Cognitive Function Over 96 weeks in Naïve Patients Randomised to Darunavir-ritonavir plus either Raltegravir or Tenofovir-Emtricitabine: a substudy of the NEAT001/ANRS143 trial.

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**Conflict of interest:**

None to declare

**Abstract:****Background:**

Improvements in cognitive function are described after initiation of combination antiretroviral therapy (cART), with sparse data on differences between cART strategies.

**Methods:**

We assessed changes in cognition, over 96 weeks, in therapy naïve HIV-positive adults randomised to darunavir/ritonavir (800/100mg once daily) with either raltegravir (400mg twice daily, Arm1) or tenofovir/emtricitabine (245/200mg once daily, Arm2). Seven cognitive tests were administered at baseline and week 96. Changes from baseline in individual cognitive test scores and composite score (NPZ) were assessed. Comparisons between treatment arms were by intention-to-treat and associations with immunological and virological parameters by regression models.

**Findings:**

Of 343 subjects enrolled, 208 completed the week 96 cognitive assessment. Baseline median (IQR) CD4+ count and plasma HIV RNA was 348(282-398) cells/uL and 4.7(4.2-5.1) log<sub>10</sub> copies/mL, respectively. At week 96, numbers with plasma HIV RNA undetectable and remaining on randomised

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cART were 85(92%) and 110(96%), and 84(90%) and 107(93%) in Arm1 and Arm2, respectively.

Overall, performance significantly improved by week 96 in 5 of 7 individual tests and in NPZ. Mean change in NPZ was 0.28 versus 0.21 for Arm1 and 2, respectively ( $p=0.37$ ). No statistically significant differences between study treatment arms were observed in individual cognitive domains apart from attention (greater improvement in Arm1,  $p=0.0499$ ). At week 96, NPZ-score increase was associated with increase in CD4+ ( $p=0.001$ ) but not HIV RNA area-under-curve ( $p=0.60$ ).

**Interpretation:**

Subsequent to the initiation of cART, immunological recovery rather than type of antiretroviral therapy is the major driver of changes in cognitive function.

**Keywords:**

HIV; antiretroviral therapy; cognitive function; nucleoside sparing; randomised clinical trial.

**Manuscript:**

**Introduction:**

Modern combination antiretroviral therapy (cART) has many beneficial effects on the central nervous system (CNS). Rates of HIV-dementia and other CNS opportunistic diseases have declined dramatically since the advent and widespread availability of cART<sup>1,2</sup> and in general, cognitive function improves after commencing antiretroviral therapy<sup>3-5</sup>. Despite these advances, impairment in cognitive function remains prevalent in otherwise effectively cART treated HIV-positive subjects<sup>6</sup>. The presence of such cognitive impairment is reported to impact on individuals' ability to maintain employment, undertake activities of daily living and comply with antiretroviral medication and has been associated with poorer overall survival<sup>7</sup>.

Data on changes in overall cognitive function and changes in individual cognitive domains in HIV-positive subjects commencing different cART regimens are sparse and no data exist on changes in cognitive function in therapy naïve individuals commencing novel antiretroviral strategies. The aim of this study was to prospectively evaluate changes in cognitive function in HIV-positive antiretroviral naïve subjects randomised to commence either a standard cART regimen of darunavir/ritonavir plus tenofovir/emtricitabine or a novel nucleos(t)ide-reverse-transcriptase-inhibitor (NRTI)-sparing cART regimen of darunavir/ritonavir plus raltegravir.

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As systemic HIV replication is a risk factor for cognitive impairment<sup>8</sup> (and HIV RNA in blood is independently associated with cognitive impairment), given a more rapid HIV RNA suppression is reported with the use of integrase-inhibitor containing antiretroviral regimens<sup>9</sup> we hypothesized that the participants in the NRTI-sparing, raltegravir-containing treatment arm would have a more favourable evolution in cognitive function compared to the darunavir/ritonavir + tenofovir/emtricitabine arm.

