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Development of the Executive Function, Attention, and Speed Symptom Inventory (EASSI) for Phenylketonuria

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Abstract

Background

Recent advances in novel therapies for phenylketonuria (PKU) have highlighted the importance of the functional benefits of better metabolic control, particularly as it relates to neurocognitive functioning. Though the neurocognitive profile of PKU is well characterized, there is a dearth of PKU-focused patient reported outcomes (PRO) measures of neurocognitive symptoms fit for use across clinical and research settings. The present study developed and validated the Executive Function, Attention, and Speed Symptom Inventory for PKU (EASSI), a new PKU-specific PRO measure of neurocognitive symptoms.

Method

An initial pool of items was developed using expert consultation and quantitative analyses of extant data. The measure's structure and content were further refined via an iterative process involving multiple rounds of concept elicitation and cognitive interviews with individuals with PKU. The resulting measure was then administered to a novel sample of individuals with (N = 27) and without PKU (N = 24) alongside extant neurocognitive PROs to assess its sensitivity, reliability, and validity.

Results

The EASSI consists of 36 symptom items, each of which is rated separately on its frequency of occurrence and impact on daily life. The measure yields a global composite score and six subdomain scores: cognitive flexibility, emotion regulation, hyperactivity/impulsivity, organization/initiation, processing speed, and attention/working memory. The EASSI demonstrated excellent internal and test-retest reliability indicating psychometric consistency and stability. Sensitivity analyses demonstrate that the measure has strong sensitivity to PKU, indicating that it captures PKU-specific symptoms of neurocognitive difficulties as intended. **S**cores on the EASSI were strongly correlated with scores on extant measures of neurocognitive function, indicating solid concurrent validity.

Conclusions

The EASSI represents a psychometrically validated PRO measure of neurocognitive symptoms in individuals with PKU. This measure is easy to administer and complete, relatively brief, and is freely available for use by healthcare providers, clinical researchers, and the PKU community. Ongoing research on this measure is focused on the development of general population norms, thresholds for clinically meaningful change, and translations to other languages.

Background

Phenylketonuria (PKU) is a rare inherited metabolic disorder characterized by a deficiency in the phenylalanine hydroxylase (PAH) enzyme, responsible for the metabolism of the amino acid phenylalanine (Phe) into tyrosine. PKU results in an accumulation of Phe in the blood and brain. The

heightened concentrations of Phe compete with large neutral amino acids (LNAAs) including tyrosine and tryptophan for uptake into the brain and further inhibit tyrosine hydroxylase and tryptophan hydroxylase activity thus reducing available dopamine and serotonin (1, 2). Excess Phe impacts several additional central processes including glutamatergic synaptic transmission and pyruvate kinase activity (3, 4)

If left untreated, PKU typically results in irreversible neurological damage and severe cognitive impairment (5). Current recommendations for the treatment of PKU suggests maintaining target blood Phe levels of < 360 μmol/L, which has been historically accomplished by minimizing the consumption of dietary protein. Best practices recommend initiating treatment at or near the time of birth (i.e., when diagnosis is made) and maintaining Phe-restriction for life to achieve optimal outcomes (6, 7).

Despite early and continuous treatment, many individuals with early-treated PKU experience neurological and cognitive sequelae. Neurologically, individuals with early-treated PKU often exhibit damage to cortical white matter, with higher Phe levels associated with more severe impact (8, 9). There is growing evidence that gray matter structures including cortex, basal ganglia, and cerebellum may also be affected (10–13). The neurocognitive endophenotype of early-treated PKU is most often characterized by a slight decrease in overall intellectual ability coupled with more significant difficulties in select domains including executive function, attention, and processing speed (14–17). Executive function encompasses higher order cognitive skills such as strategy use, planning, working memory, and cognitive flexibility. Focused and sustained attention involves the ability to actively focus on one stimulus or activity without distraction and to do so over a prolonged period of time. Processing speed refers to the pace at which someone is able to perceive, process, and respond to information. Together these abilities are critical for effectively navigating daily life - allowing us to plan, focus, and respond efficiently to our everyday world. Previous studies have generally found that poorer metabolic control (as reflected by elevation in Phe levels) is associated with more severe disruption in these abilities (14, 17). In addition, a recent meta-analysis by Thomas et al. of 46 studies found that within-person improvements in metabolic control were accompanied by subsequent improvements in executive function, processing speed, attention, and other cognitive abilities (18).

Maintaining strict adherence to therapeutic Phe targets via dietary management can be challenging (19). Difficulties with dietary compliance often contribute to elevated Phe levels, which in turn are associated with reduced quality of life and greater risk of neurocognitive complications among individuals with early-treated PKU as noted above (20). These challenges have motivated the recent development of several novel therapies including small molecule therapies (e.g., sapropterin, sepiapterin, repinatrabit) (21–23), enzyme substitution therapies (phenylalanine ammonia lyase; (24, 25), and potential future nucleic acid-based therapies (mRNA therapy, gene therapy, or gene editing) (26). For many individuals with PKU, these pharmaceutical interventions offer a less restrictive method of maintaining metabolic control by allowing the potential of increasing natural protein intake.

Individuals within the PKU community identify neurocognitive skills such as executive functioning, attention, and processing speed as key priorities for treatment-related improvements alongside lowering Phe levels (27). These abilities play a critical role in the navigation of daily life and impact adaptive functioning across domains (e.g., school and job performance, social life, and self-care; (28, 29). Within this context, while reductions in plasma Phe levels remain the primary endpoint in most clinical trials and regulatory evaluations by agencies such as the U.S. Food and Drug Administration (FDA), there is growing awareness and emphasis on the importance of also demonstrating meaningful functional benefits, including improvements in patients' daily functioning and overall well-being (27, 30).

