Developmental associations between cognition and adaptive behavior in intellectual and developmental disability

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Abstract

Background Intellectual and developmental disabilities (IDDs) are associated with both cognitive challenges and difficulties in conceptual, social, and practical areas of living, commonly referred to as adaptive behavior (DSM–5). Although cross-sectional associations between intelligence or cognition and adaptive behavior have been reported in IDD populations, no study to date has examined whether developmental changes in cognition contribute to or track with changes in adaptive behavior. The present study sought to examine associations of longitudinal developmental change in domains of cognition (NIH Toolbox Cognition Battery, NIHTB-CB) and adaptive behavior domains (Vineland Adaptive Behavior Scales-3; VABS-3) including Socialization, Communication, and Daily Living Skills (DLS) over a two year period in a large sample of children, adolescents and young adults with IDD.

Methods Three groups were recruited, including those with fragile X syndrome, Down syndrome, and other/idiopathic intellectual disability. Eligible participants ($n = 263$) included those who were between 6 and 26 years ($m_{age} = 15.52$, sd = 5.17) at Visit 1, and who had a diagnosis of, or suspected intellectual disability (ID), including borderline ID, with a mental age of at least 3.0 years. Participants were given cognitive and adaptive behavior assessments at two time points over a two year period (m = 2.45 years, range = 1.27 to 5.56 years). In order to examine the association of developmental change between cognitive and adaptive behavior domains, bivariate latent change score (BLCS) models were fit to compare change in the three cognitive domains measured by the NIHTB-CB (Fluid Cognition, Crystallized Cognition, Total Cognition) and the three adaptive behavior domains measured by the VABS-3 (Communication, DLS, and Socialization).

Results Over a two year period, change in cognition (both Crystallized and Total Composites) was significantly and positively associated with change in daily living skills. Also, baseline cognition level predicted growth in adaptive behavior, however baseline adaptive behavior did not predict growth in cognition in any model.

Conclusions The present study demonstrated that developmental changes in cognition and adaptive behavior are associated in children and young adults with IDD, indicating the potential for cross-domain effects of intervention. Notably, improvements in DLS emerged as a primary area of adaptive behavior that positively related to improvements in cognition. This work provides evidence for the clinical, "real life" meaningfulness of changes in cognition detected by the NIHTB-CB in IDD, and provides empirical support for the NIHTB-CB as a fit-for-purpose performance-based outcome measure for this population.

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Background

Intellectual and developmental disabilities (IDDs) are associated with both cognitive challenges and difficulties in conceptual, social, and practical areas of living (DSM–5) [1]. Those with IDD typically present with deficits in intellectual functioning including reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, as well as deficits in adaptive behavior that interfere with independence and living skills within the context of social and cultural developmental norms and expectations [1]. Adaptive behavior refers to one's ability to function independently across home and community contexts throughout the lifespan [2] and in many individuals with IDD, is an important measure of well-being [3–6]. There is evidence that adaptive behaviors may also serve as a better marker of overall functioning within one's environment than intellectual ability alone for this population [3, 4].

There is abundant and well characterized cross-sectional [7, 8] and longitudinal [9–12] evidence of deficits in cognition [13–17] and adaptive behavior [9, 18–20] among specific etiologies within IDD (i.e., fragile X syndrome [FXS], Down syndrome [DS], and Williams syndrome [WS]) in development. This strong foundation in the literature has identified phenotypic patterns of relative strengths and weaknesses in cognitive and adaptive domains across people with IDD over time. In particular, Hahn et al. (2015) assessed the effect of non-verbal cognition (measured by the Mullen Scales of Early Learning taken at baseline) on the rate of growth (slopes) and starting level (intercepts) of adaptive behavior subscales in children with FXS between 3 and 6 times from ages 2 to 10 years. They found that non-verbal cognition significantly predicted the rate of growth in daily living skills and motor domains, and significantly predicted the starting level in socialization, communication, and motor domains [11].

In another study that also utilized cross-domain coupling (i.e., baseline intercept of one domain predicting the slope/trajectory of another domain), intelligence (using standard scores from the Kaufman Brief Intelligence Test, 2nd Edition) and adaptive behavior (using the VABS, Second Edition) were examined longitudinally in a sample of children with WS between the ages of 14 and 49 years. In general, intelligence remained stable while adaptive behavior standard scores decreased over time [10]. Baseline intelligence was correlated with a higher intercept (i.e., starting level) of adaptive behavior across all domains (i.e., communication, daily living, socialization), however higher baseline intelligence also predicted greater decreases in adaptive behavior composite and communication scores over time [10].

Despite a robust body of research that has examined adaptive behavior and cognition in IDDs – including those that have investigated both within the same study [21–24], the extent to which change in cognition is related to change in adaptive behavior in individuals with IDDs has not been investigated in any study to our knowledge. It is critically important to characterize how these two broad domains track *within* people with IDD over time as they are core symptom domains in this population across the lifespan. Moreover, understanding both the direction and patterns of association between cognition and adaptive behavior is especially relevant to educational, behavioral, and pharmacological interventions. Specifically, there is great utility in investigating whether improvements in particular cognitive skills – measured by performance-based tests – that may be targeted in treatment, track with clinically meaningful improvements in adaptive behavior. As cognitive tests are increasingly utilized as key performance-based clinical outcome assessments (what the Food and Drug Administration [FDA] refers to as a "PerfO" [25]) in clinical trials and other treatments for people with IDD, it is necessary to understand how changes in cognition as measured by such instruments may associate with and perhaps impact adaptive or functional changes in the individual's daily life.

