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Longitudinal cognitive performance in individuals at ultra-high risk for psychosis: A 10-year follow-up

RUNNING TITLE: Longitudinal cognitive performance in UHR individuals

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Abstract

It remains unclear whether the onset of psychosis is associated with deterioration in cognitive performance. The aim of this study was to examine the course of cognitive performance in an ultra-high risk (UHR) cohort, and whether change in cognition is associated with transition to psychosis and change in functioning. Consecutive admissions to PACE between May 1994 and July 2000 who had completed a comprehensive cognitive assessment at baseline and follow-up were eligible (N=80). Follow-up ranged from 7.3 to 13.4 years (M=10.4 years; SD=1.5). In the whole sample, significant improvements were observed on the Similarities (p=.03), Information (p<.01), Digit Symbol Coding (p<.01), and Trail Making Test-B (p=.01) tasks, whereas performance on the Rey Auditory Verbal Learning Test (Trials 1-3) declined significantly (p<.01) over the follow-up period. Change in performance on cognitive measures was not significantly associated with transition status. Taking time to transition into account, those who transitioned after one year showed significant decline on Digit Symbol Coding, whereas those who did not transition improved on this measure (p=.01; ES=0.85). Small positive correlations were observed between improvements in functioning and improvements in performance on Digit Symbol Coding and Arithmetic (0.24, p=0.03 and 0.28, p=0.01, respectively). In summary, the onset of psychosis was not associated with deterioration in cognitive ability. However, specific findings suggest that immediate verbal learning and memory, and processing speed may be relevant domains for future risk models and early intervention research in UHR individuals.

Keywords: longitudinal, cognition, ultra-high risk, clinical high risk, prodrome, psychosis, functioning

Introduction

Considerable evidence suggests that cognitive impairments emerge early and are markers of vulnerability for psychosis. Offspring of parents with schizophrenia perform more poorly than offspring of unaffected people across a range of cognitive domains, e.g.,[1, 2]. Additionally, individuals at genetic risk who later develop schizophrenia have been differentiated from those who do not on tasks of attention[3, 4] and verbal memory[3, 5]. Cohort studies have shown that lower cognitive function in childhood and adolescence is associated with the later development of psychosis[6-12]. While these findings suggest neurodevelopmental vulnerability expressed as cognitive difficulties is associated with psychotic disorder, the course of cognition from pre- to post-psychosis onset remains unclear.

Assessment of the same individuals longitudinally, before and after the development of psychotic disorder, is necessary to determine whether progressive cognitive changes occur in association with psychosis onset. These investigations are relatively rare. In the Dunedin population cohort study, Meier et al.[13] prospectively examined cognition at age 7, 9, 11, 13 and 38 and compared individuals who had been diagnosed with schizophrenia, persistent depression, low childhood IQ, and healthy controls. A significant decline in IQ was only observed in the schizophrenia group, with the main drop occurring between ages 13 and 38. Analysis of raw score cognitive test performances showed that in the schizophrenia group significant decline was observed in processing speed, verbal learning, mental flexibility and motor function[14]. More recently, Mollon et al.[15] mapped IQ change from 18 months, 4, 8, 15 and 20 years of age within the Avon Longitudinal Study of Parents and Children (ALSPAC) study. Individuals who developed psychotic disorder (compared to those with depression, psychotic experiences and healthy controls) showed increasing deficits in Full-Scale and Performance IQ from 18 months to 20 years of age, whereas Verbal IQ declined early and remained statically impaired from age 8-20. Based on raw scores, increasing lag (i.e.,

attenuated improvement, but not decline/worsening of performance) in processing speed, working memory and attention were also observed from age 8-20. These studies further support the neurodevelopmental model of psychosis, with equivocal evidence of progressive decline in specific cognitive domains in association with psychotic disorder.

Studies of individuals at ultra-high risk (UHR) for psychosis show cognitive performance at an intermediate level to healthy controls and individuals with first-episode psychosis[16-19]. Those who later develop psychotic disorder are found to have larger impairments compared to their UHR counterparts who do not transition to psychosis[16-20]. Findings have been inconsistent regarding the domains affected, with intelligence[17-19, 21], verbal fluency[18, 22], working memory[18, 20], attention[16], processing speed[16], and visual[16, 18, 20] and verbal memory[16, 18] all being implicated. The magnitude of baseline impairment in UHR participants who transition to psychosis (relative to healthy controls) has been shown to be comparable to first-episode populations, particularly in IQ, visual and verbal memory and processing speed[16], suggesting that all cognitive impairment may occur before the onset of full threshold disorder. This evidence is primarily based on cross-sectional research comparing different samples across different clinical stages. Knowledge about the course of cognitive functioning prior to and during illness onset, and specifically, whether impairments in UHR individuals who develop psychotic disorder are progressive remains limited.

Longitudinal studies of UHR individuals have captured the course of cognitive functioning close to illness onset. Meta-analytic findings of four studies suggest that cognition either remains stable or improves from pre- to post-psychosis onset[23], a finding replicated in a recent study[24]. Using a healthy comparison group to reference predicted cognitive performance over one year, Woodberry et al.[25] found that a UHR sample showed progressive impairment over 12 months on tests of verbal memory and executive function, with larger (but non-significant) verbal memory impairment observed in those who

developed psychosis (*n*=10) compared with those who did not (*n*=43). Together, longitudinal UHR studies have yielded little evidence that cognitive changes are associated with transition to psychosis, which is in contrast to the population cohort studies cited above[13, 15]. However, previous UHR studies have recruited relatively small samples and assessed them over reasonably short follow-up periods (<18 months), increasing the chance of missing cases who will transition later and reducing power to detect significant change.

Differences between those who do and do not progress to psychosis has been the primary outcome of interest in UHR studies investigating cognitive change. However, this approach ignores the heterogeneous composition of the group that do transition, and the arbitrary nature of the threshold for frank psychosis[26]. Studying an alternative outcome may further clarify the course of cognition during the UHR state. One candidate is functional outcome[26, 27]. There is mounting evidence of continued functional impairment in UHR, even in those who do not transition[28, 29]. Only two small studies have examined whether longitudinal change in cognition is associated with change in functioning in UHR. One study showed change in verbal learning and memory and processing speed were associated with change in functioning over 8 months[30] and another found that change in semantic fluency was associated with changes in negative symptoms and functioning over 2 years[31]. Further studies are needed to clarify the relationship between cognitive and functional change in UHR samples.

In this study, we investigated change in cognitive performance in a UHR cohort followed-up for a mean of 10 years. We aimed to extend current knowledge by investigating cognitive performance over a longer follow-up period than previous UHR studies and to examine whether there is a relationship between cognitive changes and transition to psychosis, as well as change in functioning. Given our long follow-up period and evidence from longitudinal cohort studies, we hypothesised that significantly greater cognitive decline

would be evident in UHR individuals who transitioned to psychosis, relative to those individuals who did not transition to psychosis over a 10-year period. We also hypothesised that change in cognition would be positively associated with change in functioning.

Methods

Participants and procedure

Participants were part of a larger long-term follow-up study which aimed to locate and reassess all people identified as UHR for psychosis between 1993 and 2006 who had agreed to participate in research (*N*=416) at the PACE Clinic, Melbourne, Australia[32]. At follow-up, 268 (64.4%) participants underwent a comprehensive face-to-face interview, including assessment of psychopathology and cognition. The cognitive battery was not identical over the entire baseline period. For this report, only participants who were recruited between May 1994 and July 2000 were selected because the cognitive battery was consistent and included a comprehensive assessment of IQ and cognitive domains (*N*=80).

At baseline, participants were aged 15-30 years and met one or more of the operationalised UHR criteria, assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS)[33]. These criteria are: 1) attenuated psychotic symptoms (APS), 2) brief limited intermittent psychotic symptoms (BLIPS), and/or 3) trait vulnerability for psychotic illness (schizotypal personality disorder or a history of psychosis in a first-degree relative) and deterioration in functioning or chronic low functioning. Exclusion criteria for PACE are a previous psychotic episode (treated or untreated), organic cause for presentation, or past antipsychotic exposure equivalent to a total haloperidol dose of >50 mg. Participants in cognition research were also required to have normal (or corrected-to-normal) vision and hearing, and speak English as their preferred language. Exclusion criteria were a neurological disorder and a history of significant head injury or seizures. The study was approved by the

Research and Ethics Committee at Melbourne Health. All participants provided written informed consent at both assessments.

Outcome measures

The CAARMS[33] was used to establish UHR status at baseline and transition to frank psychosis over the follow-up period. At baseline and follow-up, functioning was measured using the Quality of Life Scale (QLS)[34], with change in functioning calculated as follow-up minus baseline total QLS score. Symptom measures included the Brief Psychiatric Rating Scale (BPRS), psychotic subscale[35], Scale for the Assessment of Negative Symptoms (SANS)[36], and Hamilton Rating Scales for Depression and Anxiety (HAMD and HAMA, respectively)[37, 38].

Cognition measures

Current IQ was measured using the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[39]. IQ was estimated using either 1) Ward's[40] 7-subtest estimate of Verbal, Performance and Full-Scale IQ (FSIQ), based on subtests Information, Picture Completion, Block Design, Arithmetic, Digit Span, Similarities and Digit Symbol Coding, or 2) Kaufman's 4-subtest[41] estimate of FSIQ, based on subtests Digit Symbol Coding, Similarities, Arithmetic and Picture Completion. Previous research in schizophrenia shows that both short-forms provide reliable estimates of IQ[42, 43]. Thus, the FSIQ estimate from either WAIS-R short-form was used in the current analysis.

Memory was assessed using Logical Memory I, Visual Reproduction I and Verbal Paired Associates I (VPA) from the Wechsler Memory Scale-Revised (WMS-R)[44]. The Verbal Memory Index (VMI) was calculated from Logical Memory I and VPA I. A modified three-trial version of the Rey Auditory Verbal Learning Test (RAVLT)[45] was used to assess immediate verbal learning and memory. The Trail Making Test (TMT)[46] was used to assess processing speed and basic attention (TMT-A total time) and divided attention and cognitive

flexibility (TMT-B total time). Apart from the IQ and memory indices, raw scores were used for all other cognitive tasks. This decision was made because the long follow-up period would result in different normative data being used for each participant at each time-point; within different normative age bands there may be variation in ability in the standardization samples, which would impact standard scores. Furthermore, normative data for each cognitive task (e.g., TMT, RAVLT, WAIS subtests) comes from different standardization samples. Participants completed identical versions of the cognitive tasks at both time points. It is important to note that for those who transitioned to psychosis, the follow-up cognitive assessment occurred after transition (range 1.2-12 years, mean 8.6, SD=2.8).

Statistical analyses

Data were analysed using R version 3.4.3[47]. To examine whether change in cognition was associated with transition to psychosis, general linear model (GLM) analysis was applied with change in cognitive scores as the dependent variable and transition status (no/yes) as the independent variable. For each cognitive measure, the corresponding baseline cognitive score and time to follow-up were included as covariates. To incorporate time to transition into the analysis, transition status was treated as a factor on three levels: (1) no known transition, (2) onset within one year (n=16) and (3) onset after one year (n=15), with one year chosen as it was the median. The GLM analysis was repeated with this transition factor and level 1 of this factor was used as the reference level. Pearson correlations (adjusting for time to follow-up and transition status) were also run to determine whether changes in cognition were associated with changes in positive, negative, depressive or anxiety symptoms. To examine whether change in cognition was associated with change in functioning, Pearson correlations were conducted between change in QLS total and change in each of the cognitive measures. These correlations were repeated adjusting for time to follow-up and transition status, producing partial correlations. Cognitive tasks were examined individually rather than

grouped into cognitive domains for several reasons. First, it may be theoretically incorrect to assume that tasks purporting to tap into similar cognitive domains assess a single cognitive process or that the effect sizes for different processes are the same[48]. Second, direct comparisons can be made with the findings of previous studies. Third, grouping tasks would have resulted in the exclusion of participants who did not complete all tasks.