Although the neurocognitive endophenotype of PKU is relatively well characterized, there is a dearth of assessment tools specifically designed and validated to capture PKU-related neurocognitive symptoms. Within this context, the present study aims to address these gaps in disease specific measurement through the development of the PKU Executive Function, Attention, and Speed Symptom Inventory (EASSI), a comprehensive neurocognitive patient-reported outcome (PRO) measure tailored to the PKU experience. To accomplish this goal, we utilized a three-phase study design that leveraged quantitative and qualitative data from adults with PKU and utilized an iterative feedback method for item development and refinement that centered feedback from the PKU community. We then evaluated the psychometric properties including internal consistency, test-retest reliability, and concurrent validity of the new measure.

Methods

As illustrated in Fig. 1, a multiphasic approach leveraging both quantitative and qualitative methods was used in the development of the EASSI. These phases consisted of the following: 1) quantitative data-driven generation of item themes and individual item content; 2) qualitative assessment of concept saturation, item comprehensibility, and item relevance; and 3) quantitative assessment of item- and measure-level sensitivity, reliability, and validity. Study procedures were approved by the University of Missouri Institutional Review Board (IRB#2098850 and 2103998) and were conducted in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from all individuals prior to participation.

Phase 1 – Initial Theme & Item Development

In phase 1, an initial item set for the EASSI was developed using quantitative data-driven methods in conjunction with a targeted literature review and consultation with PKU experts.

Procedure. We leveraged a large pre-existing set of PRO assessment data collected from adults with and without early-treated PKU across past studies conducted by our research group (31–33). As part of the aforementioned studies, participants had completed one or more of the following well-established PRO measures: the Behavior Rating Inventory of Executive Function for Adults (BRIEF-A); Conners' Adult ADHD Rating Scales –Self-Report: Long Version (CAARS-S:L); The Social Responsiveness Scale-Second

Edition (SRS-2); and the Achenbach Adult Self-Report (ASR) (34–37). The BRIEF-A is a 75-item self-report measure assessing everyday symptoms of executive dysfunction. The CAARS is a 66-item self-report measure assessing ADHD-related symptoms. The SRS-2 is a 65-item self-report measure assessing symptoms and behaviors associated with social communication difficulties. The ASR is a 126-item self-report measure used to assess aspects of adaptive functioning and problems related to a range of internalizing and externalizing disorders. In total, data from 184 participants on the BRIEF-A (N_{PKU} = 150, $N_{non-PKU}$ = 34), 72 on the CAARS and SRS-2 (N_{PKU} = 38, $N_{non-PKU}$ = 34), and 81 on the ASR (N_{PKU} = 40, $N_{non-PKU}$ = 41).

Analysis & Results. A series of item-level analyses were conducted on data from each of the aforementioned PRO measures in order to determine the extent to which items were sensitive to 1) group-related differences between PKU and non-PKU individuals and/or 2) individual differences in recent metabolic control (as reflected by concurrent Phe levels). Items surpassing a pre-determined significance threshold ($p < .05$) were examined and categorized into overarching themes. In total, nine data-driven neurocognitive themes were identified: Working memory, attention, cognitive flexibility, emotional control, hyperactivity, impulsivity, initiation, organization, and awareness/self-monitoring. Two additional themes, motor control and processing speed, were added based on extant literature (38, 39) and expert opinion (co-authors EJ and SEC).

An initial 45-item version of the EASSI was subsequently drafted. Items were designed to reflect everyday signs or symptoms of difficulties within each of the aforementioned neurocognitive domains (i.e., themes). Particular emphasis was placed on ensuring prototypicality of items and maximizing concept coverage (i.e., concurrent validity).

Importantly, the EASSI was designed to capture both the frequency and impact of each symptom item in order to assess the full spectrum of potential interference of neurocognitive difficulties on patients' day-to-day lives. For each item, the responder first rated the frequency of the symptom/behavior on a 5-point Likert scale (1-never, 2-rarely, 3-sometimes, 4-often, 5-always). They then rated the extent to which the respective symptom/behavior interfered with their daily functioning, also on a 5-point Likert scale (1-not all, 2-a little bit, 3-moderately, 4-substantially, & 5-severely). To minimize recall error and ensure responses correspond to recent symptomology, respondents were asked to reflect on their experiences over the last week (i.e., seven days) when responding to each item. The recall period was selected to maximize sensitivity to acute changes in blood Phe that may contribute to recent symptomology and has been utilized in other PKU-focused patient reported outcomes measures (40).

Phase 2A – Patient Concept Elicitation & Cognitive Interviews

During phase 2A, semi-structured interviews were used to examine concept saturation of the EASSI and to assess the relevance and clarity of the initial item set, both of which guided measure revisions.

Sample and eligibility. Participants in phase 2A consisted of 11 individuals with early-treated PKU (4M/7F; Age: *M* = 33.1 yrs, *SD* = 11.1) recruited through PKU advocacy group email list servs and social media posts in addition to a recruitment database maintained by the senior investigator (SEC). Participants were considered eligible for the study if they were English speaking, 18 years or older, and had no history of neurologic problems unrelated to PKU. PKU participants were additionally required to have been diagnosed and started treatment at/around their time of birth. The sample was further stratified into those with historically poor metabolic control (N = 3, recent & past Phe > 360 µmol/L), historically good metabolic control (N = 2, recent & past Phe < 360 µmol/L), and recently improved metabolic control (N = 6, past Phe > 360 µmol/L but recent Phe < 360 µmol/L) due to a treatment change (e.g., more strict adherence to dietary restrictions, initiation of a pharmacological treatment). The sample stratification ensured that symptoms associated with a full range of metabolic control and history were captured. Blood Phe levels were also collected within one week of study visit, with a mean level of 366 µmol/L (*SD* = 230; Range: 93–817). More detailed participant demographics can be found in Table 1.