The NIH Toolbox Cognition Battery (NIHTB-CB) offers an efficient and standardized approach to capture specific cognitive skills of individuals with IDD as a performance-based measure. Our psychometric studies of the NIHTB-CB in children, adolescents, and young adults with IDD have demonstrated its feasibility and validity [7, 26], as well as its sensitivity to developmental change [12] among this population. In addition, the NIHTB-CB includes tests that target specific cognitive skills including 1) inhibitory control (Flanker Inhibitory Control and Attention [FICA]); 2) working memory (List Sort Working Memory [LSWM]); 3) cognitive flexibility (Dimensional Change Card Sorting [DCCS]); 4) processing speed and attention (Pattern Comparison Processing Speed [PCPS]); 5) memory (Picture Sequence Memory [PSM]); 6) vocabulary (Picture Vocabulary Test [PVT]), and 7) reading/decoding

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(Oral Reading Recognition Test [ORRT]); all of which are then combined into a Fluid Cognition Composite (1–5), a Crystalized Cognition Composite (6–7), and a Total Cognition Composite (1–7) [7]. In addition to our work with the NIHTB-CB in IDD [7, 12, 26], components of the NIHTB-CB [27] detected treatment effects in a 24-week phase 2 randomized, placebo-controlled, crossover trial of a phosphodiesterase-4D allosteric inhibitor (BPN14770) in 30 adult males with FXS [28]. In this study, compared to placebo, cognitive improvement in BPN14470-treated patients was detected by the language-based NIHTB-CB Crystallized Cognition Composite score.

Multiple active and prospective clinical trials continue to build upon this important work. However, a critical question remains unanswered: Do improvements in cognitive skills, as measured by such tests, *extend to adaptive improvements* in the everyday lives of people with ID? Whether or not improvements in outcomes (i.e., cognitive skills from the NIHTB-CB) translate into identifiable and clinically significant improvements in downstream areas of functioning (such as academic skills, activities of daily living, communication, or social skills) are critically important to our understanding of developmental courses in IDD and will likely be a key determinant for clinical trials moving forward including ultimate FDA acceptance of key outcome measures and eventual targeted treatment approval decisions.

Methods

Participants

Eligible participants for this multisite longitudinal study included those who were between 6 and 26 years at Visit 1, and who had a diagnosis of, or suspected IDD. During Visit 1, ID or borderline ID criteria were based on the DSM-5 [1], with adaptive behavior deficits measured by the VABS-3 [2] and IQ < 80 on the Stanford-Binet Intelligence Scales, 5th Edition (SB5). Three groups were recruited: FXS (full mutation, with genetic confirmation), DS (with genetic confirmation if possible), and those with other or idiopathic intellectual disability (OID; with genetic confirmation of negative fragile X mutation). The DS and FXS groups were chosen specifically for this project because of the active translational research programs for these conditions and the urgent need for performance-based outcome measures. The OID group was recruited as an ID comparison group for previously published work [7, 12]. Though we have analyzed NIHTB-CB performance at the group level in these previous investigations, we chose to combine analyses across all groups in the present study given general developmental improvements observed in the NIHTB-CB across all groups previously [12], and to limit the number of analytic models (with multiple reference groups).

A mental age equivalence of at least 3.0 years as measured by the SB5 was required for inclusion, in concordance with NIHTB-CB age limits. Participants were required to be stable with usual treatment for at least 4 weeks before each visit. Exclusion criteria consisted of uncorrectable or uncorrected vision impairment, significant motor impairment preventing touch screen or keypad responses, or history of head injury, brain infection, stroke, or other neurological problems such as uncontrolled daily seizures or excessive sedation from medication. Recruitment sources consisted of research registries, flyers at local clinics, announcements through parent support foundation websites, and mailings to families registered with state departments that provide services to individuals with IDD. A total of 318 participants with IDD were recruited for Visit 1, and of those recruited, 55 individuals were ineligible: 21 with IQ > 79 and 34 with mental age below 3.0 years, leaving a final sample of 263. Participant retention at visit 2 was 81.36% ($n = 214$, $mean_{age} = 17.90$ years). Full protocol, details of the NIHTB-CB, and its performance at baseline in the present IDD samples has been reported previously [7, 12, 26].

Protocol

The NIHTB-CB, VABS-3 interview and SB5 were completed at Visit 1. For some participants, assessments were conducted over two days. After completion of the SB5, participants completed the NIHTB-CB while their parent/caregiver completed the VABS-3 with a psychologist or trained personnel. The same procedure was conducted again approximately 2 years later at Visit 2.

Measures

The NIHTB-CB [29] (Version 2.0) is an iPad-based battery that assesses Fluid Cognition, Crystalized Cognition, and a Total Cognition Composite through 7 tests as described above in the Introduction. A published manual of standardized NIHTB-CB administration procedures for IDD is available [30]. Unadjusted standard scores (USSs; non age-adjusted) were used for all NIHTB-CB tests. USSs have a mean of 100 and SD of 15. The USSs are recommended for longitudinal measurement because, like change sensitive or growth scale scores, they scale performance across all individuals on the measure based on the difficulty of items they received and their performance relative to everyone else in the original norming sample, allowing scores to be compared across time [31].

The VABS-3 [2] interview form was used to measure adaptive behavior (AB) domains including

Communication (consisting of Expressive Language, Receptive Language, and Written Language), Daily Living Skills (DLS; consisting of Personal, and Community skills), and Socialization (consisting of Interpersonal Relationships, Play and Leisure, and Coping Skills). VABS-3 growth scale values (GSVs) were used for all analyses as they have been shown to be sensitive in individuals with IDD, particularly given their robust performance longitudinally and being less susceptible to floor effects [32, 33].