Results

Sample characteristics

The UHR criteria of participants at intake was: 35 (43.8%) APS, 8 (10.0%) BLIPS, 13 (16.2%) trait vulnerability, 6 (7.5%) APS+BLIPS, 14 (17.5%) APS+trait vulnerability, and 3 (3.8%) met all three UHR criteria. Intake criteria were not available for one participant (1.2%). Other baseline participant details are reported in Table 1. Among the 80 participants, 31 (38.8%) made a transition to psychotic disorder (UHR-P) and the remainder (*n*=49; 61.2%) did not experience a psychotic episode (UHR-NP) within the follow-up period. The mean time to transition from baseline was 1.8 years (SD 2.2; range 0.2-9.7 years). The transition diagnosis for the 31 who transitioned was: schizophrenia, 12 (38.7%); major depressive disorder with psychotic features, 5 (16.1%); bipolar disorder with psychotic features, 5 (16.1%); brief psychotic disorder, 3 (9.7%); delusional disorder, 2 (6.5%); substance induced psychotic disorder, 2 (6.5%); and schizoaffective disorder, 1 (3.2%). The diagnosis for one participant was not available. The mean length of follow-up was 10.4 years (SD=1.4, range 7.3-13.1 years), corresponding to a mean age at follow-up of 30.5 years (SD=3.7, range 24-40 years).

Change in cognition over the follow-up period and relationship to psychosis transition

Table 2 shows performance on the cognitive measures at baseline, follow-up and change over this period (follow-up minus baseline) for the whole sample. Performance on most cognitive measures was relatively stable over the two time points. Significantly

improved performances were observed on Similarities (p=.03), Information (p<.01), Digit Symbol Coding (p<.01), and TMT-B (p=.01). Performance on the RAVLT significantly declined (p<.01) over the follow-up period. Changes in positive, negative, and anxiety symptoms were not associated with any of these cognitive changes (all p>.05). Reduction in depressive symptoms was only associated with improvement in Digit Symbol Coding performance (r=-.23, p=.049).

Next, we examined whether change in cognition was associated with transition status (UHR-P or UHR-NP), while controlling for baseline performance and time to follow-up. Table 3 shows the results of these analyses, which indicate that change in cognition was not significantly associated with transition status on any measure (also see Supplementary Figures). While non-significant, the decline in RAVLT performance was moderately larger in the transition group than the non-transition group (ES =-0.37, p=.18). As time to transition might be important in relation to change in cognition over the follow-up period, we examined this with transition status treated as three levels: 1) no transition (n=49), 2) transition within one year (n=16), and 3) transition after one year (n=15), with no transition treated as the reference level. There was only one significant finding, which was in relation to change in Digit Symbol Coding (p=.01), showing that those who transitioned after one year had a decline in score (mean change -1.5, SD 7.0), whereas those who did not transition had an improved score (mean change 2.9, SD 6.1). The effect size for the change in Digit Symbol Coding performance between those who did not transition and those who transitioned after one year was large (0.85). The mean change of those who transitioned within one year indicated an improvement in Digit Symbol Coding performance (Supplementary Table 1).

Change in cognition over the follow-up period and relationship to change in functioning

The overall sample significantly improved in functioning (QLS total) over the follow-up period (mean change=19.7, SD=30.9, p<.001), with no difference between the UHR-P and

UHR-NP groups in change in functioning (p=.103). Pearson correlations between change in cognitive scores and change in functioning showed two significant, small positive correlations; Digit Symbol Coding (r=0.29, p=.01) and Arithmetic (r=0.26, p=.03). Partial correlations adjusting for time to follow-up and time to transition (no transition, <1 year, >1 year) were conducted next, since change in Digit Symbol Coding showed a significant association with transition status. The partial correlations between change in functioning and Digit Symbol Coding and Arithmetic remained positive and significant (r=0.24, p=0.03 and r=0.28, p=0.01, respectively; Table 4).

Discussion

Cognitive functioning over a mean of 10 years was examined in 80 UHR individuals, with a focus on whether an association existed between change in cognition and transition to psychosis and change in functioning over this period. To our knowledge, this is the longest follow-up of cognitive functioning in a UHR cohort, with notable strengths being that the same tests were administered at both time-points and there was a relatively large subgroup (38.8%) who transitioned to psychosis. The key findings were that: 1) cognition was generally stable or improved, with the exception of immediate verbal learning and memory (RAVLT), which declined significantly in the UHR sample over the follow-up period; 2) cognitive changes were generally not associated with changes in symptoms; 3) change in cognitive performance was not associated with transition status; 4) taking time of transition into account revealed that those who transitioned after one year post service entry had a significant decline in Digit Symbol Coding score, whereas those who did not transition had an improved score; and 5) there were small significant correlations between improvements in functioning and Digit Symbol Coding and Arithmetic, which remained after accounting for time to follow-up and transition status.

Stability or improvement in performance on most cognitive tests is consistent with the findings of previous studies[23, 24] and is inconsistent with the notion of a generalized deteriorating course of cognition in UHR, and specifically, in association with the onset of psychosis. Significantly improved performance was observed in verbal skills (Similarities/Information), processing speed (Digit Symbol Coding), and mental flexibility (TMT-B). A reduction in depressive symptoms was associated with improvements on Digit Symbol Coding, but the other cognitive performance changes were not related to symptom changes. The improvements observed are unlikely to be due to practice effects given the long follow-up period[49]; however, without a matched healthy comparison group, we do not know whether the cognitive stability or improvements observed over the 10-year period is consistent with typical performance. Developmental lag (attenuated gain) in cognitive abilities remains possible in this sample as has been found in previous cohort studies that included healthy controls[15, 50].

The distinct decline in immediate verbal learning and memory in this UHR cohort is noteworthy. While the mechanism is unclear, our findings indicated that this decline was not associated with changes on any of the symptom measures. A decline in verbal memory (as well as failure to improve as expected in executive functioning) in comparison to healthy controls was previously observed in a 1-year follow-up study of clinical high risk individuals[25]. In lieu of a healthy comparison group, Australian normative data of RAVLT performance in individuals aged 18-34 years shows similar mean raw score performances as our UHR group at baseline (30.0 versus 28.9, respectively), while the performance of the UHR group at follow-up fell over half a standard deviation below the normative sample mean (25.9 versus 30.0, respectively)[51]. As the normative sample mean is cross-sectional and covers the mean age of our cohort across both time-points, whether the decline in our UHR cohort is a marker of progression of verbal memory impairment remains unclear. In the

Dunedin birth cohort study, immediate verbal learning and memory (measured using a 4-trial version of the RAVLT) significantly declined by a mean of 7 words between age 13 and 35 in those with schizophrenia[14]. In contrast, the healthy and persistent depression groups recalled 3 fewer words from age 13 to 35, suggesting that the ability to learn and remember verbal information normatively declines from early adolescence to adulthood, but such decline may be accelerated in schizophrenia[14]. Longitudinal studies of first-episode psychosis have shown that poorer verbal learning and memory (including decline over time) is associated with poorer clinical outcomes, such as incomplete symptomatic recovery and relapse[52-54]. While the course of verbal learning and memory did not significantly differ between the UHR-P and UHR-NP groups in our study, the decline was greater in those who transitioned (group difference ES=-0.37). Again, similar findings were observed by Woodberry and colleagues[25], who found a larger non-significant decline in those who transitioned to psychosis. A longer follow-up and/or larger sample may be necessary to reveal a significantly greater decline in UHR-P and in association with more chronic illness[13]. Future hypothesis-driven research should investigate whether change in verbal learning and memory is a specific marker of frank psychosis.

Nevertheless, our findings indicate that the course of cognition in UHR may not be useful for differentiating transition from non-transition UHR individuals in the initial year after ascertainment. This is broadly consistent with the findings of previous UHR studies that had follow-up periods of 6-18 months[24, 55-57]. Due to our long follow-up period, we were able to explore whether timing of transition was associated with cognitive change and found that a decline in processing speed (Digit Symbol Coding) was associated with later transition (after 1 year). It is not clear why only later transition was associated with processing speed decline. It may be speculated that those who transition later have a more insidious onset of psychotic disorder and/or that type and dose of treatment received may differ, which may associated

with greater decline in processing speed. Post-hoc analysis showed no significant difference in duration of symptoms prior to clinic entry between those who transitioned within or after 1 year. The Dunedin birth cohort study revealed that, in individuals with schizophrenia, processing speed declined more than any other cognitive domain and the greatest decline in processing speed was observed after adolescence[13]. In the ALSPAC study, an increasing developmental lag in processing speed (ESΔ=−0.68) was observed in the group with psychotic disorder, which was larger than other cognitive domains[15]. In the most recent and comprehensive meta-analysis of cognitive test performance in UHR individuals, verbal and visual learning and memory and processing speed were the cognitive domains suggested to be the most promising risk markers for psychosis, with the recommendation that these domains should be further examined as potential candidates for complex risk prediction models and further longitudinal investigation[16].

Some discussion is warranted in relation to the lack of evidence for progressive IQ impairment in the current and previous UHR studies, which is in contrast to longitudinal birth cohort studies[13, 15]. UHR individuals in the current study may have passed through the period of peak vulnerability to IQ decline, relative to more fluid cognitive functions. Emerging evidence suggests that the pattern of IQ impairment in psychotic disorders, particularly schizophrenia, is characterised by early and relatively static verbal IQ impairments with progression of nonverbal IQ impairments, particularly during early adolescence[13, 15]. Our sample on average had entered the third decade of life at baseline assessment (mean age 20.2 years), and any decline in IQ differentiating true psychotic disorder cases (especially schizophrenia) may have already occurred in early adolescence. In contrast, vulnerability to ongoing decline in fluid functions such as verbal learning and memory and processing speed may be observed in young adults with persistent psychotic symptoms.

The findings of significant associations between changes in processing speed (Digit Symbol Coding) and auditory verbal working memory (Arithmetic) and changes in functioning are partially consistent with Niendam et al.[30], who showed that improved functioning was associated with improvements in processing speed and visual learning and memory over 8 months. In contrast, Shin et al.[31] found that change in semantic fluency was significantly associated with changes functioning over 2 years. The association between these cognitive domains and functioning remained regardless of psychosis transition status, adding to the evidence in the psychosis literature for a robust relationship between cognition and functioning is independent of positive symptoms[58, 59]. The strength of the relationship between change in cognition and functioning was small, and based on previous research, cognition at ascertainment rather than change in cognition, may provide greater clinical utility with respect to predicting functional outcome in UHR (particularly over the long term)[60, 61].