## **Methods:**

### *Subject selection*

Antiretroviral therapy naïve adults entering the NEAT001/ANRS143 study<sup>10</sup> at selected sites were eligible to enter this cognitive sub-study. Participating sites were located in Belgium, France, Germany, Ireland, Italy, Spain and the United Kingdom, as validated cognitive tests were available in the languages of these countries. Further detailed eligibility criteria have been described previously<sup>11</sup>. In brief, eligible subjects were required to have a CD4+ lymphocyte count below 500 cells/uL or symptomatic HIV-infection. Specific sub-study exclusion criteria were current or past opportunistic infections or tumors of the central-nervous-system, non HIV-related major neurological or psychiatric disorders, active recreational drug use and linguistic difficulties. Human ethics committee approval was gained at all participating sites, and all subjects provided written informed consent for the core trial and sub-study participation.

Participants were randomly assigned in a 1:1 ratio to receive oral open-label therapy comprising 800 mg darunavir and 100 mg ritonavir once daily with either 400 mg twice daily raltegravir (Arm1, NRTI-sparing) or 245/200 mg once daily tenofovir/emtricitabine (Arm 2, standard therapy).

Randomisation was stratified by country, and sub-study consent was obtained prior to randomisation to limit imbalanced distribution of baseline characteristics between the sub-study arms.

### *Study procedures*

A standardised cognitive assessment battery was undertaken at baseline and after 96 weeks of antiretroviral therapy by trained study staff. The battery was specifically chosen to assess the cognitive domains reported to be affected in chronic HIV-infection<sup>12</sup>, and deemed practical to undertake in a large multicentre study. In addition, Lawton's questionnaire of Instrumental Activities

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of Daily Living (5 items) and a short questionnaire to assess the patient's perception of cognitive abilities (6 items<sup>13</sup>) were undertaken to assess patient reported outcomes.

The cognitive battery comprised of trail making test (TMT) part A and B (attention and mental flexibility)<sup>14</sup>, digit symbol substitution test (psycho-motor speed)<sup>15</sup>, backward digit span task (working memory)<sup>15</sup>, free and cued selective reminding test (retrieval ability and episodic memory)<sup>16</sup>, semantic and formal fluency tests (verbal fluency) and the frontal assessment battery (frontal executive function)<sup>17</sup>.

### *Statistical analysis*

The primary outcomes were psychomotor speed and overall cognitive function at week 96. Secondary outcomes were all other individual cognitive testing results and patient reported outcomes. Sample size was estimated from data gathered from the ANRS CO3 Aquitaine Cohort<sup>18</sup>. Assuming that mean score on the digit symbol substitution test is 44.5 (SD 12.9) and that a difference of 10% would be of clinical significance, a sample size of 182 subjects in each study treatment arm would be required to detect this difference between the two study treatment groups with 90% power and with a significance level of 5%. Due to possible study dropouts, a sample size of 400 subjects (200 per study arm) was proposed.

A composite cognitive score (NPZ) was calculated from the 7 neuropsychological tests. For this, raw test scores were first transformed to z-scores at W0 and W96, respectively, by subtracting the mean and dividing by the standard deviation of the total study sample at baseline. TMT-A and B were log<sub>10</sub>-transformed, and the signs reversed so that for all tests a score above zero would denote above-average and scores below zero denote below-average cognitive function within the study population. The NPZ was then calculated as the average of the 7 individual z-scores at W0 and W96, respectively, in participants with ≤1 missing test. Activities of daily living and cognitive complaints were analysed as binary outcome (any help needed / any complaint), and cumulative score.

For each test and NPZ, week 96 results were compared between the arms using multivariable linear regression of absolute values, adjusting for the baseline value. Similarly, activities of daily living and cognitive complaints at week 96 were analysed using ordered and logistic regression. The primary analysis excluded participants with missing week 96 data, and was adjusted for years of education, ethnic group and age at baseline (because of strong correlation with test results), and multiple

imputation was used to impute missing baseline values from the same three factors using Stata's `mi impute` command (version 13.1) creating 25 simulations.

Various sensitivity analyses were performed including analysis of only patients with non-missing baseline results (complete cases), adjusting for baseline test results only, multiple imputation additionally using other cognitive test results or other covariates, or using mixed effect regression models.

We examined the association of early HIV RNA suppression (<50 copies/mL at a) week 8 or b) week 12) with week 96 NPZ-score using multivariable regression models, adjusting for randomised arm, age, ethnicity, education, baseline HIV RNA and baseline NPZ. We also looked at HIV RNA area under the curve until week 96. In similar but post-hoc analyses, we assessed the association between CD4+ and CD8+ lymphocyte count with week 96 NPZ-score, examining area under the curve, week 96 result and (for CD4+) time to reach a count above 500 cells/uL as possible explanatory variables.