The SB5, which is standardized for individuals between 2–85 years, provides an overall index of intellectual ability reported as the Full-Scale IQ (FSIQ). In part, due to its broad developmental range, the SB5 has performed well in our prior studies of IDD [7, 26, 34]. Our protocol utilizes mental (rather than chronologic) age to select some NIHTB-CB test versions (e.g., PSM) and VABS-3 start points, which were derived from the SB5 FSIQ [30] for each participant. Deviation IQ scores were used to avoid inaccurate assessments of intelligence that can occur with standard score flooring in persons with IDD [34].

Statistical analyses

Our previous work has identified some limitations using the NIHTB-CB in individuals with IDDs, particularly for those with lower mental ages (i.e., < 5 years) [7]. A specific limitation relates to composite scores in the NIHTB-CB. For instance, the Fluid Cognition Composite is comprised of five subtests, all of which are required to generate a composite score. Many individuals in our sample are unable to pass practice and thus complete all five subtests. Therefore, they do not have composite scores available, thus limiting our power to test hypotheses at the construct level. Structural equation modeling (SEM) provides an analytic framework to help combat this issue, given that this modeling approach is robust to missing data, aiding our ability to retain the full sample in our models. In the present study, bivariate latent change score (BLCS) models provided two-year estimates of both cognitive and adaptive behavior change in individuals with FXS, DS, and OID. This modeling framework allowed us to examine the association between latent change for cognition and adaptive behavior across construct levels of each assessment.

In order to examine the association of developmental change between cognitive and adaptive behavior domains, permutations of BLCS models were used to compare change in the three cognitive domains measured by the NIHTB-CB (Fluid, Crystallized, Total Cognition Composites) and the three AB domains measured by the VABS-3 (Communication, DLS, and Socialization), resulting in the evaluation of nine models plus one full model (including all cognitive domains

and all AB domains). Latent change score models are a type of structural equation modeling that provide estimates of change as latent variables based on two or more time points. In the BLCS framework, each model can assess the association between the latent change estimated for two constructs of interest [35]. We have utilized latent change scores previously to characterize developmental change in this sample across individual NIHTB-CB subtests [12]. Missing data were handled with full information maximum likelihood estimation, which is a standard recommendation to provide accurate parameter estimates in the presence of missing data [36].

Generally, each model contained latent scores for cognition and AB at Visit 1 and Visit 2 that were derived from the observed scores from each domain's respective subtests [35, 37–40]. Latent change scores for cognition (ΔCOG) and adaptive behavior (ΔAB) were included to model change from Visit 1 to Visit 2. Furthermore, we included an estimate of the correlated change between ΔAB and ΔCOG in each model to assess cross-domain coupling of cognition and adaptive behavior. Time between visits and participant age were each used as covariates at the latent level in all models to control for any differences in cognitive and AB change due to variations in timing between Visit 1 and Visit 2, as well as age-related changes – modeled as those between 6 and 16 years at Visit 1, and those 16 years or older at Visit 1, which we have previously demonstrated in this population [12]. Analyses included all participants with a valid NIHTB-CB score, even without completion of visit 2 as BLCS models are robust to missingness [35]. Supplementary Figure 1 graphically presents a generic representation of these models, and Table 3 provides details of each model's specification. For model fit we first specified base models in which nothing was correlated, and each variable received an equated intercept and variance across time [41]. We then assessed each model's fit by comparing to its base model (utilizing robust fit parameters including CFI, TLI, and RMSEA) using methods from Savalei et al. [42], and indices of fit based on Little [43] [i.e., CFI > 0.85; TLI > 0.85; RMSEA < 0.08]. In order to control for false discovery rates, Benjamini–Hochberg procedures [44] were conducted for every class of analysis for the models with adequate fit.

Results

Descriptive statistics

A sample of 263 individuals were included in the present analyses. Descriptive statistics for sex assigned at birth, race, ethnicity, and diagnostic group are provided in Table 1 and for cognitive and adaptive behavior scores at Visit 1 in Table 2.

Table 1 Descriptive statistics for participants at each visit

	Visit 1	Visit 2
	Percentage (n)	Percentage (n)
Sex		
Female	40.7 (107)	40.2 (86)
Male	59.3 (156)	59.8 (128)
Race		
American Indian/Alaskan Native	1.1 (3)	0.9 (2)
Asian	2.3 (6)	2.8 (6)
Native Hawaiian or Other Pacific Islander	1.1 (3)	0.9 (2)
Black or African American	10.3 (27)	8.9 (19)
White	69.6 (183)	71.5 (153)
More than one race	12.2 (32)	11.7 (25)
Unknown/not reported	3.4 (9)	3.3 (7)
Ethnicity		
Hispanic/Latinx	18.3 (48)	17.3 (37)
Not Hispanic/Latinx	77.6 (204)	79.0 (169)
Unknown/not reported	4.2 (11)	3.7 (8)
Diagnosis		
Idiopathic/other intellectual disability	33.1 (87)	29.9 (64)
Fragile X syndrome	31.2 (82)	33.6 (72)
Down syndrome	35.7 (94)	36.4 (78)

Table 2 Descriptive statistics for study variables (Visit 1)