The main limitation of our study is the absence of a healthy control group to examine how the longitudinal course of cognition in UHR compares to typically developing individuals. Nevertheless, practice effects are unlikely given the long interval between assessments[49]. Another limitation is the variable times the follow-up assessments were conducted, ranging from 7-13 years. However, time to follow-up was controlled for in all analyses. Finally, we were unable to take into account use of antipsychotics (participants were only asked if they had ever taken antipsychotics, without any indication of frequency or dose), which are shown to be associated with a decline in verbal learning and memory in UHR individuals[62]. Future research should carefully evaluate the role of medication in association with cognitive performance in UHR.

In conclusion, this is the longest study to track the cognitive performance of a UHR sample over the period of transition to psychosis. Cognition was generally stable or improved

over the 10-year period, with the exception of immediate verbal learning and memory, which significantly declined. Those who transitioned to psychosis after one year showed a significant decline in processing speed relative to the non-transition group who showed a significant improvement. Small significant relationships between change in processing speed and auditory verbal working memory and functioning were observed. More work is needed to understand the course and timing of cognitive impairment in psychotic illness and its relationship to symptomatology, medication use and functioning. To achieve this, large samples that include healthy and non-UHR clinical controls need to be assessed with comprehensive cognitive batteries at multiple time points over a long period.

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Table 1. Baseline characteristics of the sample (*N*=80)

	Mean	SD
Gender (Female)	54%	
Age (years)	20.2	3.2
Duration of symptoms[a] (days)	419.9	511.3
BPRS psychotic	8.4	2.7
SANS total	18.0	12.9
HAM-A total	16.7	8.1
HAM-B total	19.5	10.7
QLS total	74.2	23.0

BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symtoms; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; QLS = Quality of Life Scale; SD = standard deviation

[a]Duration of symptoms is the time between any symptom onset and first contact with the PACE clinic.

Table 2. Cognition scores at baseline and follow-up and change in performance in whole UHR sample

	Baseline		Follow-up		Change		
	Mean	SD	Mean	SD	Mean	SD	*N*
FSIQ[a]	96.2	13.5	97.5	14.4	1.2	8.3	79
VIQ	95.2	13.4	94.1	13.3	-1.1	6.9	58
PIQ	98.1	16.5	99.7	16.5	1.6	8.9	57
Similarities	18.9	4.8	19.8	4.3	0.9*	3.6	77
Information	15.3	6.3	17.3	6.4	1.9**	2.8	57
Picture Completion	15.0	3.5	15.2	3.4	0.2	2.5	77
Block Design	30.5	10.2	30.9	11.3	0.4	5.6	57
Digit Symbol Coding	55.2	11.4	57.7	11.8	2.5**	6.6	78
Arithmetic	9.3	3.4	9.7	3.6	0.4	2.1	77
Digit Span	14.2	4.4	14.4	4.3	0.3	3.4	77
TMT A (secs)[b]	27.6	9.0	28.9	11.1	1.3	8.4	58
TMT B (secs)[b]	72.6	28.0	64.8	18.6	-7.7*	21.2	57
VMI	89.4	18.2	93.2	16.6	3.7	13.8	53
Logical Memory I	24.0	8.5	24.1	8.1	0.1	6.8	57
VPA I easy	10.7	1.7	10.6	1.8	-0.1	2.0	77
VPA I hard	7.7	2.9	7.1	2.9	-0.6	3.0	77
Visual Reproduction I	33.4	6.7	34.2	7.3	0.9	5.2	55
RAVLT total[c]	28.9	5.2	25.9	7.1	-3.0**	6.2	58

FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; TMT = Trail Making Test; VMI = Verbal Memory Index; VPA = Verbal Paired Associates; RAVLT = Rey Auditory Verbal Learning Test; SD = standard deviation

[a]Based on Ward's 7-subtest or Kaufman's 4-subtest WAIS-R short-form

[b]Lower scores mean better performance

[c]Modified three-trial version

*p<.05; **p<.01

Table 3. Change in cognition scores in relation to transition status

	UHR-NP			UHR-P				
	Mean change	SD	n	Mean change	SD	n	p*	ES[†]
FSIQ	0.4	7.2	49	2.6	9.7	30	0.37	0.21
VIQ	-1.1	7.0	36	-1.0	7.1	22	0.68	-0.11
PIQ	2.0	9.8	35	0.9	7.3	22	0.35	-0.26
Similarities	0.6	3.2	47	1.3	4.1	30	0.77	0.07
Information	1.9	2.8	35	2.0	2.9	22	0.89	-0.04
Picture Completion	0.2	2.5	47	0.2	2.5	30	0.43	-0.19
Block Design	0.6	5.7	35	0.1	5.5	22	0.68	-0.11
Digit Symbol Coding	2.9	6.1	47	2.0	7.5	31	0.39	-0.20
Arithmetic	0.1	2.1	47	0.8	2.1	30	0.25	0.28
Digit Span	-0.2	3.4	47	0.9	3.4	30	0.31	0.24
TMT A (secs)	1.5	8.6	35	1.1	8.3	23	0.92	0.03
TMT B (secs)	-4.4	20.2	34	-12.7	22.0	23	0.90	0.04
VMI	3.2	12.5	32	4.6	15.7	21	0.92	-0.03
Logical Memory I	-0.4	5.9	35	0.8	8.1	22	0.71	0.10
VPA I easy	-0.2	1.9	47	0.0	2.0	30	0.70	0.09
VPA I hard	-0.3	2.9	47	-1.1	3.3	30	0.22	-0.29
Visual Reproduction I	0.9	4.9	33	0.8	5.7	22	0.40	-0.25
RAVLT total	-2.3	5.6	35	-4.1	7.0	23	0.18	-0.37

*p-value of general linear model analysis comparing transition status in terms of change in each cognitive measure with baseline score and time to follow-up as covariates.
[†]ES = Effect size based on the general linear model analysis.
UHR-NP = no transition to psychosis; UHR-P = transition to psychosis; SD = standard deviation; FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; TMT = Trail Making Test; VMI = Verbal Memory Index; VPA = Verbal Paired Associates; RAVLT = Rey Auditory Verbal Learning Test

Table 4. Pearson correlation between change in QLS total and change in cognition scores

	No covariates		Adjusting for time to follow-up		Adjusting for time to follow-up and transition status	
	Correlation	*p*	Correlation	*p*	Correlation	*p*
FSIQ	0.15	0.19	0.09	0.45	0.09	0.41
VIQ	-0.01	0.95	-0.05	0.71	-0.10	0.45
PIQ	0.11	0.40	0.10	0.44	0.10	0.47
Similarities	0.03	0.82	0.00	0.98	-0.02	0.87
Information	-0.09	0.51	-0.10	0.47	-0.12	0.38
Picture Completion	0.01	0.95	-0.03	0.79	-0.04	0.73
Block Design	0.10	0.44	0.10	0.45	0.09	0.51
Digit Symbol Coding	**0.29**	**0.01**	**0.27**	**0.02**	**0.24**	**0.03**
Arithmetic	**0.26**	**0.03**	**0.23**	**0.04**	**0.28**	**0.01**
Digit Span	-0.13	0.26	-0.14	0.23	-0.13	0.27
TMT A (secs)	0.01	0.93	0.02	0.87	0.03	0.80
TMT B (secs)	-0.01	0.95	0.01	0.92	-0.02	0.90
VMI	0.01	0.95	0.05	0.72	0.00	0.99
Logical Memory I	-0.01	0.93	0.03	0.81	0.01	0.92
VPA I easy	0.18	0.12	0.19	0.10	0.18	0.12
VPA I hard	-0.06	0.59	-0.04	0.70	-0.08	0.51
Visual Reproduction I	0.04	0.75	0.10	0.48	0.07	0.61
RAVLT total	0.14	0.29	0.16	0.23	0.14	0.30

FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; TMT = Trail Making Test; VMI = Verbal Memory Index; VPA = Verbal Paired Associates; RAVLT = Rey Auditory Verbal Learning Test

Supplementary Table 1. Comparing the three levels of transition status in terms of change in cognitive measures.

	Transition status													
	No			Yes, onset ≤ 1 year			Yes, onset > 1 year							
	Mean change	SD	n	Mean change	SD	n	Mean change	SD	n	p-value1*	p-value2*	effect size1†	effect size2†	Total n
FSIQ	0.4	7.2	49	4.3	9.1	16	0.6	10.3	14	0.07	0.59	0.53	-0.17	79
Digit Symbol Coding	2.9	6.1	47	5.2	6.5	16	-1.5	7.0	15	0.21	0.01	0.37	-0.85	78
VPA I easy	-0.2	1.9	47	0.5	1.3	16	-0.6	2.6	14	0.14	0.35	0.43	-0.29	77
VPA I hard	-0.3	2.9	47	-0.9	2.5	16	-1.3	4.1	14	0.63	0.15	-0.14	-0.45	77
Picture Completion	0.2	2.5	47	0.3	2.3	16	0.1	2.8	14	0.81	0.29	-0.07	-0.33	77
Similarities	0.6	3.2	47	2.8	4.3	16	-0.3	3.2	14	0.06	0.11	0.57	-0.50	77
Arithmetic	0.1	2.1	47	0.8	2.3	16	0.9	1.8	14	0.26	0.51	0.33	0.21	77
Digit Span	-0.2	3.4	47	1.5	3.4	16	0.3	3.5	14	0.08	0.78	0.52	-0.09	77
RAVLT total	-2.3	5.6	35	-3.6	8.5	12	-4.6	5.4	11	0.42	0.18	-0.27	-0.47	58
TMT A	1.5	8.6	35	-0.4	7.4	12	2.6	9.3	11	0.55	0.41	-0.20	0.30	58
VIQ	-1.1	7.0	36	1.4	6.4	12	-4.0	6.9	10	0.27	0.06	0.38	-0.75	58
Logical Memory I	-0.4	5.9	35	3.1	8.1	12	-1.9	7.8	10	0.12	0.26	0.54	-0.42	57
Block Design	0.6	5.7	35	0.6	7.0	12	-0.5	3.2	10	0.99	0.51	-0.01	-0.25	57
Information	1.9	2.8	35	2.3	2.7	12	1.5	3.2	10	0.65	0.45	0.15	-0.28	57
TMT B	-4.4	20.2	34	-11.7	23.8	12	-13.9	20.9	11	0.39	0.23	-0.29	0.46	57
PIQ	2.0	9.8	35	0.8	7.9	12	1.0	7.0	10	0.56	0.37	-0.20	-0.34	57
Visual Reproduction I	0.9	4.9	33	2.3	3.6	12	-1.0	7.3	10	0.95	0.13	0.02	-0.58	55
VMI	3.2	12.5	32	10.7	13.4	11	-2.2	15.9	10	0.12	0.07	0.57	-0.69	53

* P-values of transition status from general linear model analysis with baseline score and time to follow-up as covariates; p-value1: 'yes, onset ≤ 1 year' vs. 'no'; p-value2: 'yes, onset > 1 year' vs. 'no'