Table 1

Sample Characteristics					
	PKU				**Non-PKU**
Variable	Overall	Phase 2A	Phase 2B	Phase 3	Phase 3
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
N	41	11	3	27	24
Age (years)	34.9 (9.7)	33.1 (11.1)	40.3 (10.3)	35.0 (9.3)	33.4 (9.4)
Sex (M/F)	18/23	4/7	3/0	11/16	9/15
Education (years)	15.0 (3.8)	16.4 (2.5)	14.7 (2.3)	14.2 (4.3)	17.4 (3.0)
Concurrent Phe Levels (µmol/L)	534 (438)	366 (230)	812 (676)	575 (469)	---
Current Treatment(s)					
Phe-Restricted Diet	59%	55%	33%	63%	---
Medical Foods	54%	45%	33%	59%	---
Sapropterin	17%	18%	0%	19%	---
Pegvaliase	34%	36%	33%	33%	---
Note. Phe = phenylalanine					

Procedure. Phase 2A was completed with study staff remotely via a HIPAA-compliant cloud-based video and phone conferencing system (Zoom). Study sessions were audio-recorded and transcribed for later

analysis. Participants were encouraged to take regular breaks and were allowed to complete the study over multiple sessions as needed.

Participants completed a semi-structured concept elicitation interview aimed at better understanding the frequency and impact of their neurocognitive symptoms as well as the sensitivity of such symptoms to changes in metabolic control. Further description of the content and structure of the interviews are provided in the supplemental materials. In addition, prototypical examples of symptom-level experiences identified by participants are documented in Supplementary Table S1.

Following the concept elicitation interview, participants completed the initial 45-item draft of the EASSI, which took approximately 15 minutes. After completion of the EASSI, a semi-structured cognitive interview was conducted with each participant in order to assess the relevance and understanding of individual item content as well as overall measure instructions. Further details on the interview methodology are provided in the supplemental materials. All participants were given regular breaks throughout the study session.

Analysis & Results.

Concept Saturation. Thematic analyses were conducted on concept elicitation interviews from phase 2A using MaxQDA, a qualitative data analysis software (41). Each transcript was coded independently by two trained raters and discrepancies resolved by a third rater (author SB) in order to ensure reliable application of codes. Concept saturation was determined using the code frequency count method with a predetermined stopping criterion of N = 2. This method involves sorting participant comments into thematic bins and considering concept saturation complete once a predetermined number of successive interviews generate no new themes. This method of establishing concept saturation has been successfully leveraged in other qualitative studies (42) and is well-suited to the structure of our data. In order to account for order effects on the saturation point, we incorporated a bootstrapping procedure into our code frequency count analyses. This procedure consisted of performing 200 iterations of code frequency count concept saturation analyses with the aforementioned stop criteria of N = 2. The number of successive interviews required to reach a stopping point across all 200 iterations was then averaged, resulting in a mean concept saturation point of 7.4. This indicated that sufficient data were collected after 8 patient interviews. Potential thematic gaps in the EASSI were identified by cross referencing theme codes with data-driven themes identified in Phase 1. The resulting conceptual model of the EASSI comprising of central themes and corresponding symptom areas can be seen in Fig. 2.

Cognitive Interviews. Content of cognitive interviews from phase 2A were coded and analyzed using a standard spreadsheet software in order to assess item interpretation, clarity, and relevance to PKU. All participants were able to correctly restate the EASSI instructions in their own words and affirmed that instructions were easy to understand. Ten of eleven participants stated that the EASSI was relevant to their experiences with PKU and did not contain any irrelevant questions. (The remaining participant was unsure if the EASSI was relevant/irrelevant to their experiences because they have not monitored their

blood Phe level in the recent past.) There was also general consensus among participants that items on the EASSI described symptoms that get worse with higher Phe levels.

During the item-by-item portion of cognitive interviews, all but one participant was able to correctly restate each measure item in their own words to affirm understanding. (The aforementioned participant misinterpreted two items.) Thirteen total items were rated as difficult to understand by one participant (26%), six by two participants (13%), and only two by three participants (4%). All items (N = 8) rated as difficult to understand by two or more participants were considered for revision.

Phase 2B – Item Revision & Follow-Up Cognitive Interviews

Based on the results of phase 2A, the EASSI item set was revised. Specifically, to address thematic gaps identified via the concept elicitation interviews, 15 new items were added. In addition, the wording of 25 existing items was revised based on the cognitive interviews. To confirm clarity of the updated version of the measure, previous study participants (N = 11, see above) completed the revised EASSI and received follow-up cognitive interviews focused on the new and revised items. In addition, cognitive interviews covering the full (60) item set were conducted with an additional small sample of 3 naïve individuals with PKU.

Procedure. The 11 participants from phase 2A as well as 3 additional naïve individuals with PKU (3M/0F; age range: 29–49 yrs) were administered a revised 60-item version of the EASSI. Following completion of the EASSI, participants completed a brief semi-structured cognitive interview during which the clarity and understandability of the revised and new items (N = 15 and 25, respectively) were assessed.

Analysis & Results. Content of cognitive interviews from phase 2B were coded and analyzed in a standard spreadsheet software to assess item interpretation, clarity, and relevance to PKU. Of the 15 new items, one item was rated as difficult to understand by 3 participants, one item was rated difficult to understand by 2 participants, and four items were rated difficult to understand by only one participant. Of the 25 revised items, three items were rated as difficult to understand by two participants, and six items were rated as difficult to understand by only one participant.