	Mean	SD	Missing (n)
Chronological age (years)	15.52	5.17	0
SB5 Full Scale mental age* (years)	4.83*	2.12*	0
SB5 Full Scale deviation IQ	53.52	16.31	0
SB5 Nonverbal deviation IQ	55.59	15.19	0
SB5 Verbal deviation IQ	51.45	19.30	0
Vineland-3 ABC	52.60	17.01	16
			Percent Valid
NIHTB-CB DCCS[1]	65.60	22.19	60.4 (n = 160)
NIHTB-CB FICA[1]	66.29	24.02	77.7 (n = 206)
NIHTB-CB PVT[2]	67.82	13.40	97.0 (n = 257)
NIHTB-CB PSM[1]	84.50	16.09	89.8 (n = 238)
NIHTB-CB PCPS[1]	70.63	20.62	78.1 (n = 207)
NIHTB-CB ORRT[2]	74.51	14.65	94.0 (n = 249)
NIHTB-CB LSWM[1]	63.99	15.08	54.7 (n = 145)

DCCS Dimensional Change Card Sorting, *FICA* Flanker Inhibitory Control and Attention, *PVT* Picture Vocabulary Test, *PSM* Picture Sequence memory, *PCPS* Pattern Comparison Processing Speed, *ORRT* Oral Reading Recognition Test, *LSWM* List Sorting Working Memory, *ABC* Adaptive Behavior Composite, *SB5* Stanford Binet Intelligence Scale, Fifth Edition

* Non-normal distribution, median and IQR are reported

[1] indicates NIHTB-CB Fluid Composite subtest

[2] indicates NIHTB-CB Crystallized Composite subtest

Bivariate latent change score model fit evaluation

Twelve bivariate latent change score models were conducted assessing the relationship between change in the adaptive behavior (ΔAB) domains and change in the cognition (ΔCOG) domains from Visit 1 to Visit 2. The interval between Visit 1 and Visit 2 in years ($M = 2.45$, $SD = 0.81$) was included as a covariate at the latent level, and age, split into those between 6 and 16 years, and 16 years or older at Visit 1 was included as a covariate at the Visit 1 level, as well as the latent level. A model fit statistics summary is presented in Table 3.

The first six models (Models 1–6) assessed ΔAB, where AB was modeled as one of three VABS-3 subscales: Communication, DLS, and Socialization, and ΔCOG, where COG was modeled as one of two NIHTB-CB composites (Fluid and Crystallized). Of these models, Model 1 (Crystallized COG and AB Communication) and Model 2 (Fluid COG and AB Communication) demonstrated relatively poor model fit. These models were followed up with Models 1.1 and 2.1, which omitted Written Communication from the AB Communication domain, and were subsequently found to have good fit. Model 6 (Fluid COG and AB Socialization) did not demonstrate adequate model fit, and was not further evaluated. Models 3 (Crystallized COG and AB DLS), 4 (Fluid COG and AB DLS), and 5 (Fluid COG and AB Socialization) were deemed to have good fit.

The next set of models (Models A-C) assessed ΔAB across the three subscales of the VABS-3 (Communication, DLS, and Socialization) and ΔCOG across the full NIHTB-CB (comprised of its seven subtests). Of these models, Models B (Total COG and AB DLS) and C (Total COG and AB Socialization) were deemed to have acceptable fit. See Fig. 1 for a graphical representation of the SEM for Model B (Total COG and AB DLS).

A final model (Full Model) assessed ΔAB across the VABS-3 (all domains) and ΔCOG across the full NIHTB-CB. The model fit was poor and not examined further. Notably, none of the models where AB was modeled using the VABS-3 Communication subscales were shown to have good fit until removing the Written Communication subdomain. However, for the other two AB domains (DLS & Socialization), models wherein COG was defined as either Crystallized, Fluid, or the Total NIHTB-CB were shown to have good fit.

Correlation between cognitive and adaptive behavior change

In two of the seven models of good fit, a significant relationship was observed between the change in cognition (ΔCOG) and change in adaptive behavior (ΔAB). A positive relationship between the ΔCOG and ΔAB was

Table 3 Model fit statistics summary

MODEL	COG	AB	CHI-SQ	SCALED CHI-SQ	DF	CFI	TLI	RMSEA
Model 1	Crystallized	Comm	241.92	243.50	57	0.899	0.845	0.124
Model 2	Fluid	Comm	300.48	309.24	150	0.909	0.887	0.079
Model 3	**Crystallized**	**DLS**	**128.22**	**128.86**	**57**	**0.964**	**0.945**	**0.075**
Model 4	**Fluid**	**DLS**	**243.23**	**250.42**	**150**	**0.941**	**0.927**	**0.067**
Model 5	**Crystallized**	**Soc**	**127.68**	**116.59**	**57**	**0.954**	**0.930**	**0.073**
Model 6	Fluid	Soc	423.65	435.87	150	0.782	0.732	0.115
Model A	Total	Comm	590.01	613.48	232	0.857	0.832	0.099
Model B	**Total**	**DLS**	**416.21**	**429.72**	**232**	**0.924**	**0.911**	**0.074**
Model C	**Total**	**Soc**	**406.70**	**417.30**	**232**	**0.899**	**0.882**	**0.078**
Full	Total	ABC	1393.46	1372.52	573	0.850	0.836	0.085
Model 1.1	**Crystallized**	**Comm w/o written**	**81.59**	**84.58**	**34**	**0.960**	**0.928**	**0.081**
Model 2.1	**Fluid**	**Comm w/o written**	**201.57**	**209.97**	**115**	**0.923**	**0.901**	**0.073**

Shaded models determined to have adequate fit. Goodness of fit according to Little (2013) [43]:

RMSEA: < 0.01 = great, 0.05–0.01 = good, 0.08–0.05 = acceptable, 0.10–0.08 = mediocre, > 0.10 = poor