All significance tests were two-sided, and raw p values without multiplicity adjustment are shown. P values < 0.05 were considered statistically significant.

## Results:

### *Participant characteristics*

Of 343 participants enrolled, 302 had at least one cognitive assessment: 283 (94%) at baseline, and 208 (69%) at week 96, with 189 subjects completing both assessments. A consort diagram describing participant numbers is shown in *Figure 1*. Baseline characteristics of participants with week 96 results are shown in *Table 1*.

Of these 208 subjects, 91% were male, 10% of black ethnicity and mode of HIV-acquisition was men-having-sex-with-men (MSM) in 70%. On comparing the baseline characteristics of the 208 subjects who completed the week 96 cognitive assessment battery with the rest of the NEAT001/ANRS143 study population there were no statistically significant differences in randomisation arm, age, ethnicity, weight, smoking status or HIV viral load. Differences were present in years of known HIV-infection and nadir CD4+ cell count (1.1 years (IQR 0.2 to 3.1) versus 1.3 year (IQR 0.3 to 3.8) and 304 cells/uL (IQR 235 to 370) versus 329 cells/uL (IQR 261 to 378) for the main study only versus the sub-study population, respectively). Differences were also present in country subjects were recruited

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from (11% versus 7%, 24% versus 41%, 12% versus 15%, 9% versus 29% and 45% versus 7% of subjects recruited from Spain, France, the United Kingdom, Italy and other countries for the main study versus this sub-study, respectively).

At the time of week 96 cognitive testing, 84/93 (90%) and 107/115 (93%) subjects in Arm1 and Arm2 remained on randomised therapy. There were no significant differences in the proportion of patients with plasma HIV RNA <50 copies/mL (7 (92%) and 5 (96%), respectively,  $p=0.32$ ), in CD4+ cell count (mean 604 and 584 cells/uL, respectively,  $p=0.49$ ) or in CD4+ cell count change from baseline (mean 267 and 257 cells/uL in Arm1 and Arm2, respectively, adjusted for baseline CD4+;  $p=0.67$ ).

#### *Changes in cognitive function over 96 weeks*

Results on changes in individual cognitive domains and overall cognitive function from multivariable linear regression models and adjusted for age, education and ethnicity are shown in *Table 2*. Overall, performance significantly improved by week 96 in all individual cognitive tests, except for TMT-B and Verbal Fluency Test. There was no statistically significant difference between the arms in change of any of the tests apart from TMT-A ( $p=0.0499$ ), which showed a greater improvement in Arm1 versus Arm2. Mean increase in NPZ was 0.28 and 0.21 in Arm1 and Arm2, respectively (difference -0.07 (95% CI -0.23 to 0.09);  $p=0.37$ ).

Results of sensitivity analyses were similar (*data not shown*). For TMT-A, the  $p$ -value became smaller, for example in the complete case ( $p=0.016$ ); of note, the difference of 0.04 on the  $\log_{10}$  scale corresponds to a 10% (~4 sec) faster time to complete the task in Arm1.

#### *Patient reported outcomes*

At week 96, 1/93 (1%) participants in Arm1 and 6/114 (5%) in Arm2 reported to need help in at least one activity of daily living (adjusted  $p=0.080$ ), and 30/93 (32%) and 47/114 (41%), respectively, reported one or more cognitive complaints (adjusted  $p=0.16$ ). There also was no difference between study treatment arms when analysing cumulative scores of patient reported outcomes.

#### *Associations between cognitive function and changes in virological and immunological parameters*

At weeks 8 and 12, 60/90 (67%) and 70/92 (76%) participants in Arm1 and 36/114 (32%) and 59/113 (52%) in Arm2 had HIV RNA < 50 copies/mL. From week 24 onwards there were no differences between the study arms (>85% in both). For neither HIV RNA < 50 copies/mL at week 8 (-0.05 versus  $\geq 50$  copies/mL (95% CI -0.18 - 0.08);  $p=0.44$ ) nor at week 12 (-0.10 (95% CI -0.22 - 0.02);  $p=0.09$ ) was

there evidence of an association with NPZ-score at week 96, and similarly for HIV RNA area under the curve ( $p=0.60$ ).