Phase 3 – Optimized Item Set, Scoring Rubric, & Psychometric Properties

The goal of Phase 3 was to identify the optimal item set and scoring rubric for the EASSI as well as evaluate the psychometric properties of the resulting measure. Within this context, data were collected from a naïve sample of adults with and without PKU on the full set of 60 items from Phase 2 at two timepoints one week apart (in order to assess test-retest reliability). Data were also collected on three well-established PROs of cognitive symptoms in order to assess concurrent validity.

Sample and Eligibility. Participants for phase 3 consisted of 27 adults (11M/16F) with early-treated PKU aged 21 to 55 (M = 35.0, SD = 9.3) and a demographically similar sample of 24 healthy adults without PKU (9M/15F, Age: M = 33.4, SD = 9.4). Additional participant demographics are included in Table 1.

Procedure. All but one participant completed the 60-item EASSI at two timepoints, approximately one week apart (M = 7.84 days; range: 7–19 days). Fasting Phe levels were collected at the first timepoint. During the initial session, all participants completed the following additional measures (also administered remotely):

Adult ADHD Self-Report Scale (ASRS). The ASRS (43) is an 18-item self-report measure assessing DSM-IV-TR criteria for ADHD. Items are rated on frequency of occurrence using a 5-point Likert scale ranging from “0-Never” to “4-Very Often”. The first six items (Part A) were designed to act as a screener for ADHD due to their predictive power. The remaining 12 items (Part B) consist of additional symptoms that can be used to further characterize an individual’s ADHD symptom presentation but are not formally scored. Although the ASRS screener was originally designed to be scored in a binary fashion, Kessler (2007) established that scoring using the full 5-point Likert scale (yielding a total score of 0 to 18 points) is more favorable and has shown good reliability and validity. The ASRS has been validated for use within PKU populations and clinical trials for PKU (44).

Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A). The BRIEF-A is a standardized 75-item self-report questionnaire designed to assess executive function problems that may appear in day-to-day life (34). Each item is rated on a 3-point Likert scale including the following response options: “1-Never”, “2-Sometimes”, or “3-Often” is a problem. Individual item scores contribute to a number of age-normed composite scores including the Global Executive Composite (GEC), which reflects overall executive ability. Score. The BRIEF-A has shown good reliability and validity in adult samples and has been used widely in the PKU literature (32, 34).

Patient Global Impression Severity (PGI-S). The present set of 12 PGI-S items were adapted from those used previously (45, 46) and included an item on overall cognitive and thinking skills as well as domain-specific items related to particular aspects of cognition (e.g., working memory, attention, emotional control). For each item, participants rated the extent of their difficulties in their respective cognitive domain on a 5-point Likert scale (1-No difficulty, 2-Mild, 3-Moderate, 4-Severe, 5-Very Severe). A copy of the PGI-S scale is included in the Supplemental Materials.

Analysis & Results. Data from phase 2b, 2c, and 3 were combined for analytical purposes (N = 41 PKU & 24 Non-PKU). For analyses examining concurrent validity, only data from Phase 3 in which participants completed additional PRO measures were utilized.

Optimized Item Set & Measure Structure. In order to lessen potential patient burden, we explored whether a smaller subset of items (as compared to the full 60-item version) would provide equivalent (or even superior) sensitivity to PKU-related symptoms. As a starting point, effect sizes (PKU vs non-PKU) were calculated for each item, and those items demonstrating a small effect ($d < 0.30$) were not considered

further. This resulted in 10 items being discarded. Next, based on theoretical conceptualization and examination of inter-item correlations, the remaining 50 items were consolidated into 6 neurocognitive domains: Cognitive Flexibility (n = 7), Emotional Regulation (n = 10), Hyperactivity-Impulsivity (n = 9), Organization-Initiation (n = 7), Processing Speed (n = 8), and Attention-Working Memory (n = 9). In order to balance item coverage across the aforementioned domains, the item set was further trimmed to 36 items, with 6 items per domain. For each domain, all possible combinations of items were calculated in subsets of 6 items. Logistic regression was then applied to the data for each possible subset of items, and the set of 6 items associated with the maximal effect size (R-squared value) for predicting group membership (PKU vs non-PKU) was identified.

As seen in Supplementary Table 2, scores on the resulting 36-item version were highly correlated with those on the 60-item version, both in terms of overall score (r = .993, $p < .001$) as well as domain subscores (r = .970-.992, $p < .001$ in all instances). In addition, the 36-item version demonstrated equivalent or better sensitivity to group-related differences in overall global and domain scores (Cohen's $d = 0.70–1.25$) as compared to the full 60-item version ($d = 0.61–1.14$).

EASSI Scoring Rubric and Data Completeness Criteria. The final version of the EASSI consists of 36 items assessing behavioral manifestations of neurocognitive problems in daily life. For each item, the responder first rates the frequency of the symptom/behavior over the past 7 days on a 5-point Likert scale (1-never, 2-rarely, 3-sometimes, 4-often, 5-always). They then rate the extent to which the respective symptom/behavior interfered with their daily functioning during that same time period, also on a 5-point Likert scale (1-not all, 2-a little bit, 3-moderately, 4-substantially, & 5-severely). Scores on individual items (item score = frequency response + impact response) contribute to the calculation of six non-overlapping clinical scales reflecting different neurocognitive domains including: cognitive flexibility, emotional regulation, hyperactivity-impulsivity, organization-initiation, processing speed, and attention-working memory (see Fig. 2). In addition, a composite score based on all 36 items and reflecting overall neurocognitive ability (Global Composite Score) can be computed. For ease of use and interpretation, domain scores and the global composite score are converted to a standard scale (0 to 100) by dividing the raw score sum by the number of completed items then multiplying by 10.