CFI: > 0.99 = great, 0.95–0.99 = good, 0.90–0.95 = acceptable, 0.85–0.90 = mediocre, < 0.85 = poor

TLI: > 0.99 = great, 0.95–0.99 = good, 0.90–0.95 = acceptable, 0.85–0.90 = mediocre, < 0.85 = poor

AB Adaptive Behavior, *Comm* Communication, *Soc* Socialization, *DLS* Daily Living Skills, *ABC* Adaptive Behavior Composite
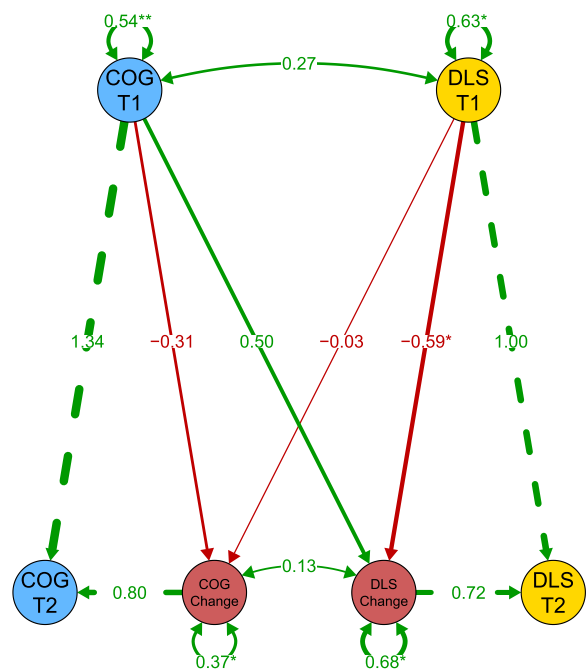

Fig. 1 Structural equation model diagram of representative Model B showing association between latent constructs of total cognition composite (COG; NIH Toolbox Cognition Battery) and adaptive behavior (AB; Vineland-3 Daily Living Skills [DLS]) at Visits 1 and 2 and latent change of these constructs across 2 years of development in youth with IDD. Manifest variables omitted for visual clarity

observed in Model 3 (Crystallized COG and AB DLS), where COG was a variable comprised of the NIHTB-CB subscales in the Crystallized domain (PVT and ORRT) and AB was comprised of the VABS-3 subscales in the DLS domain (Personal, Domestic, and Community). Similarly, a positive relationship between ΔCOG and ΔAB was observed in Model B (Total COG and AB DLS), where AB was again comprised of the VABS-3 subscales in the DLS domain, but COG was comprised of all of the NIHTB-CB subscales (Fig. 2). These findings indicate that change in cognition, specifically in the Crystallized domain, relates to change in daily living skills over time in our sample. A summary of the parameters of interest from these models is provided in Table 4.

Visit 1 Cross-domain coupling of AB and COG

Tables 5 and 6 present regression parameters for COG at Visit 1, and AB at Visit 1 respectively predicting ΔCOG and ΔAB. Regression components of the models with good fit (i.e., Models 3, 4, 5, B, C, 1.1 and 2.1) were evaluated to examine the influence of COG at Visit 1 on ΔAB and ΔCOG (Table 5), and AB at Visit 1 on ΔAB and ΔCOG (Table 6).

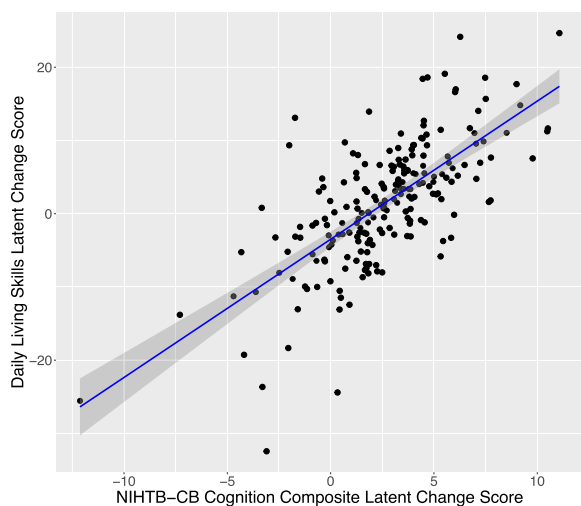COG at Visit 1 significantly predicted increased developmental change in AB for Models 4 (Fluid COG and

Fig. 2 Linear association (with SE shaded) between latent change scores for VABS-3 Daily Living Skills (y-axis) and NIHTB-CB Cognition Composite (x-axis) for Model B

AB DLS), and 2.1 (Fluid COG and AB Communication without Written Language), as well as Models B (Total COG and AB DLS) and C (Total COG and AB Socialization), however COG at Visit 1 did *not* predict ΔCOG in any model. This pattern of results indicates that Crystallized Cognition, Fluid Cognition and the Total Cognition Composites are good indicators of developmental change in daily living skills, socialization, and expressive/receptive language; however individual starting cognition

scores are not predictive of individuals' subsequent cognitive development.

For the cross-domain coupling of AB at Visit 1 on ΔCOG, AB at Time 1 did *not* predict ΔCOG in any model. AB at Visit 1 predicted less change in ΔAB for all models (i.e., Models 3, 4, 5, 1.1, B, and C) indicating that those with higher DLS, Socialization, and Expressive/Receptive Communication scores at Visit 1 reported *less* improvement in those respective adaptive behavior skills after two years.