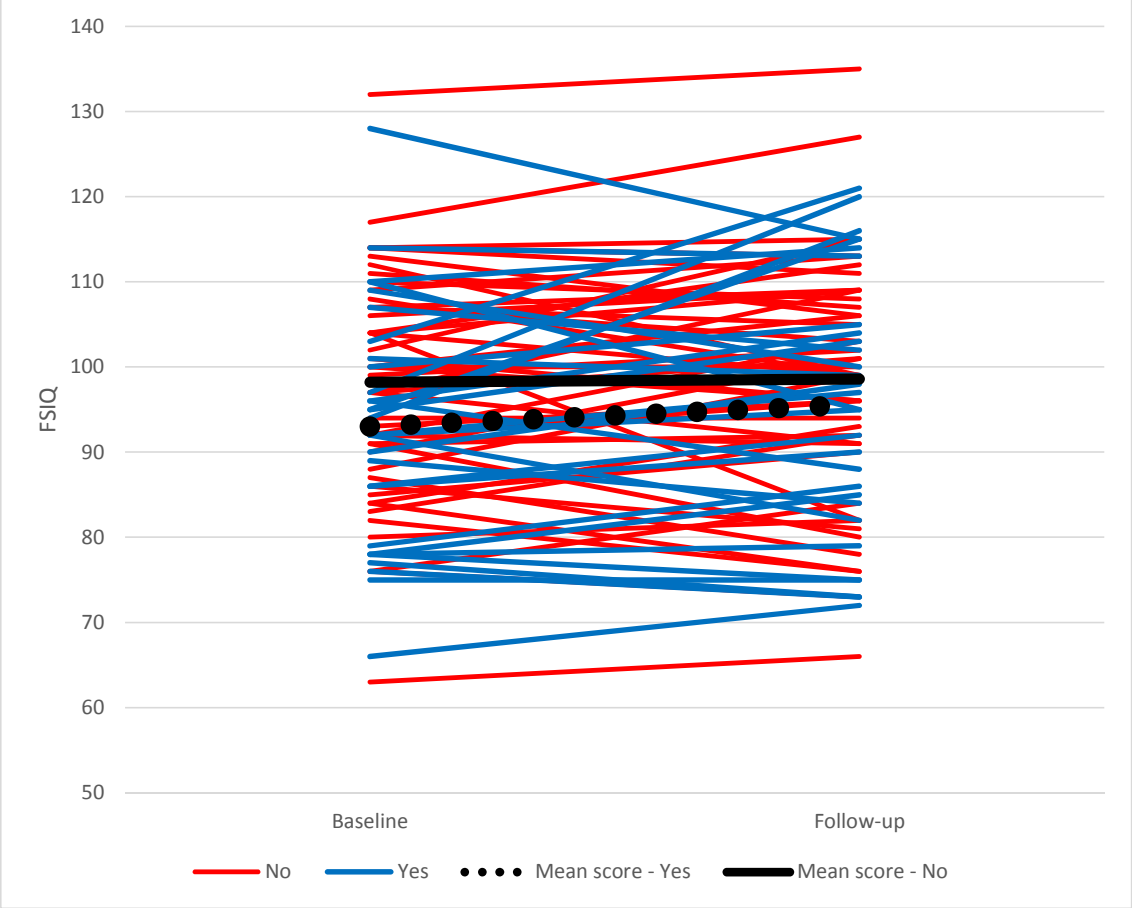
† Effect sizes of transition status based on the general linear model analysis; effect size1: 'yes, onset ≤ 1 year' vs. 'no'; effect size2: 'yes, onset > 1 year' vs. 'no'

SD = standard deviation; FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; TMT = Trail Making Test; VMI = Verbal Memory Index; VPA = Verbal Paired Associates; RAVLT = Rey Auditory Verbal Learning Test

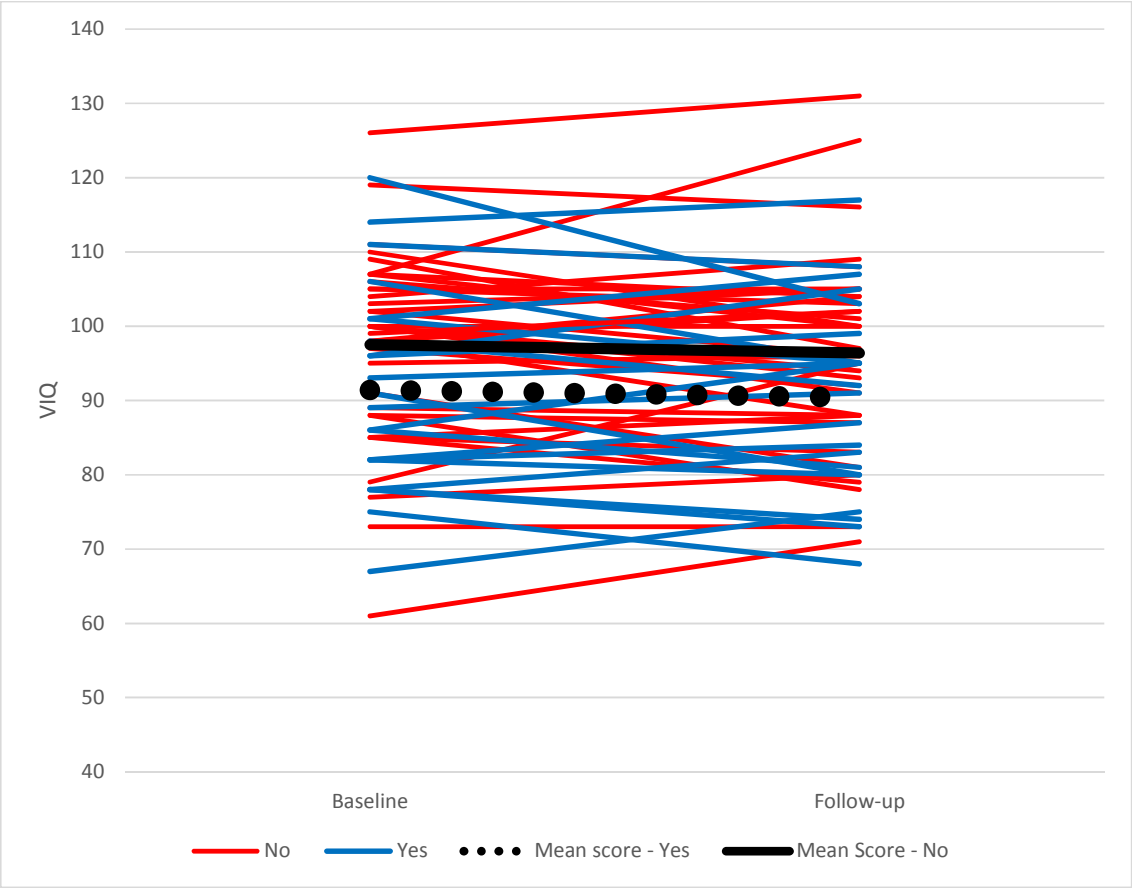
Supplementary Figures.

Change in performance on each cognitive measure for each participant and mean for those who transitioned to psychosis (YES) and those who did not (NO).

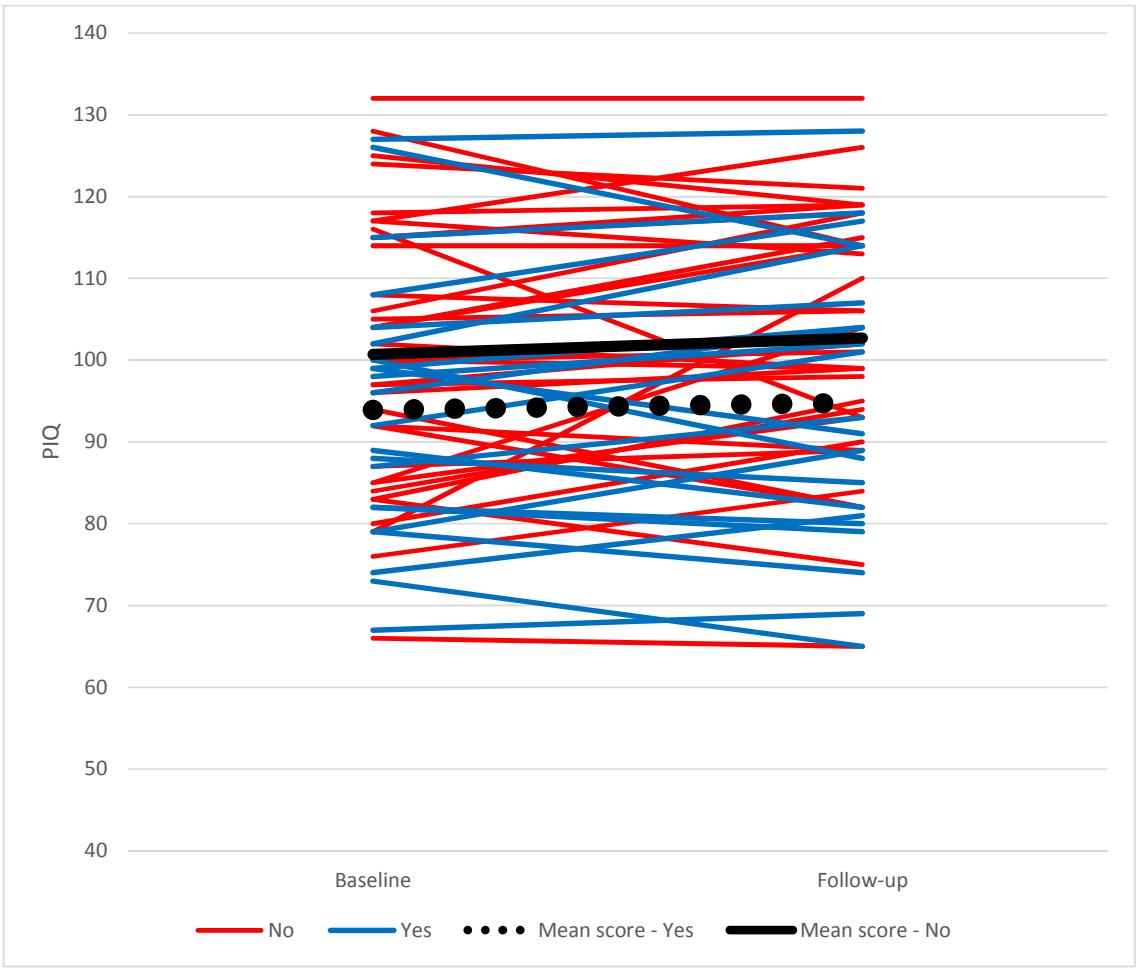
a) FSIQ



b) VIQ


140
130
120
110
100
90
80
70
60
50
40
VIQ
Baseline
Follow-up
No
Yes
Mean score - Yes
Mean Score - No