In terms of data completion, at least 5 of the 6 items within a given domain must be fully completed (i.e., both frequency and impact) for the corresponding domain score to be deemed valid. For the Global Composite score, at least 30 of the 36 items must be completed, with no more than two missing items permitted within any single domain. To confirm the acceptability of these criteria, the present dataset was used to simulate random missing data under each of these conditions (i.e., one item missing within a given domain; up to six items missing overall, with no more than two missing from any single domain). Reliability and validity statistics were computed based on the resulting global and subdomain scores. This process was repeated for 1,000 iterations. As shown in Supplemental Table S4, psychometric indicators were unaffected.

Sensitivity to PKU-Related Neurocognitive Symptoms. As illustrated in Fig. 3, the PKU group scored significantly more poorly than the non-PKU group on the Global Composite [$t(61) = 4.93$, $p < .001$, $d = 1.16$] as well as all contributing domain scores [$t > 2.82$, $p < .005$, $d > .70$ in all instances]. Within the PKU group, EASSI scores were significantly correlated in several instances with patient-reported historic Phe levels during adolescence (see Table 2). No relationship, however, was observed with patient-reported Phe levels during other developmental epochs (childhood, adulthood) nor with measurements of concurrent Phe ($r < .12$ in all instances). Interestingly, BRIEF and ASRS scores also did not correlate with concurrent Phe (r = − .06 & − .34, respectively; $p > .05$ in both instances) in the present study.

Table 2

Correlations Between Metabolic Markers and EASSI Scores

Variable	Self-Reported Childhood Levels (< 12 yrs)	Self-Reported Adolescent Levels (13–17 yrs)	Self-Reported Adult Levels (18 + yrs)	Concurrent Phe Levels
Global Composite	0.11	0.38*	0.06	-0.01
Cognitive Flexibility	0.08	0.43*	0.05	0.02
Emotional Regulation	0.21	0.42*	0.02	0.00
Hyperactive/Impulsivity	0.03	0.18	-0.03	-0.09
Organization/Initiation	0.06	0.25	0.21	0.10
Processing Speed	0.10	0.34*	0.04	-0.09
Attention/Working Memory	0.13	0.35*	0.03	0.00

Note. Concurrent phenylalanine (Phe) levels were measured on the day of testing. Pearson's correlation was used to analyze the relationship with concurrent Phe levels. Spearman's rank-order correlation was used to analyze the relationship to self-reported historic Phe levels.

*$p < .05$

Test Reliability, Consistency, and Sensitivity. As can be seen in Table 3, the EASSI showed strong internal reliability with a Cronbach's α value of .958 for the overall item set and values of 0.754-.851 within each domain subset. Overall measure cohesion was further reflected in the item-total correlations which ranged from .366-.757 (in reference to the overall global score). Indicators of test-retest reliability were also excellent in terms of both overall global score ($r = .897$) as well as domain subscores ($r = .822$-$.908$). As indicated earlier, large and medium-to-large effect sizes for group (PKU vs non-PKU) were observed for the overall global and domain scores, respectively (Global: $d = 1.13$; Domains: $d = 0.70–1.25$) thus demonstrating the measure's relevance and sensitivity to the neurocognitive difficulties experienced by individuals with PKU. [For comparison, effect sizes for the BRIEF GEC and ASRS were 1.08 and 0.89,

respectively.] Results for additional sensitivity and specificity metrics are included in Table S5 & S6 of the Supplemental Materials.

Concurrent Validity. As illustrated in Fig. 4 and seen in Table 4, the EASSI also demonstrated concurrent validity as evidenced by strong correlations with BRIEF-A scores (Global: $r = 0.861$; Domains: $r = .634 - .830$; $p < .001$ in all instances). A significant correlation was also observed with ASRS scores (Global: $r = 0.672$; Domains: $r = .411\text{-}.671$; $p < .005$ in all instances) and the global PGI-S item assessing overall thinking skills (Global: $r = 0.703$; Domains: $r = .534\text{-}.688$; $p < .001$ in all instances). Correlations between EASSI subscale scores and corresponding individual PGI-S items are detailed in Supplementary Table S3.

Table 3

Reliability and Sensitivity Metrics for the EASSI

Variable	Cronbach's Alpha (α)	Item-Total Correlation (Range)	Test-Retest Correlation	Dx Group Effect Size (*d*)
Global Composite	0.959	0.367–0.757	0.897	1.16
Cognitive Flexibility	0.857	0.597–0.735	0.840	1.03
Emotional Regulation	0.834	0.444–0.783	0.908	0.73
Hyperactive/Impulsivity	0.806	0.429–0.665	0.887	1.00
Organization/Initiation	0.884	0.619–0.779	0.846	0.89
Processing Speed	0.758	0.296–0.620	0.822	1.25
Attention/Working Memory	0.824	0.455–0.717	0.842	1.00

Note. *d* = Cohen's *d*.

Table 4

Concurrent Validity: Correlations Between EASSI and Other Measures

Variable	BRIEF-A (GEC)	ASRS (Total Score)	PGI-S Scale (Global Item)
Global Composite	0.861	0.672	0.703
Cognitive Flexibility	0.722	0.585	0.579
Emotional Regulation	0.634	0.411	0.581
Hyperactive/Impulsivity	0.791	0.604	0.677
Organization/Initiation	0.830	0.671	0.534
Processing Speed	0.727	0.624	0.612
Attention/Working Memory	0.758	0.588	0.688

Note. All correlations were significant at the $p < .001$ level. BRIEF-A = Behavior Rating Inventory of Executive Function - Adult Version. GEC = Global Executive Composite. ASRS = Adult ADHS Self-Report Scale. PGI-S = Patient Global Impression Severity.