Discussion

The present study examined the association between developmental change in cognition and adaptive behavior in children, adolescents and young adults with IDD. We modeled this association using bivariate latent change score models. We found that developmental improvements in language-based crystallized cognition and overall cognition as measured by the NIHTB-CB were related to improvements in daily living skills. Models that included the VABS-3 Communication domain (i.e., Models 1, 2, A, and the Full Model) did not have adequate model fit to report reliable results. Follow-up analyses indicated that the measurement model for VABS-3 Communication did not fit due to a high degree of written communication covariance with the other VABS-3 Communication areas (i.e., Receptive Communication and Expressive Communication). Models excluding Written Communication were subsequently fit (Model 1.1, 2.1).

Table 4 Correlation of latent change (ΔAB and ΔCOG)

MODEL	COG	AB	r	ESTIMATE	SE	*P*
Model 1	Crystallized	Comm	0.496	6.21	2.71	.004
Model 2	Fluid	Comm	0.250	3.14	5.34	.557
Model 3	Crystallized	DLS	0.471	16.92	6.32	0.007**
Model 4	Fluid	DLS	-0.106	-1.76	6.985	.801
Model 5	Crystallized	Soc	0.230	10.34	7.38	0.161
Model 6	Fluid	Soc	0.979	3545.33	6.79	<.001***
Model A	Total	Comm	0.539	6.31	3.20	.049*
Model B	Total	DLS	0.462	10.30	4.99	.039*
Model C	Total	Soc	0.322	7.49	4.70	.111
Full	Total	ABC	0.462	8.58	4.15	.039*
Model 1.1	Crystallized	Comm	0.447	12.44	7.47	.096
Model 2.1	Fluid	Comm	0.395	5.79	6.80	.394

Significant paths are denoted by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Shaded rows denote models with good fit

AB Adaptive Behavior, *Comm* Communication, *Soc* Socialization, *DLS* Daily Living Skills, *ABC* Adaptive Behavior Composite

Table 5 Cross-domain coupling of cognition at Visit 1 and ΔAB and ΔCOG

MODEL	PREDICTOR	OUTCOME	β	ESTIMATE	SE	P	$P_{ADJUSTED}$
Model 1	Crystallized	ΔAB COMM	0.39	0.180	0.960	.062	
		ΔCOG CRYS	0.26	-0.225	0.072	.002**	
Model 2	Fluid	ΔAB COMM	0.32	0.114	0.047	.015*	
		ΔCOG FLUID	0.33	0.120	0.099	.223	
Model 3	Crystallized	ΔAB DLS	0.28	0.217	0.117	.063	.132
		ΔCOG CRYS	-0.06	-0.027	0.077	.728	.728
Model 4	Fluid	ΔAB DLS	0.49	0.272	0.066	<.001***	.001**
		ΔCOG FLUID	0.43	0.153	0.093	.100	.175
Model 5	Crystallized	ΔAB SOC	0.23	0.176	0.092	.055	.132
		ΔCOG CRYS	-0.05	-0.024	0.049	.622	.669
Model 6	Fluid	ΔAB SOC	-47.5	-83.4	23.90	<.001***	
		ΔCOG FLUID	-235	-222	63.46	<.001***	
Model A	Total	ΔAB COMM	.46	0.215	0.117	.065	
		ΔCOG Total	-0.01	-0.002	-.102	.987	
Model B	Total	ΔAB DLS	0.38	0.323	0.113	.004**	.014*
		ΔCOG Total	0.24	0.086	0.069	.218	.357
Model C	Total	ΔAB SOC	.312	0.295	0.096	.002**	014*
		ΔCOG Total	.22	0.080	0.052	.123	.191
Full	Total	ΔAB FULL	0.35	0.237	0.088	.007**	
		ΔCOG Total	0.21	0.074	0.065	.257	
Model 1.1	Crystallized	ΔAB COMM	0.31	0.158	0.086	.066	.132
		ΔCOG CRYS	-.09	-0.041	0.073	.581	.669
Model 2.1	Fluid	ΔAB COMM	0.33	0.138	0.047	.003**	.014*
		ΔCOG FLUID	0.34	0.124	0.084	.138	.193

Significant paths are denoted by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Shaded rows denote models with good fit. $P_{ADJUSTED}$ utilized Benjamini–Hochberg procedures to control false discovery rate

AB Adaptive Behavior, *Comm* Communication, *Soc* Socialization, *DLS* Daily Living Skills, *ABC* Adaptive Behavior Composite

The present study is the first, to our knowledge, to assess the relation between developmental change in cognition and adaptive behavior in individuals with IDD, the two central domains of functioning for this population. The results may indicate the potential for cross-domain effects of intervention. Notably, improvements in daily living skills emerged as a primary area of adaptive behavior that positively related to improvements in cognition. In addition, cognitive skills at Visit 1 predicted developmental change in all domains of adaptive behavior after an average of a little over two years; specifically fluid cognition at Visit 1 predicted improvements in daily living skills and communication, and overall cognition at Visit 1 predicted improvement in daily living skills and social skills.

These findings demonstrate some of the "real-life" improvements that are associated with, and perhaps in part driven by cognitive growth in youth with IDD. Previous work has shown that cognitive ability, as measured by IQ testing, is correlated with adaptive functioning [45] at the population level. With the strength of this relationship in mind, it begs the question whether treatment-related improvements in cognition may accelerate the development of adaptive skills. Establishing such reciprocity has implications for how treatment trials in IDD are designed and implemented [10, 21, 46]. However, the present study cannot draw any causal inferences as it was correlational. Future innovative controlled, randomized clinical trials [47, 48], examining the impact of cognition-enhancing medications or behavioral interventions (e.g., to improve flexibility, problem-solving, and executive function), could be fruitful.