c) PIQ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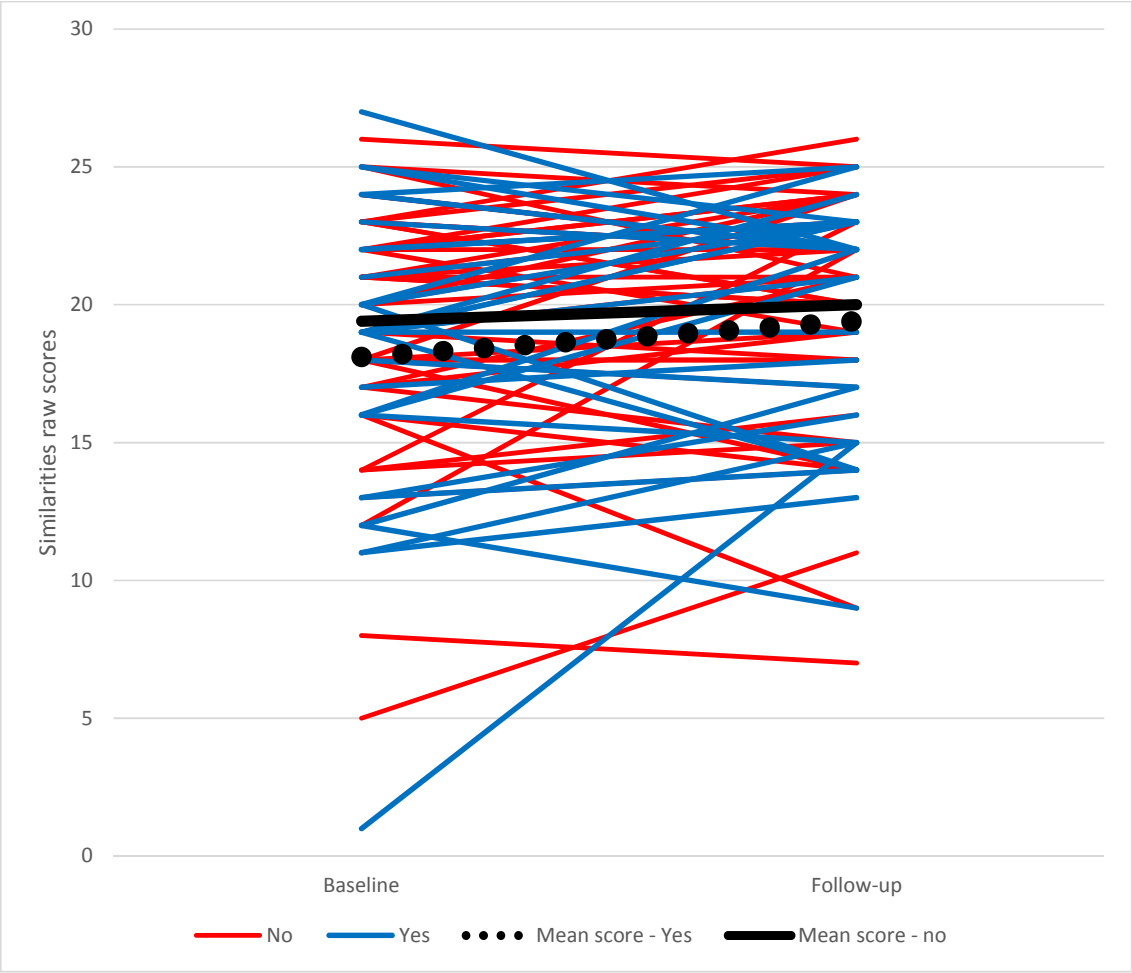
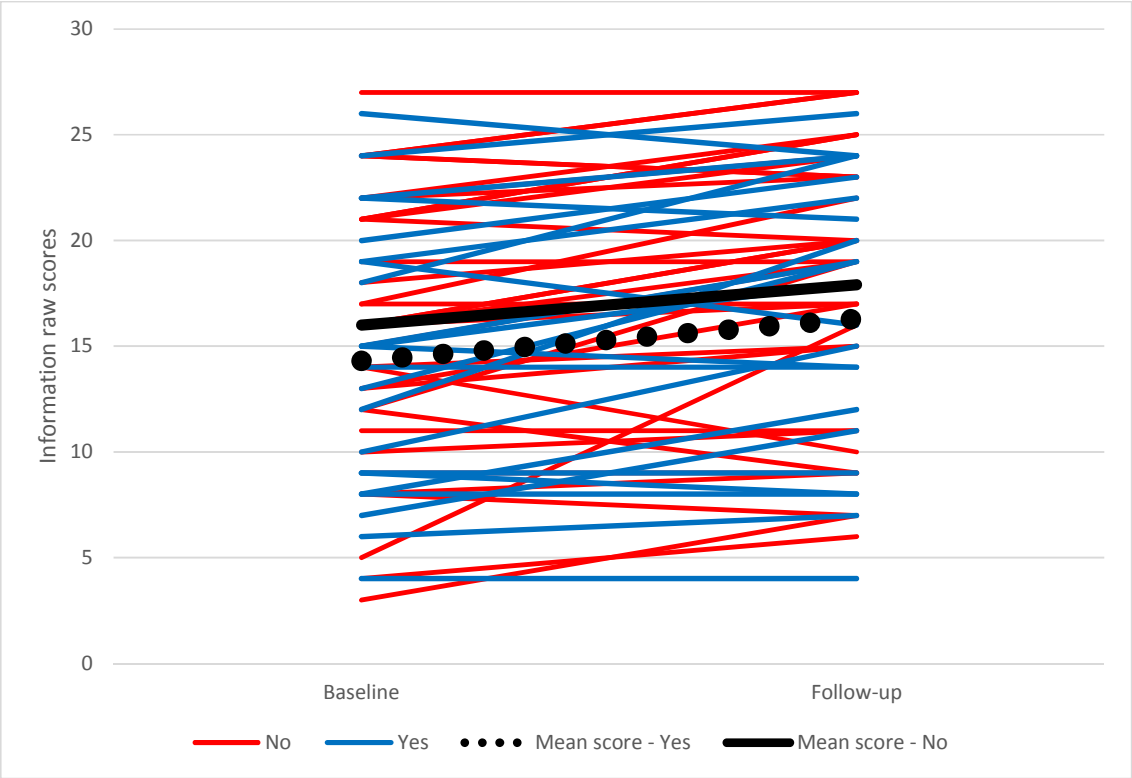
130
120
110
100
90
80
70
60
50
40
PIQ
Baseline
Follow-up
No
Yes
Mean score - Yes
Mean score - No