Discussion

In recent years, growing attention has been given to the impact of neurocognitive symptoms associated with PKU and their relation to treatment adherence and everyday life (18). As a result, there is an increasing need for psychometrically sound assessment tools that capture these symptoms and are appropriate for use across clinical and research settings. To this end, we developed the EASSI. The EASSI represents a valid, reliable, and standardized PRO measure that captures common neurocognitive symptoms impacted by metabolic control in individuals with early-treated PKU. Unlike other PRO measures, the EASSI explicitly captures not only the frequency of symptoms assessed, but also their functional impact, which is an area of increasing importance for both patients and clinical research guidance bodies (27, 30). Furthermore, the EASSI leverages a one-week recall period in order to minimize recall error and maximize reliable tracking of metabolic control-linked symptom changes over time, making it well suited for a range of clinical and research applications. Importantly, this measure is freely available to the PKU community, including metabolic clinicians, researchers, and industry, can be administered in-person via paper or remotely online, and is minimally burdensome for patients to complete and researchers/clinicians to score and interpret.

The EASSI was developed using a mixed methods approach leveraging both quantitative analyses of extant PRO data and qualitative interviews from PKU patients. Interviews included concept elicitation in which patients provided insights on their day-to-day experiences with neurocognitive symptoms as well as cognitive interviews in which patients provided their perspectives on the relevance and

comprehensibility of the tool. Qualitative analyses were used to refine the EASSI and ensure concept saturation. In order to reduce the time commitment and cognitive burden of completing the measure, the measure was further refined to a final set of 36 items that contribute to a global composite score and six neurocognitive subdomain scores including cognitive flexibility, emotion regulation, hyperactivity/impulsivity, organization/initiation, processing speed, and attention/working memory.

The present study found that the EASSI has sound psychometric properties. Reliability analyses indicate that the EASSI shows good internal consistency, meaning that individual items comprising the measure assess the same overarching neurocognitive symptom profile. Specifically, results indicate strong inter-item correlations on the measure as a whole, within each subdomain, and between individual item scores and EASSI global composite scores. Consistency across administrations was also examined, revealing strong test-retest reliability for the global index as well as subdomain scores. This indicates that the EASSI is a stable measure, with consistent responses over time in the absence of substantial changes in metabolic control.

A central motivation for the development of the EASSI was to create a measure tailored to the PKU experience and thus highly sensitive to PKU vs non-PKU effects. Analyses indicate that the EASSI global index and subdomain scores demonstrate medium-to-large sensitivity to PKU, with the global index effect size falling in the large range. This indicates that the EASSI successfully captures the specific neurocognitive profile of PKU, rather than overarching neurocognitive symptoms experienced by the general population. EASSI scores were also highly correlated with scores on other extant measures assessing related constructs (BRIEF-A, ASRS, and PGI-S) thus demonstrating concurrent validity for the new measure.

Limitations and Future Directions

Taken together, our findings indicate that the EASSI is a psychometrically sound, reliable measure that effectively captures symptoms associated with the neurocognitive endophenotype of PKU. Though our sample size was sufficient for establishing validity and reliability as intended, it was not extensive enough to complete factor analysis procedures to statistically confirm our proposed factor structure (i.e., six cognitive domains). Given the low base-rate of PKU in the population, gathering a sample powerful enough for reliable factor analyses is challenging and involves more long-term recruitment. To this end, we are continuing to collect data on the EASSI with the hopes of completing confirmatory factor analysis in the future.

Contrary to expectations, concurrent Phe levels were not correlated with participants' scores on the EASSI nor on any other neurocognitive measures examined (i.e., BRIEF-A, ASRS, or PGI-S). A number of factors likely contributed to this finding (or lack thereof). For example, while the EASSI was designed to be sensitive to within-person changes in neurocognitive symptoms, the present analyses were cross-sectional. In addition, extensive historic Phe level data were unavailable for study participants. Analysis were limited to Phe levels collected the day of testing and self-reported Phe level ranges (e.g., < 360

μmol/L, 360–600 μmol/L, > 600 μmol/L). Looking forward, it will be important to collect longitudinal data in individuals with PKU to examine the sensitivity of the EASSI to within-person symptom changes over time.

Though we leveraged extensive patient-focused interviews to ensure concept saturation and measure comprehensibility, the present sample was limited to young and middle-aged adults with PKU (18–57 years of age). As a result, the EASSI is not yet validated for use in younger individuals (< 18 years of age) or those of advanced age (> 60 years of age), who may experience different day-to-day neurocognitive symptoms. To this end, future work should aim to validate the EASSI across the developmental continuum, including the possibility of adapting the measure into alternate forms such as parent-report and observed-report (e.g., spouse, healthcare provider). Initial steps towards adolescent validation are already underway (see supplemental materials for more details) and indicate preliminary validity. Additional adaptations of interest include translation of the EASSI to other languages (e.g., Spanish, French, German) and subsequent validation, which is likewise underway.

A neurotypical comparison group was included alongside the patient group during the validation phase of the present study. This approach allowed us to directly assess and confirm the EASSI's sensitivity to PKU versus non-PKU status, a critical step in establishing its validity. Although a non-PKU comparison group was included, the sample size was insufficient to establish meaningful normative scores for the general population. Accordingly, future research should focus on establishing non-PKU norms for the EASSI to determine the base rate of these symptoms in the general population. Doing so would enable patient scores to be anchored against age-based "neurotypical" benchmarks and facilitate the meaningful identification of clinically elevated neurocognitive symptoms. In line with this goal, our research group has initiated a large-scale normative study using the EASSI in a sample of over 200 young and middle-aged adults.