In contrast, we found that a greater increase in CD4+ cell count to week 96 was statistically significantly associated with greater improvement in NPZ-score (0.05 (95% CI 0.02-0.08) higher NPZ-score per 100 cells/ $\mu$ L more increase;  $p=0.001$ ) in multivariable models. A similar association with NPZ-score change was found for the average CD4+ count from week 0 to week 96 as measured by area under the curve ( $p=0.006$ ) whereas time to reach a CD4+ count  $\geq 500$  cells/ $\mu$ L was not associated with NPZ-score at week 96 ( $p=0.79$ ). No statistically significant associations were observed between change in CD8+ count and NPZ change (0.00 per 100 cells/ $\mu$ L more (95% CI -0.02 - 0.02),  $p=0.78$ ); when jointly looking at CD4+ and CD8+, the significant association of CD4+ with NPZ-score remained statistically significant and unchanged compared with model without CD8+ whereas CD8+ was not associated.

#### **Discussion:**

To our knowledge, this is the first longitudinal randomised comparison of the effects of NRTI-sparing cART to standard therapy on cognitive function in HIV-positive individuals initiating therapy. We found no evidence of differences in changes in overall cognitive function or specific cognitive domains between the treatment arms we assessed, but observed change in CD4+ lymphocyte count to be the factor most strongly associated with the evolution of changes in cognitive function.

Previous studies have reported cognitive benefits after commencing cART<sup>5</sup>, although no benefit in changes in cognitive function has been reported in patients commencing cART at high CD4+ counts above 500 cells/ $\mu$ L<sup>19</sup>. Improvements in cognition in longitudinal studies may in part be secondary to practice effects<sup>20</sup>. By undertaking only two cognitive assessments 96 weeks apart we may have minimised the impact of such a practice effect due to this relatively long time interval between cognitive testing. Few studies have included randomised comparisons of different cART regimens. In two prospective studies comparing cognitive function in HIV-positive subjects initiating different cART regimens, poorer cognitive outcomes have been reported in subjects allocated to receive efavirenz-containing cART regimens compared to outcomes in subjects allocated to receive other standard cART regimens<sup>21,22</sup>. However no studies have assessed NRTI-sparing cART regimens.

Cognitive function has been examined within longitudinal studies assessing other novel antiretroviral strategies. In treatment-experienced patients on suppressive antiretroviral therapy switching to



NEAT 001 cognitive sub study protease-inhibitor monotherapy, no significant difference in cognitive function was reported compared to patients remaining on standard cART<sup>23,24</sup>. Our study differs from this approach in several ways. First, we have assessed cognitive function in therapy naïve subjects electively commencing antiretroviral therapy, rather than subjects switching from an already virological suppressive antiretroviral regimen. Second, the strategy we have assessed was an NRTI-sparing antiretroviral strategy, comprised of two active antiretroviral agents, namely darunavir and raltegravir, not one active antiretroviral agent as is the case with protease-inhibitor monotherapy.

We hypothesized that the participants in the NRTI-sparing, raltegravir-containing treatment arm would have a more favourable evolution in cognitive function compared to the darunavir/ritonavir + tenofovir/emtricitabine arm. The rationale for this being patients on the integrase-inhibitor containing arm may achieve undetectable plasma HIV RNA more rapidly compared to the non-integrase-inhibitor containing cART strategy. Our study is one of the first to assess associations between the rate of decay of HIV RNA with evolution of cognitive function. As expected, in our study time to undetectable HIV RNA was slightly faster in Arm1 with the number of subjects with HIV RNA <50 copies/mL greater at weeks 8 and 12 than in Arm2. We did not observe any associations between measures of HIV RNA in our study and cognitive function at week 96. However, if changes in cognition associated with the speed of plasma HIV RNA decay were to have occurred and only be evident during the early phase after commencing antiretroviral therapy which disappears at a later stage, we would not have observed such changes given the timing of the cognitive assessments in our study.

The magnitude of CD4+ count recovery after the initiation of antiretroviral therapy has been reported to be associated with the degree of improvement in cognitive function previously<sup>25</sup>. Interestingly we observed significant associations between change in CD4+ count to week 96 with overall changes in cognitive function in multivariable models. These associations were not present with CD8+ count. These data suggest that immune system recovery is associated with improvements in cognitive function in therapy naïve HIV-positive individuals after the initiation of antiretroviral therapy. The lack of significant difference in changes in cognitive function between the two treatment arms assessed in our study may be related to the lack of a significant difference in changes in CD4+ counts between the treatment arms.