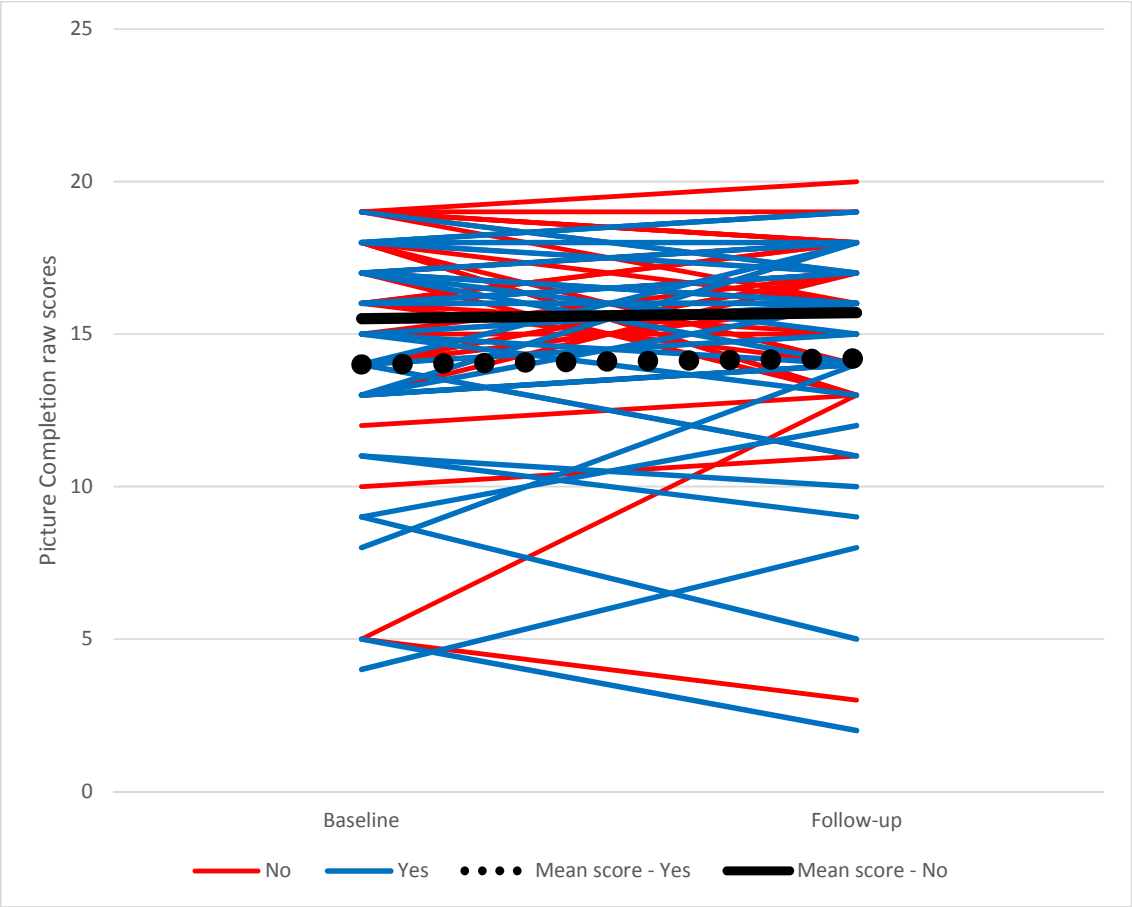
d) Similarities



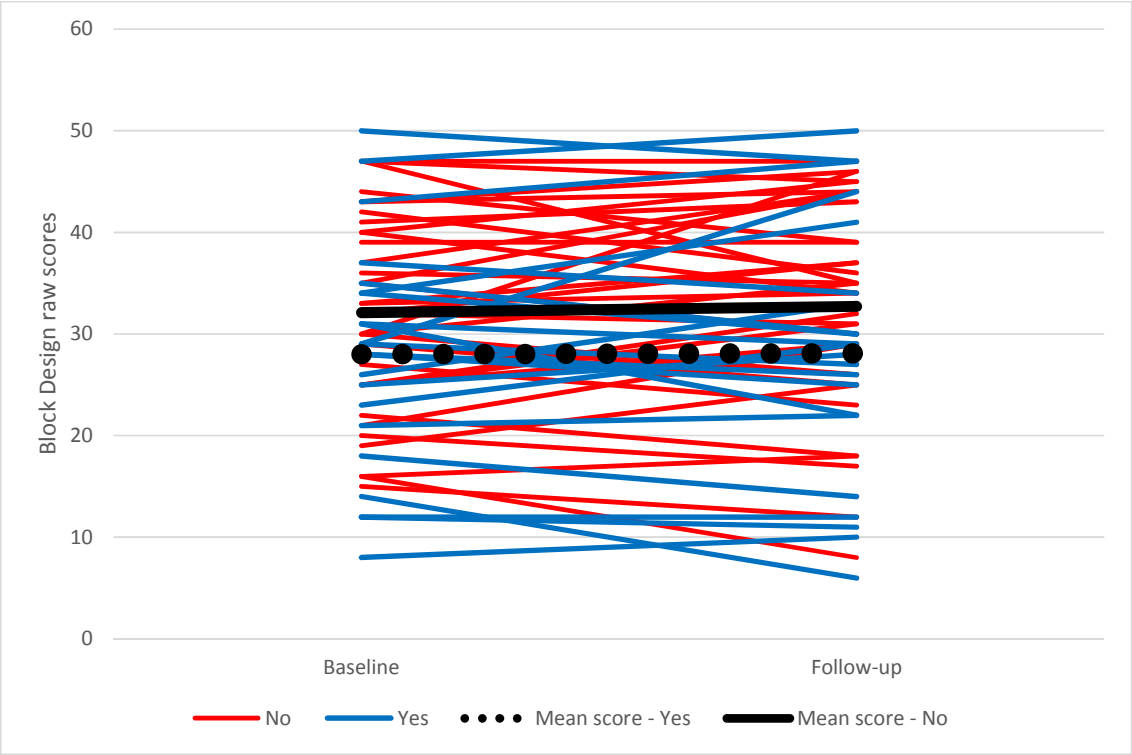
e) Information



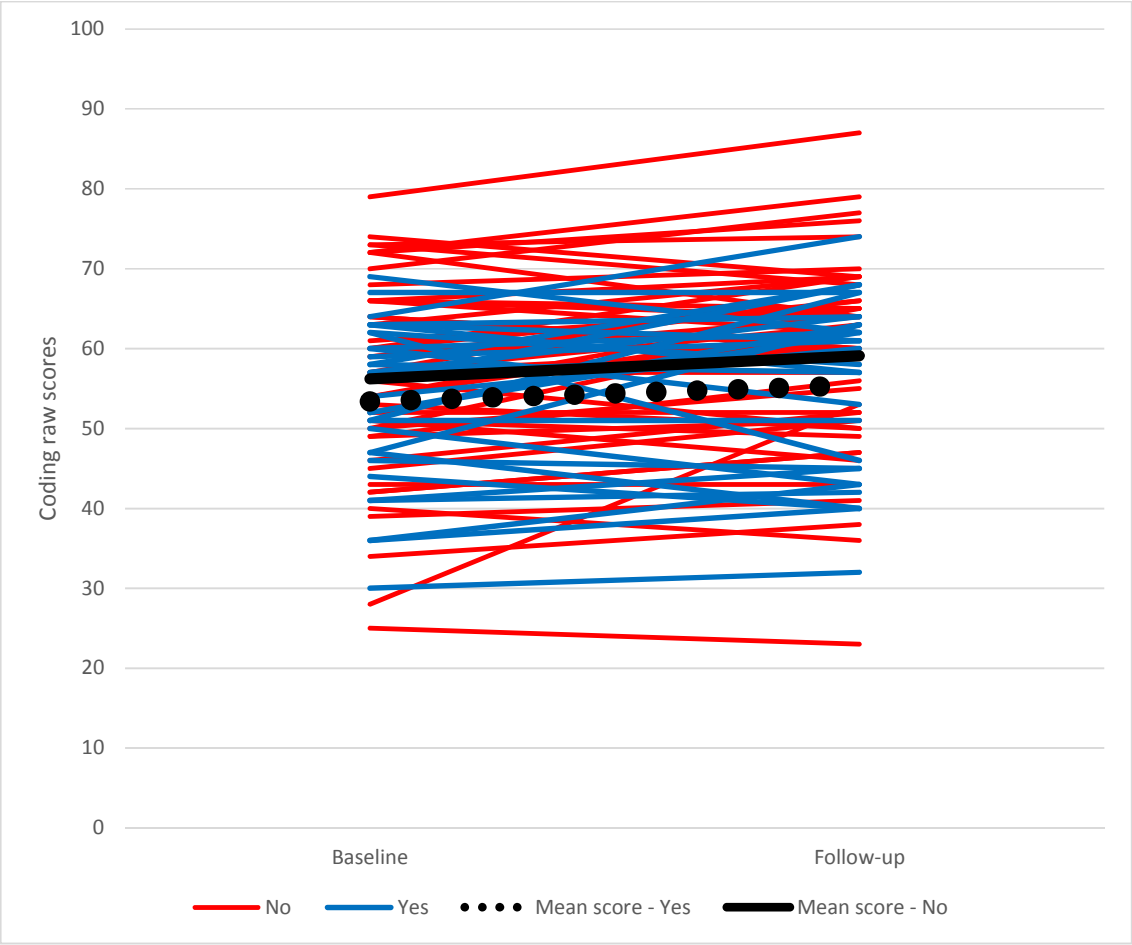
f) Picture Completion



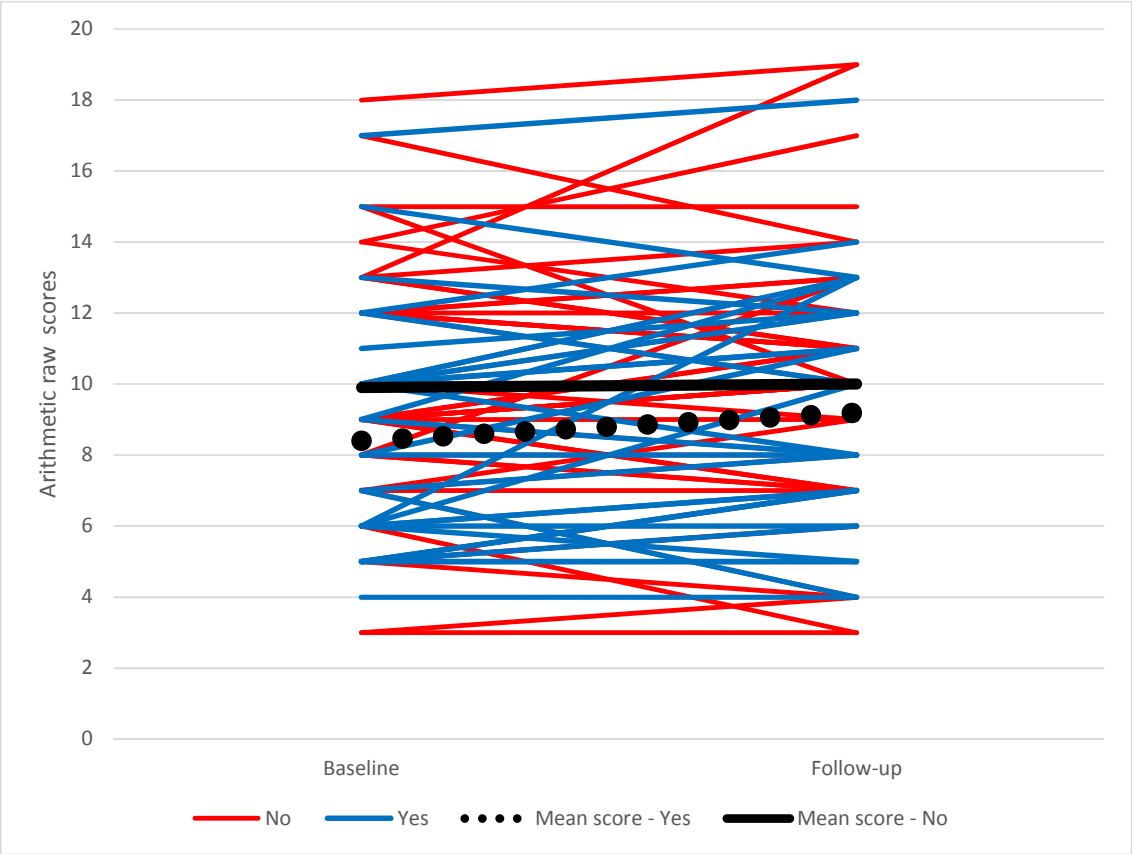
g) Block Design