The importance of developing endpoint measures in the field of IDD is evident [49], with many existing measures of the concept of interest (i.e., cognition) deemed inadequate or not fully "fit for purpose." Measures commonly used in clinical trials have been critiqued for their limitations in validation, sensitivity to change, or clinical meaningfulness in individuals with IDD [50]. Historically, when evaluating clinical outcome assessments (COAs)

Table 6 Cross-domain coupling of AB at Visit 1 and ΔAB and ΔCOG

MODEL	PREDICTOR	OUTCOME	β	ESTIMATE	SE	P	P_ADJUSTED
Model 1	AB COMM	ΔAB COMM	-0.73	-0.433	0.127	.001**	
		ΔCOG CRYS	0.55	0.298	0.095	.002**	
Model 2	AB COMM	ΔAB COMM	-0.46	-0.298	0.107	.005**	
		ΔCOG FLUID	0.14	0.091	0.169	.590	
Model 3	AB DLS	ΔAB DLS	-0.58	-0.436	0.122	<.001***	<.001***
		ΔCOG CRYS	0.03	0.014	0.069	.835	.974
Model 4	AB DLS	ΔAB DLS	-0.70	-0.527	0.107	<.001***	<.001***
		ΔCOG FLUID	-0.06	-0.031	0.126	.806	.974
Model 5	AB SOC	ΔAB SOC	-0.54	-0.413	0.094	<.001***	<.001***
		ΔCOG CRYS	-0.00	-0.001	0.045	.989	.996
Model 6	AB SOC	ΔAB SOC	32.9	24.17	14.19	.089	
		ΔCOG FLUID	165	65.34	37.54	.082	
Model A	AB COMM	ΔAB COMM	-0.73	-0.440	-0.175	.012*	
		ΔCOG TOTAL	0.26	0.122	0.128	.338	
Model B	AB DLS	ΔAB DLS	-0.65	-0.489	0.113	<.001***	<.001***
		ΔCOG TOTAL	-0.04	-0.013	-0.058	.825	.974
Model C	AB DLS	ΔAB SOC	-0.57	-0.432	0.091	<.001***	<.001***
		ΔCOG TOTAL	-0.00	-0.000	0.033	.996	.996
Full	AB	ΔAB FULL	-0.53	-0.394	0.094	<.001***	
		ΔCOG TOTAL	0.02	0.006	0.063	.920	
Model 1.1	AB COMM w/o Written Comm.	ΔAB COMM	-.36	-0.277	0.135	.040*	.093
		ΔCOG CRYS	0.10	0.063	0.114	.582	.821
Model 2.1	AB COMM w/o Written Comm.	ΔAB COMM	-0.34	-0.267	0.142	.061	.122
		ΔCOG FLUID	0.15	0.104	0.142	.465	.813

Significant paths are denoted by *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Shaded rows denote models with good fit. $P_{ADJUSTED}$ utilized Benjamini–Hochberg procedures to control false discovery rate

AB Adaptive Behavior, *Comm* Communication, *Soc* Socialization, *DLS* Daily Living Skills, *ABC* Adaptive Behavior Composite

for IDD, PerfO's (i.e., direct assessments), have excluded intelligence tests as they have been considered inappropriate for shorter-term interventions because they tap "stable" traits that are less likely to show dynamic changes during these time frames; thus, COAs for IDD often consist of observer ratings or clinician reported outcomes [51]. The NIHTB-CB was developed, in part, with the express purpose of filling the performance outcome gap for cognition in intervention studies, and it includes tests of fluid cognitive constructs that may be more sensitive to interventions. However, it was not created, validated, or normed with consideration of IDD, a population currently undergoing clinical trials targeting cognition and in urgent need of suitable primary outcome measures. Nonetheless, validity evidence for the NIHTB-CB has been collected in IDD [7] and it shows sensitivity to change in this population [12]. Evaluating the clinical

meaningfulness of the NIHTB-CB was an important next step. The present study established the clinical meaningfulness of the NIHTB-CB through its relation to adaptive behaviors. Note that while the VABS-3 is often used as an outcome measure in clinical trials for ID, it is not a direct assessment (it is a combination of an observer report outcome and clinician-reported outcome), perhaps limiting its sensitivity.

The negative association between baseline adaptive behavior level and subsequent change in adaptive skills was a surprising finding. Specifically, higher adaptive behavior skills at the first visit was associated with less growth in adaptive behavior over the following 2 years in all models. Such a pattern could be indicative of a regression to the mean, or evidence that as an individual approaches a skill ceiling, their growth in that domain will begin to slow. Conversely, this finding also indicates

that individuals with lower baseline adaptive levels demonstrated, on average, greater rates of growth over two years. Interestingly, this effect was not apparent within the cognitive domain, as cognitive ability at Visit 1 was not significantly associated with change in cognitive ability, only with change in adaptive behavior. The models revealed a positive relationship such that higher cognitive ability at Visit 1 was related to increased growth in adaptive behavior.