Based on our initial sample size calculation, we aimed for a total study population of 400 subjects with approximately 200 subjects in each treatment arm. Although we recruited 343 subjects to this study, only 208 subjects completed the week 96 cognitive testing and were included in our analysis.

Based on the assumptions we made to calculate the sample size, our study was underpowered. However our sample size, of approximately 100 subjects in each treatment arm, compared to other studies represents a relatively large number of subjects to undertake basic cognitive observations. This sub-study involved cognitive testing at baseline and then after 96 weeks, with no interval testing. This relatively long interval and the duration of the cognitive battery we utilised may be factors which have influenced the poor retention to the sub-study procedures. Interval cognitive testing at more frequent intervals, such as yearly intervals, would have provided further information on the dynamics of cognitive changes within this study and therefore strengthened the statistical analysis. This also may have enhanced the retention of subjects to the sub-study if it was not the duration of the cognitive battery which limited retention. However the available resources did not permit us to increase the number of cognitive testing visits within this sub-study. A further limitation was the lack of measurement of CSF HIV RNA, which may have provided more strength in the findings we have reported.

We observed trends for numerically greater improvements in 5 out of the 7 cognitive domains assessed and in global cognitive score in Arm1 (NRTI-sparing) compared to Arm2. However, apart from TMT-A these changes were not statistically significant and the magnitude of the differences between the arms were generally small; for instance difference in NPZ score between the treatment arms was 0.07 with a change in z-score approximately 0.5 often considered of clinical relevance. Given the observations we have made are all of a small magnitude we do not consider them to be of clinical relevance and acknowledge that the differences in TMT-A could be a chance finding.

In summary, our observations suggest subsequent to the initiation of antiretroviral therapy, immunological recovery rather than type of antiretroviral therapy is the major factor associated with changes in cognitive function.

**Presentation of results:**

Some of the data contained in this manuscript was presented as an oral presentation at the 15th European AIDS Conference (Barcelona, Spain, October 21-24, 2015; abstract number PS11/6).

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**Figure 1:**

**Study Consort Diagram**

**Table 1:****Baseline characteristics for all subjects with W96 cognitive data.**

Factor		DRV/r+RGV	DRV/r+TDF/FT	Overall	p-value
		N=93	C N=115	N=208	
Gender:	male	87 (94%)	102 (89%)	189 (91%)	0.23
	female	6 (6%)	13 (11%)	19 (9%)	
Age (years)		36 (31-46)	41 (31-48)	40 (31-47)	0.053
Origin:	black	11 (12%)	10 (9%)	21 (10%)	0.58
	caucasian	77 (83%)	101 (88%)	178 (86%)	
	other	5 (5%)	4 (3%)	9 (4%)	
Mode of HIV infection:					0.10
	homosexual/bisexual	72 (77%)	74 (64%)	146 (70%)	
	heterosexual	18 (19%)	32 (28%)	50 (24%)	
	other/unknown	3 (3%)	9 (8%)	12 (6%)	
HIV stage:	Stage A	83 (89%)	101 (88%)	184 (88%)	0.52
	Stage B	9 (10%)	10 (9%)	19 (9%)	
	Stage C	1 (1%)	4 (3%)	5 (2%)	
Education (years)		13 (10-17)	13 (10-15)	13 (10-16)	0.19
Years since first positive HIV serology		1 (0-3)	2 (0-4)	1 (0-4)	0.21
CD4 nadir (cells/uL)		332 (254-370)	327 (268-383)	330 (262-379)	0.53
CD4 (cells/uL)		348 (280-393)	347 (286-401)	348 (282-398)	0.80
HIV-RNA (log <sub>10</sub> copies/mL)		4.8 (4.3-5.2)	4.7 (4.2-5.0)	4.7 (4.2-5.1)	0.13
Height (cm)		176 (172-181)	175 (170-180)	175 (171-180)	0.27
Weight (kg)		74 (65-81)	71 (63-80)	73 (64-81)	0.44
Systolic blood pressure (mmHg)		120 (114-130)	120 (110-130)	120 (110-130)	0.45
CNS-related disorder at screening		3 (3%)	8 (7%)	11 (5%)	0.23
Country:	France	38 (41%)	48 (42%)	86 (41%)	0.84
	Spain	7 (8%)	8 (7%)	15 (7%)	
	UK	13 (14%)	18 (16%)	31 (15%)	
	Italy	30 (32%)	31 (27%)	61 (29%)	
	Other country	5 (5%)	10 (9%)	15 (7%)	
Smoking:	Never smoked	56 (60%)	50 (43%)	106 (51%)	0.030
	Stopped	5 (5%)	15 (13%)	20 (10%)	
	Current	32 (34%)	50 (43%)	82 (39%)	
Hepatitis C, any marker positive		2 (2%)	5 (4%)	7 (3%)	0.38
Free Selective Reminding Test * (Cumulative number of words recalled)		35 (30-38)	34 (30-37)	34 (30-38)	0.14
Digit Symbol Substitution Task * (Number of correct marks)		53 (41-59)	55 (41-64)	55 (41-61)	0.43
Trial Making Test A †		30 (25-41)	33 (27-41)	32 (26-41)	0.26