Conclusions

The EASSI is a new PRO tool that assesses neurocognitive symptoms impacted by metabolic control in individuals with PKU. The EASSI was developed using a mixed-methods approach that leveraged both quantitative data and qualitative input from the PKU community to ensure that the lived experience of PKU patients was accurately and adequately captured. Reliability and validity indices indicate that the EASSI is a cohesive, valid measure of neurocognitive symptoms, is sensitive to PKU, and is well suited for use in repeated measures contexts. Future work would benefit from examining within-person, treatment-related changes in scores on the EASSI as well as establishing general population norms to determine thresholds for clinically significant neurocognitive symptoms. Additionally, future studies should aim to adapt and validate the EASSI for use in a wider range of ages (e.g., adolescents, older adults) as well as additional languages. To request a copy or information related to the EASSI, please contact the senior author (S.E.C).

Abbreviations

ADHD
attention-deficit hyperactivity disorder
ASR
Adult Self-Report
ASRS
Adult Self-Report Scale
BRI
Behavior Regulation Index
BRIEF-A
Behavior Rating Inventory of Executive Function for Adults
CAARS-S:L
Conners' Adult ADHD Rating Scales – Self-Report: Long Version
DSM-IV-TR
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
FDA
Food and Drug Administration
GEC
Global Executive Composite
HIPAA
Health Insurance Portability and Accountability Act
IRB
Institutional Review Board
LNAA
large neutral amino acid
MI
Metacognition Index
mRNA
messenger ribonucleic acid
PAH
phenylalanine hydroxylase
Phe
phenylalanine
PGI-S
Patient Global Impressions - Severity
PKU
phenylketonuria
EASSI
Executive Function, Attention, and Speed Symptom Inventory for Phenylketonuria
PRO
patient-reported outcome

SRS-2
The Social Responsiveness Scale-Second Edition
µmol/L
micromoles per liter

Declarations

Ethics Approval and Consent to Participate

The present study was approved by the University of Missouri's Internal Review Board (#2098850 and 2103998) and was carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki. Informed consent was obtained for all individuals prior to participation.

Consent for Publication

Not applicable.

Competing Interests

S.E.C. has received consulting fees from BioMarin Pharmaceutical, Jnana Therapeutics, Otsuka Pharmaceutical, and PTC Therapeutics; and BioMarin has funded past and current research. E.R.J. has served as a consultant for Jnana Therapeutics, Otsuka Pharmaceutical, Arcturus Therapeutics, Agios Therapeutics, Travere Therapeutics, and participated in advisory boards for Jnana Therapeutics, Otsuka Pharmaceutical, and Sanofi. S.B. reported no biomedical financial interests or potential conflicts of interest.

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Author Contribution

S.B. and S.E.C. contributed to all aspects of the project including study design, data collection, analysis, & manuscript preparation. E.R.J. contributed to study design & manuscript preparation.

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Data Availability

The EASSI assessment tool and scoring guidelines are available from the corresponding author (S.E.C.) on reasonable request. The datasets analyzed during the current study are not publicly available due to restrictions related to internal review board policies and informed consent limitations under which the data was originally collected but are available from the corresponding author on reasonable request.