Latent change score models were used to resolve issues with missing data and utilized growth scale values (GSVs) to more accurately model change in the present study. Missing data were particularly problematic for NIHTB-CB tests in the Fluid domain, notably Flanker and DCCS. These tasks are challenging for individuals with IDD [7] as well as individuals of young mental ages, including young typically developing children [52]. Unfortunately, missing scores on any individual NIHTB-CB test prohibits the generation of Fluid, Crystallized, and Composite scores. For this reason, large portions of our sample would have been excluded from the analyses if a latent variable approach had not been used to model the cognitive domains. Additionally, VABS-3 GSVs are only available at the subdomain level. GSVs cannot be averaged across subdomains to create composites for Communication, Socialization, and DLS domains because they are "a unitless measure and therefore cannot be compared or combined across subdomains" [53]. By utilizing latent change score models, we were able to use our data in full to examine the broader constructs of cognition and adaptive functioning. However, this approach presents practical challenges. Namely, the latent variable "scores" in these models do not match the composite or domain scores generated by the NIHTB-CB or the VABS-3. For this reason, the correlations between latent variables cannot be translated into practical terms regarding the standard output that are generated by these tests (e.g., "An *x* point change in the NIHTB-CB Crystallized Composite is associated with a *y* point change in the VABS-3 ABC"). The present study instead provides evidence that change in certain domains of cognitive function and adaptive behavior are associated at the latent level.

Related to the data missingness of the NIHTB-CB tests, future development of the NIHTB-CB could involve individuals with IDD in test development and norming to improve feasibility. The development of the NIH Infant and Toddler (Baby) Toolbox (NBT), including domains of cognition and executive function, language, numeracy/early mathematics, motor, and social functioning, is currently underway. The NBT aims to capture neurodevelopment at younger ages (1–42 months old) for both research and clinical use. Individuals with IDD represent a clear clinical population of interest for this measure, particularly due to the much lower mental ages often seen in this population, and the limited feasibility we have observed for some fluid reasoning tests in individuals with these lower mental ages.

We have previously demonstrated that rates of change vary depending on the chronological age of the participants [12]. Even among those with IDD, more change is anticipated at younger ages than at older ages, when growth plateaus (and eventually decreases). As such, we dichotomized age to represent these two groups—those where more change is anticipated versus those where less may be expected. Simply mean-centering age and using it as a continuous variable would fail to account for these different developmental expectations. We chose to dichotomize age into these developmental epochs as age at baseline was not the primary concern for our hypotheses and we wanted to reduce model complexity where possible. Another study caveat pertains to the time span between assessments (slightly over two years on average), and the number of observations across development (maximum of two), factors that likely reduced power to detect associations of cognition and adaptive behavior growth. More observations over a longer period of development would likely produce better and stronger estimates of these associations.

Conclusions

In summary, the present study demonstrated that cognitive level, as well as change in cognition over a two-year period of development, as measured by the NIHTB-CB, are associated with growth in adaptive behavior, especially daily living skills, among youth with IDD. This work provides evidence for the clinical, "real life" meaningfulness of the NIHTB-CB in IDD, and important empirical support for the NIHTB-CB as a fit-for-purpose performance-based outcome measure for this population.

Abbreviations

IDD	Intellectual and developmental disability
DSM	Diagnostic and Statistical Manual of Mental Disorders
NIHTB-CB	National Institutes of Health Toolbox Cognition Battery
VABS-3	Vineland Adaptive Behavior Scales, Third Edition
BLCS	Bivariate latent change score
DLS	Daily Living Skills
FXS	Fragile X syndrome
DS	Down syndrome
WS	Williams syndrome
FDA	Federal Drug Administration
SB5	Stanford Binet Intelligence Scales, Fifth Edition
FICA	Flanker Inhibitory Control and Attention
DCCS	Dimensional Change Card Sort
PCPS	Picture Comparison Processing Speed
LSWM	List Sorting Working Memory
PSM	Picture Sequence Memory
PVT	Picture Vocabulary Test

ORRT	Oral Reading Recognition Test
USS	Unadjusted standard score
AB	Adaptive behavior
CFI	Comparative fit index
RMSEA	Root mean square error of approximation
TLI	Tucker-Lewis index
IQR	Inter-quartile range
COG	Cognition
COA	Clinical outcome assessment
GSV	Growth scale value
ABC	Adaptive Behavior Composite
NBT	National Institutes of Health Baby Toolbox

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s11689-024-09542-z.

Supplementary Material 1: Supplementary Figure 1. Structural equation model diagram of the full bivariate latent change score model.

Availability of data and materials
Data are available from the NIMH Data Archive (nda.nih. gov/)—ID C3738.

Declarations

Ethics approval and consent to participate
Institutional review board approval was obtained at each site before study initiation. Written consent was obtained from each guardian (or adult participants in the case of individuals who were capable to provide their own consent).

Consent for publication
Not applicable.

Competing interests
AJK, JK, AD, EC, ES, D. Harvey and KR: no relevant disclosures; EBK has received funding from the following, all of which are directed to Rush University Medical Center in support of rare disease programs, and she receives no personal funds and has no relevant financial interest in any of the commercial entities listed: Acadia, Alcobra, Anavex, Biogen, BioMarin, Cydan, Fulcrum, GeneTx, GW, Ionis, Lumos, Marinus, Neuren, Neurotrope, Novartis, Orphazyme, Ovid, Roche, Seaside Therapeutics, Tetra, Ultragenyx, Yamo, and Zynerba to consult on trial design and development strategies and/or to conduct clinical studies in FXS or other NNDs or neurodegenerative disorders; Vtesse/Sucampo/Mallinckrodt Pharmaceuticals to conduct clinical trials in Nieman Pick; and Asuragen Inc to develop testing standards for *FMR1* testing; D. Hessl has received funding from the following, all of which are directed to the UC Davis, in support of fragile X treatment programs, and he receives no personal funds and has no relevant financial interest in any of the commercial entities listed: Autifony, Ovid, Tetra/Shionogi, Healx, and Zynerba pharmaceutical companies to consult on outcome measures and clinical trial design. D. Hessl and EBK are members of the Clinical Trials Committee of the National Fragile X Foundation.

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