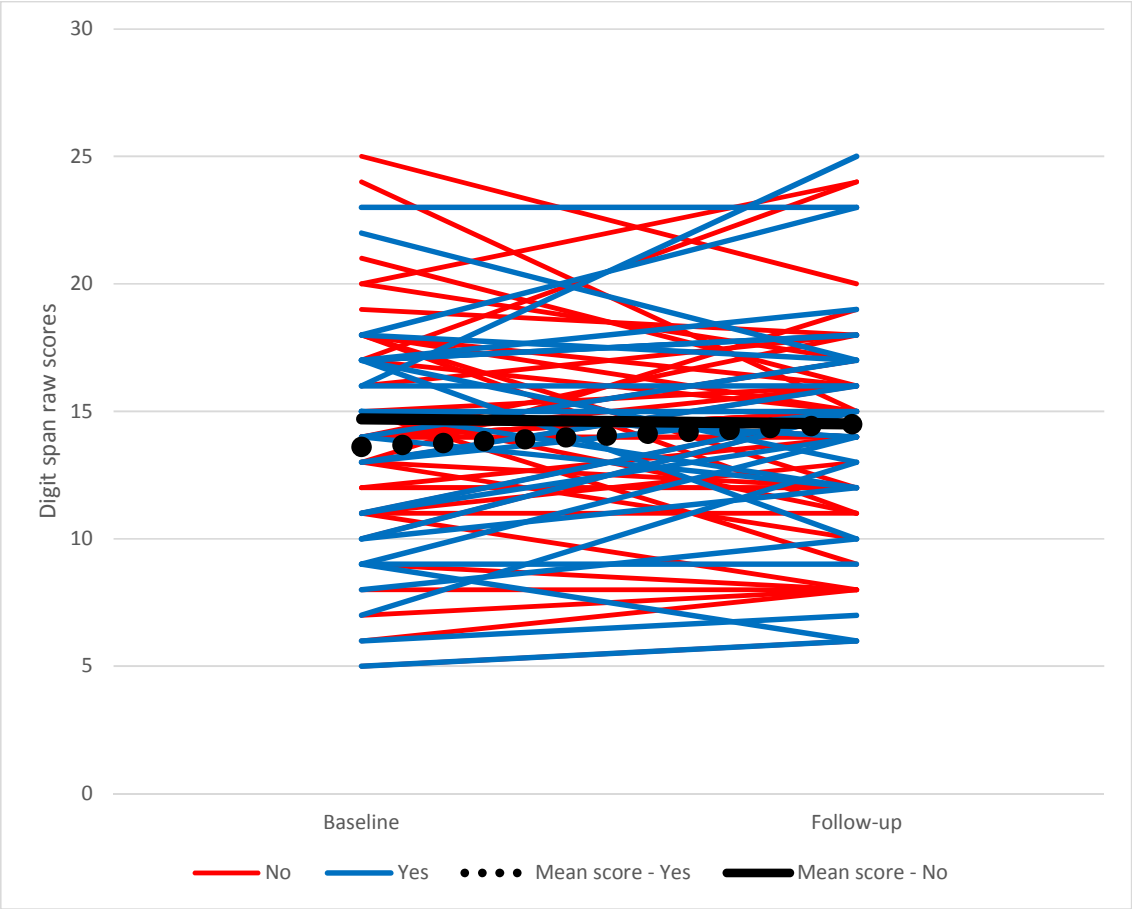
h) Digit Symbol Coding



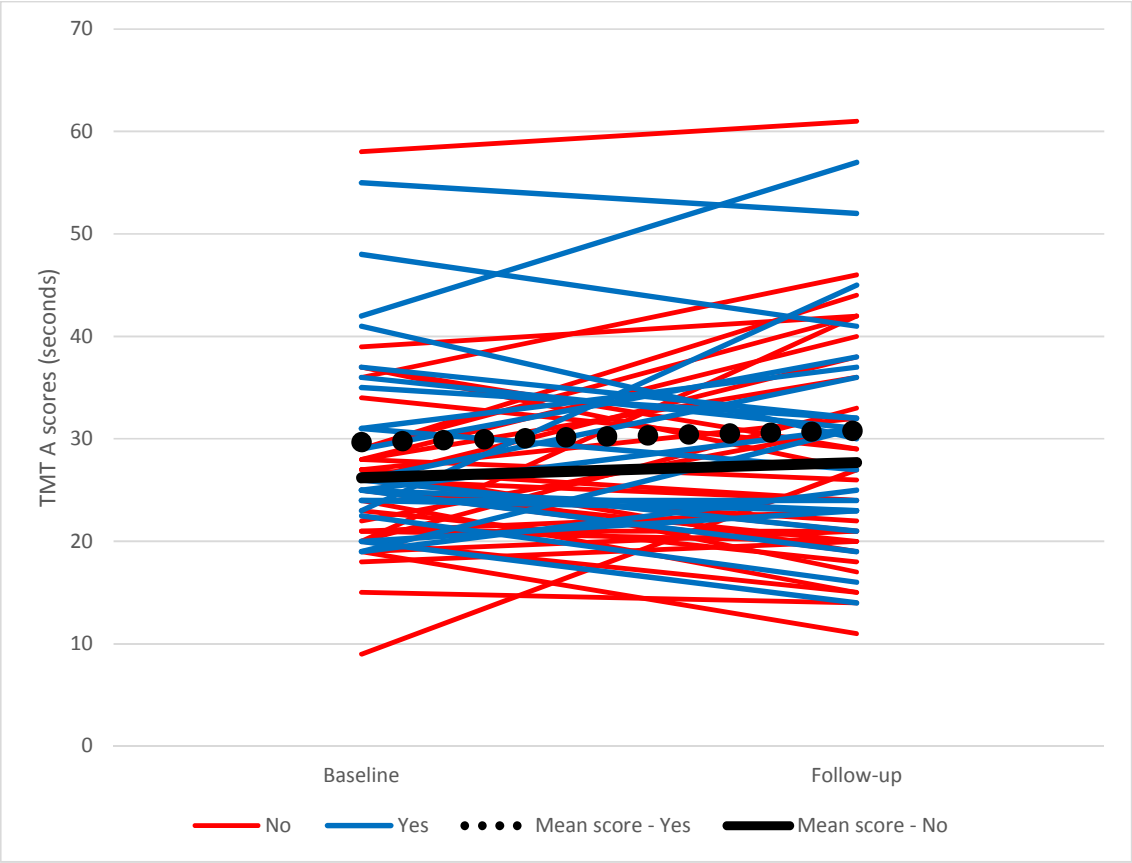
i) Arithmetic



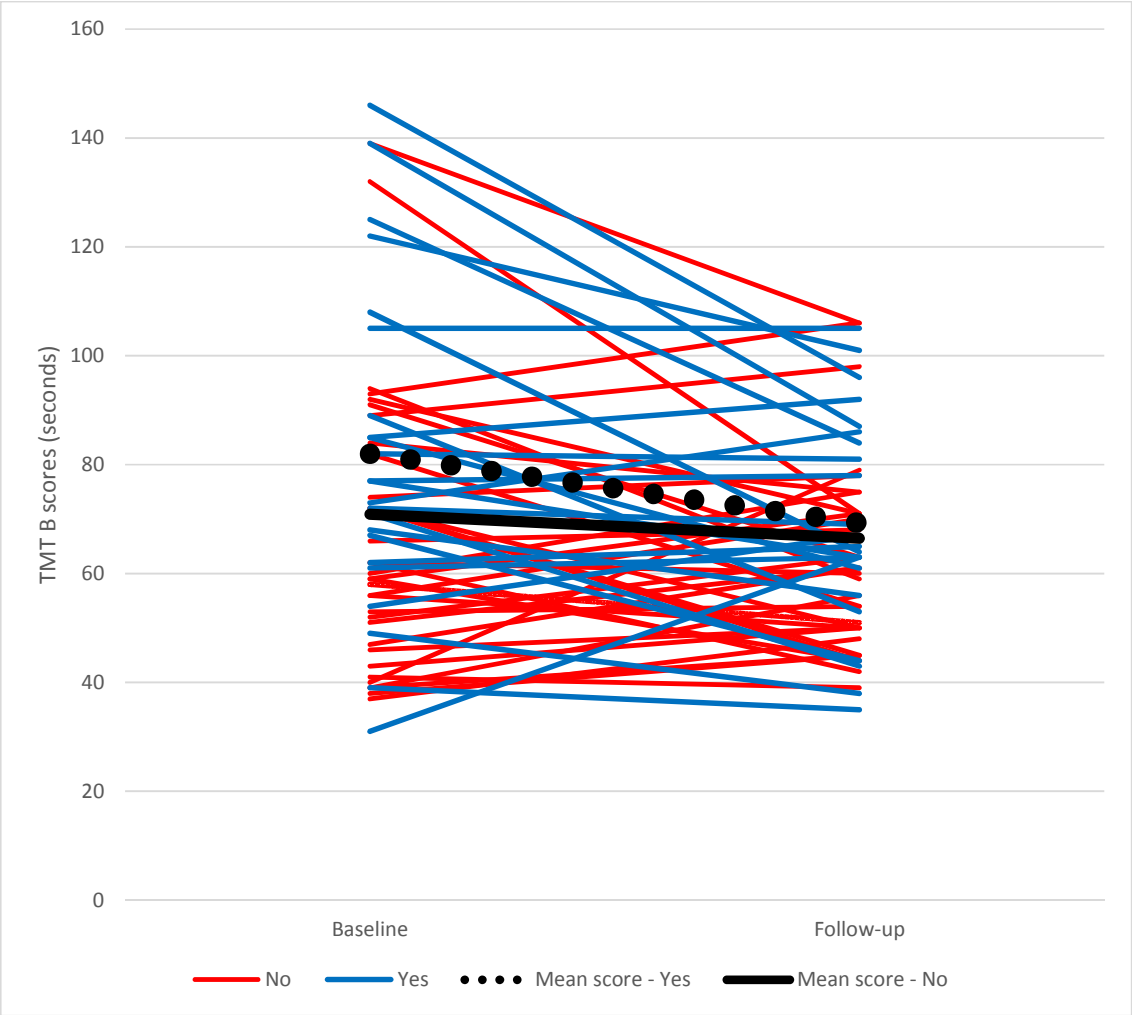
j) Digit Span


30
25
20
15
10
5
0
Digit span raw scores
Baseline
Follow-up
No
Yes
Mean score - Yes
Mean score - No