(Time to completion [(secs)])				
Trial Making Test B † (Time to completion [secs])	57 (45-83)	62 (49-83)	58 (47-83)	0.41
Verbal Fluency Test * (Number of words named)	34 (29-40)	33 (29-41)	33 (29-40)	0.80
Backwards Digit Span * (Number of digits)	4 (3-5)	4 (3-5)	4 (3-5)	0.85
Frontal Assessment Battery (cumulative score) *	18 (17-18)	18 (16-18)	18 (16-18)	0.55

*Table 1 Legend:*

number (percentage) or median (interquartile range) are presented. \* higher score represents better performance; † lower score represents better performance.

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**Table 2:****Changes in cognitive function scores over 96 weeks between study treatment arms.**

Cognitive domain	N available, mean change ( $\pm$ SE) to week 96			Difference between arms	
	Overall (p-value for change) (n=208)	Arm1 DRV/r/RTG (n=93)	Arm2 DRV/r/TDF/FT C (n=115)	(95% CI)	p-value for difference
Free Selective Reminding Test * (Cumulative number of words recalled)	n=200 2.45 $\pm$ 0.34 (p<0.001)	n=91 2.57 $\pm$ 0.48	n=109 2.34 $\pm$ 0.44	-0.24 (-1.47 - 1.00)	0.706
Digit Symbol Substitution Task * (Number of correct marks)	n=195 2.64 $\pm$ 1.08 (p=0.016)	n=86 4.17 $\pm$ 1.64	n=109 1.42 $\pm$ 1.41	-2.74 (-6.98 - 1.49)	0.203
Trial Making Test A † (Time to completion [ $\log_{10}$ secs])	n=204 -0.03 $\pm$ 0.01 (p=0.004)	n=91 -0.05 $\pm$ 0.01	n=113 -0.01 $\pm$ 0.01	0.04 (0.00 - 0.07)	0.0499
Trial Making Test B † (Time to completion [ $\log_{10}$ secs])	n=203 -0.02 $\pm$ 0.01 (p=0.179)	n=90 -0.02 $\pm$ 0.02	n=113 -0.01 $\pm$ 0.02	0.01 (-0.03 - 0.05)	0.637
Verbal Fluency Test * (Number of words named)	n=201 0.49 $\pm$ 0.58 (p=0.402)	n=91 0.37 $\pm$ 0.87	n=110 0.59 $\pm$ 0.78	0.22 (-2.06 - 2.51)	0.848
Backwards Digit Span * (Number of digits)	n=206 0.24 $\pm$ 0.08 (p=0.005)	n=91 0.21 $\pm$ 0.12	n=115 0.27 $\pm$ 0.11	0.07 (-0.26 - 0.39)	0.690
Frontal Assessment Battery (cumulative score) *	n=198 0.30 $\pm$ 0.10 (p=0.004)	n=88 0.37 $\pm$ 0.14	n=110 0.24 $\pm$ 0.13	-0.14 (-0.50 - 0.23)	0.458
NPZ score *	n=197 0.24 $\pm$ 0.04 (p<0.001)	n=87 0.28 $\pm$ 0.06	n=110 0.21 $\pm$ 0.05	-0.07 (-0.23 - 0.09)	0.373

*Table 2 legend: \* higher score represents an improvement; † lower score represents an improvement. All results shown are from multivariable linear regression models and adjusted for age, education, ethnicity and baseline test (missing data imputed).*

**Figure 1:**  
**Study Consort**  
**Diagram**