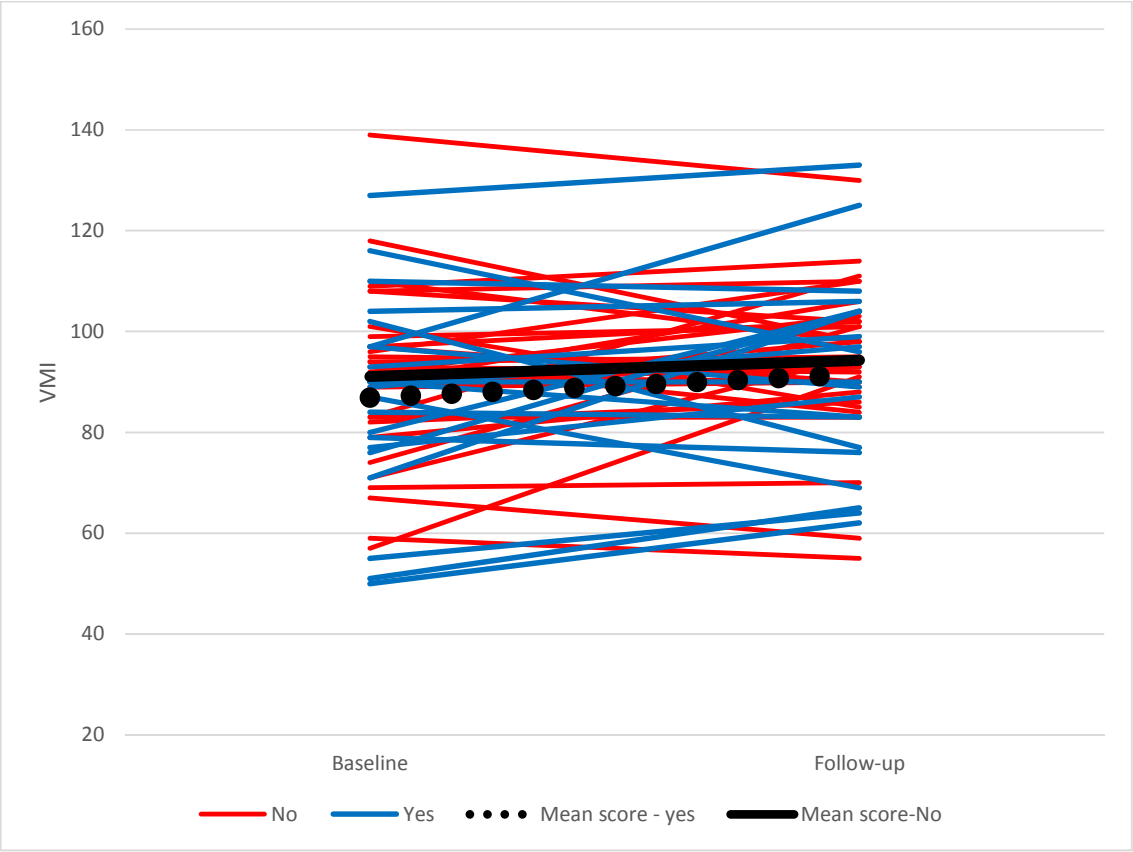
k) Trail Making Test – A



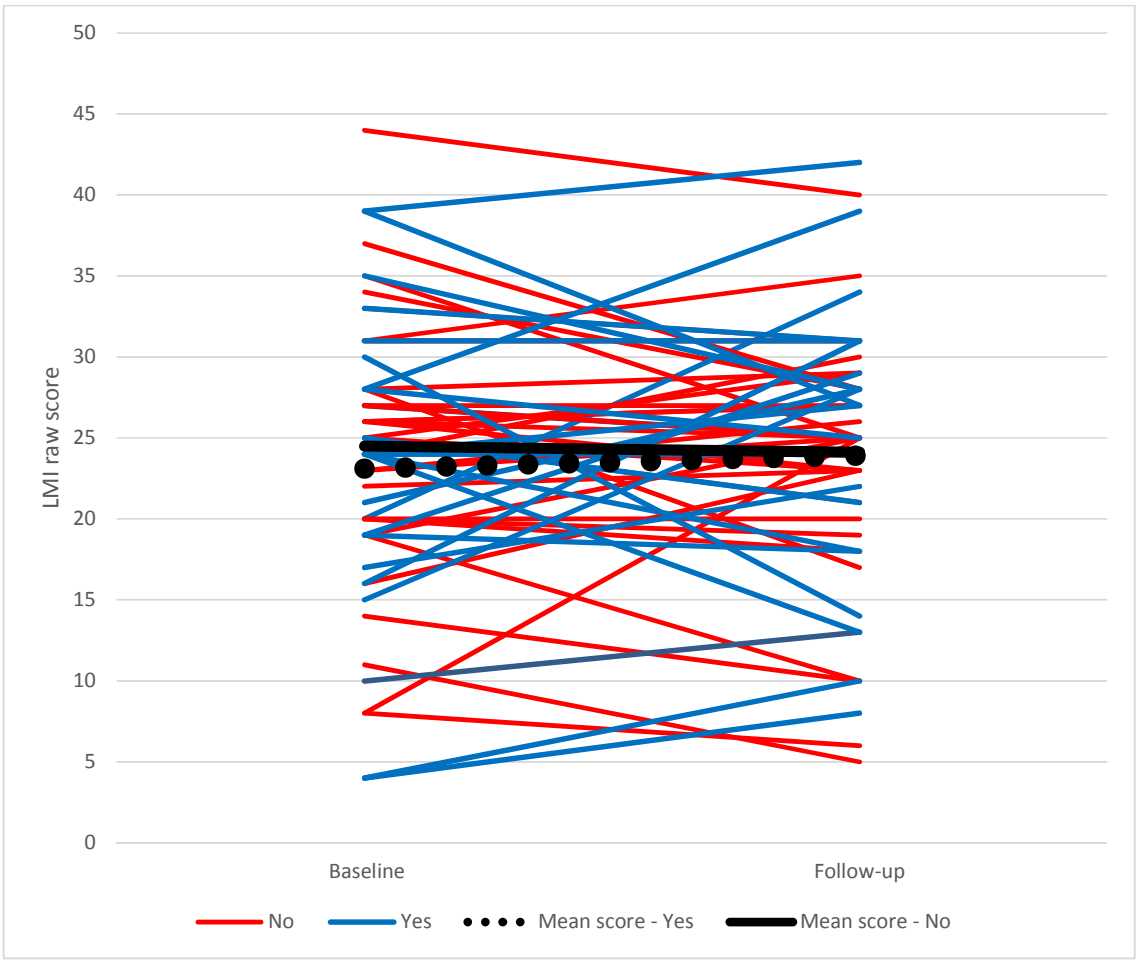
l) Trail Making Test – B



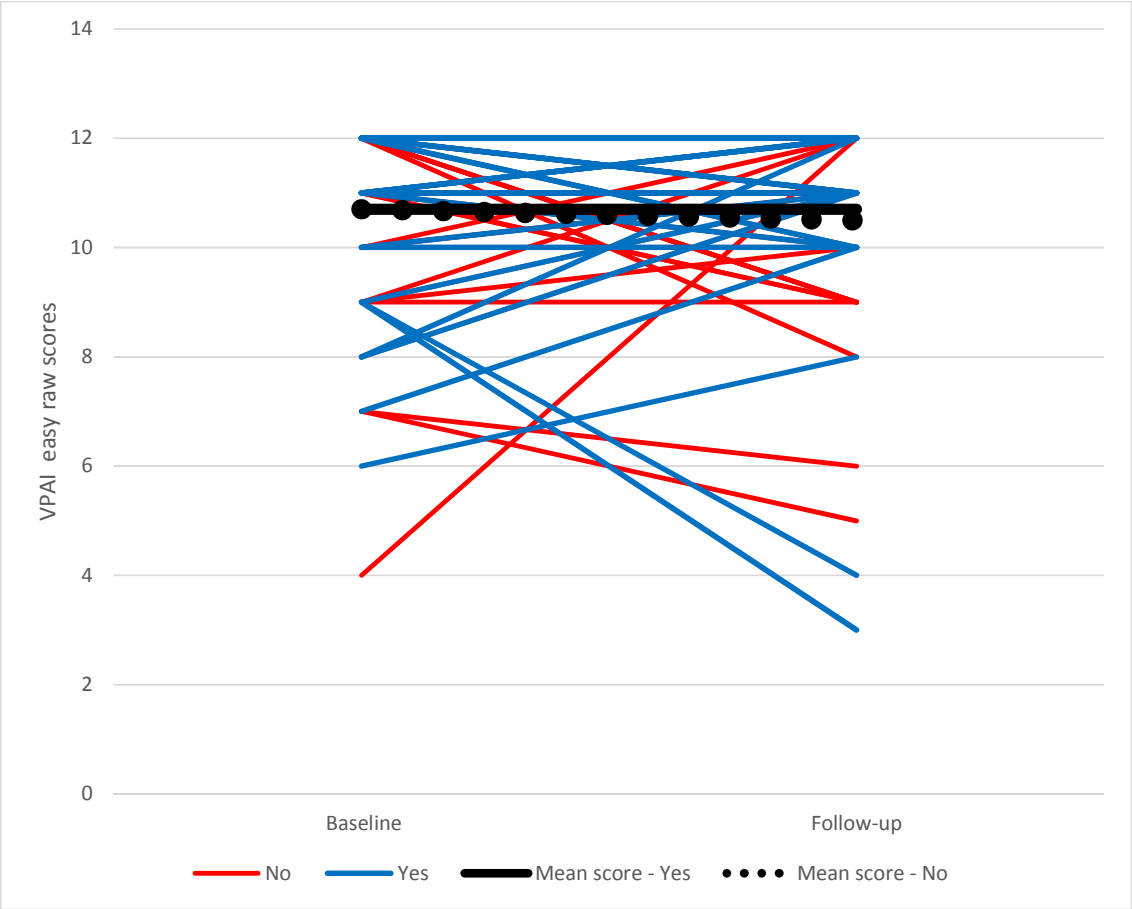
m) Verbal Memory Index



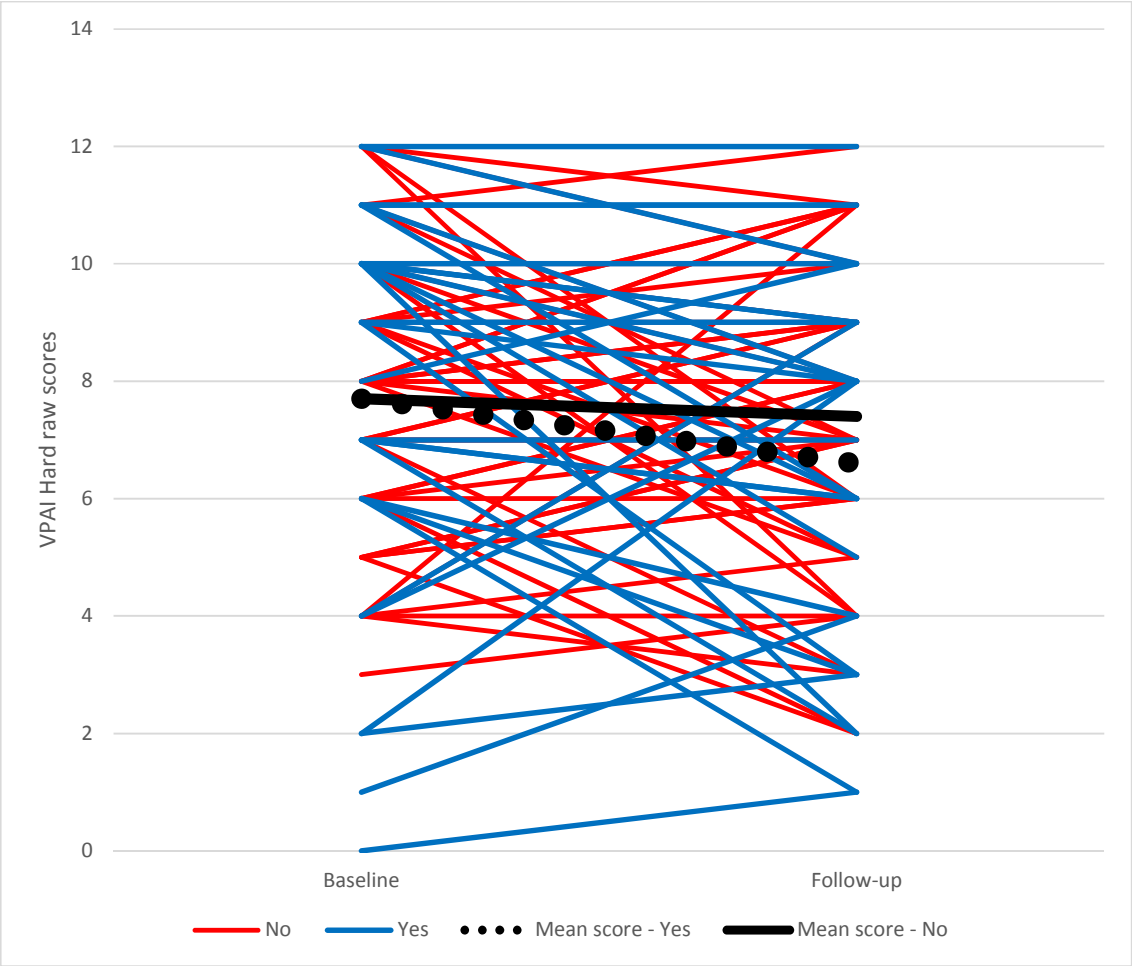
n) Logical Memory I



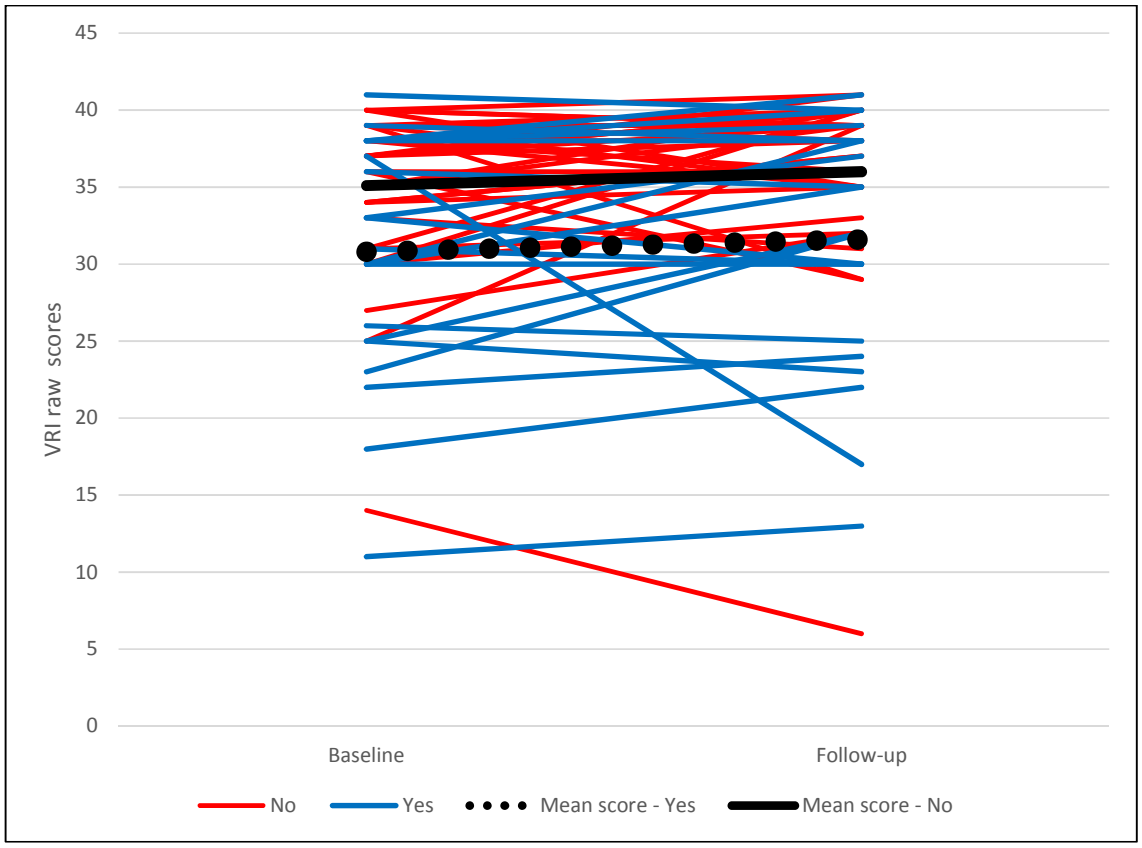
o) Verbal Paired Associates I (easy)



p) Verbal Paired Associates I (hard)



q) Visual Reproduction I



r) RAVLT Total 1-3