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Figures

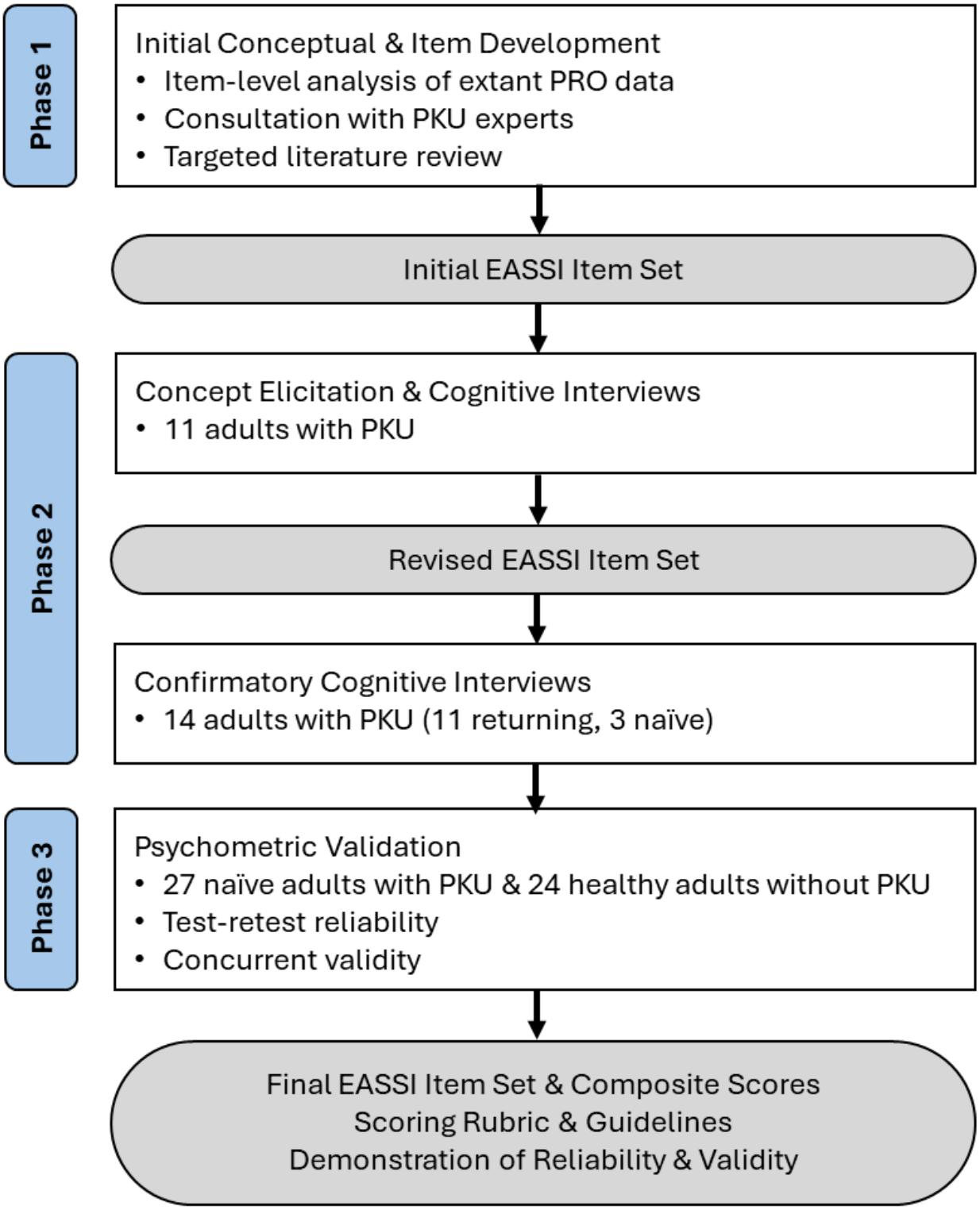


Figure 1

Schematic figure illustrating the EASSI development process.



Figure 2

Conceptual model for the EASSI

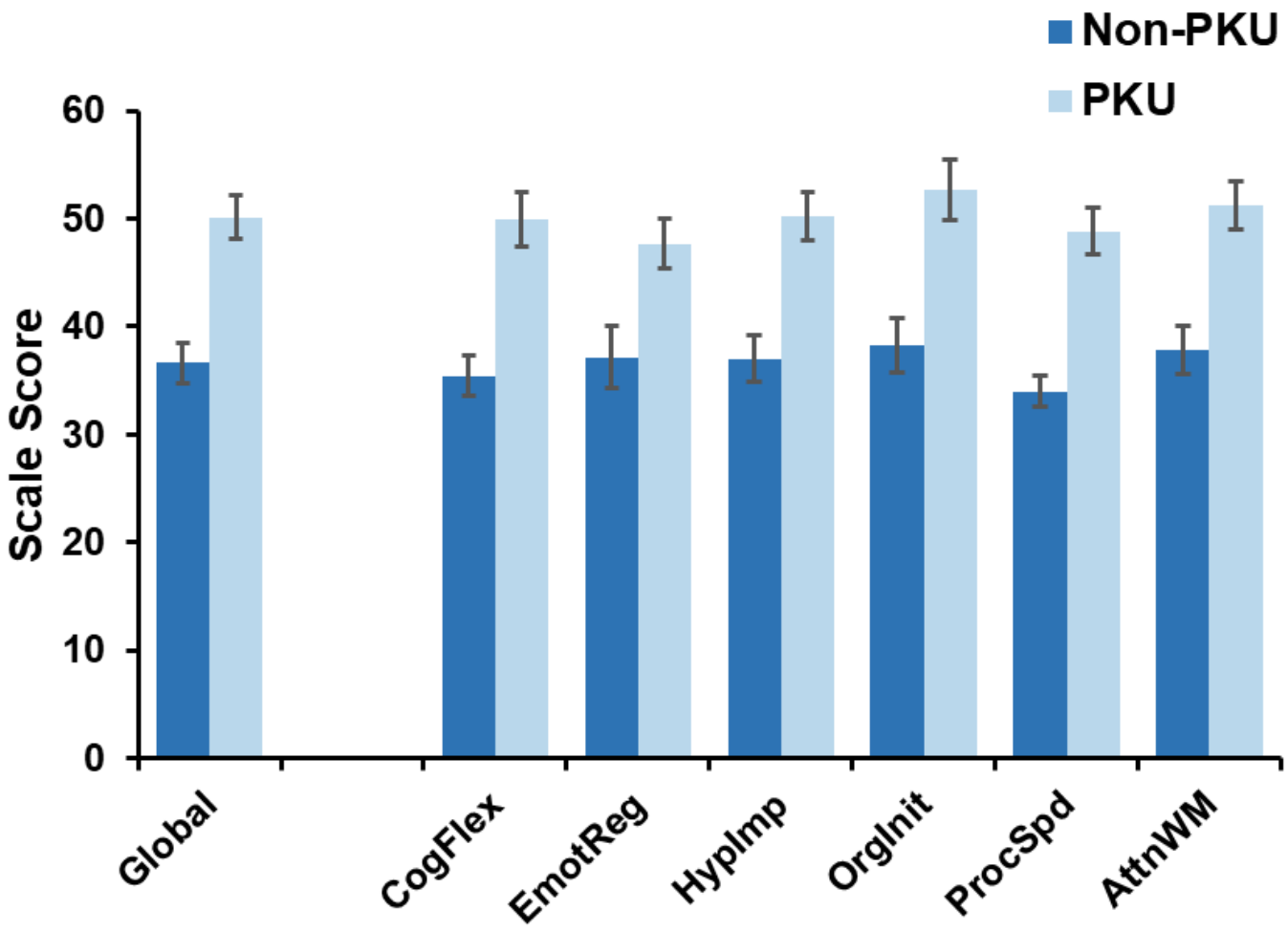


Figure 3

Mean scores for the EASSI shown separately for subdomain and group (PKU and non-PKU). Higher scores are indicative of higher symptom report. Error bars represent the standard error of the mean. Global = Global Composite; CogFlex = Cognitive Flexibility; EmotReg = Emotional Regulation; HypImp = Hyperactive/Impulsivity; OrgInit = Organization/Initiation; ProcSpd = Processing Speed; AttnWM = Attention/Working Memory.

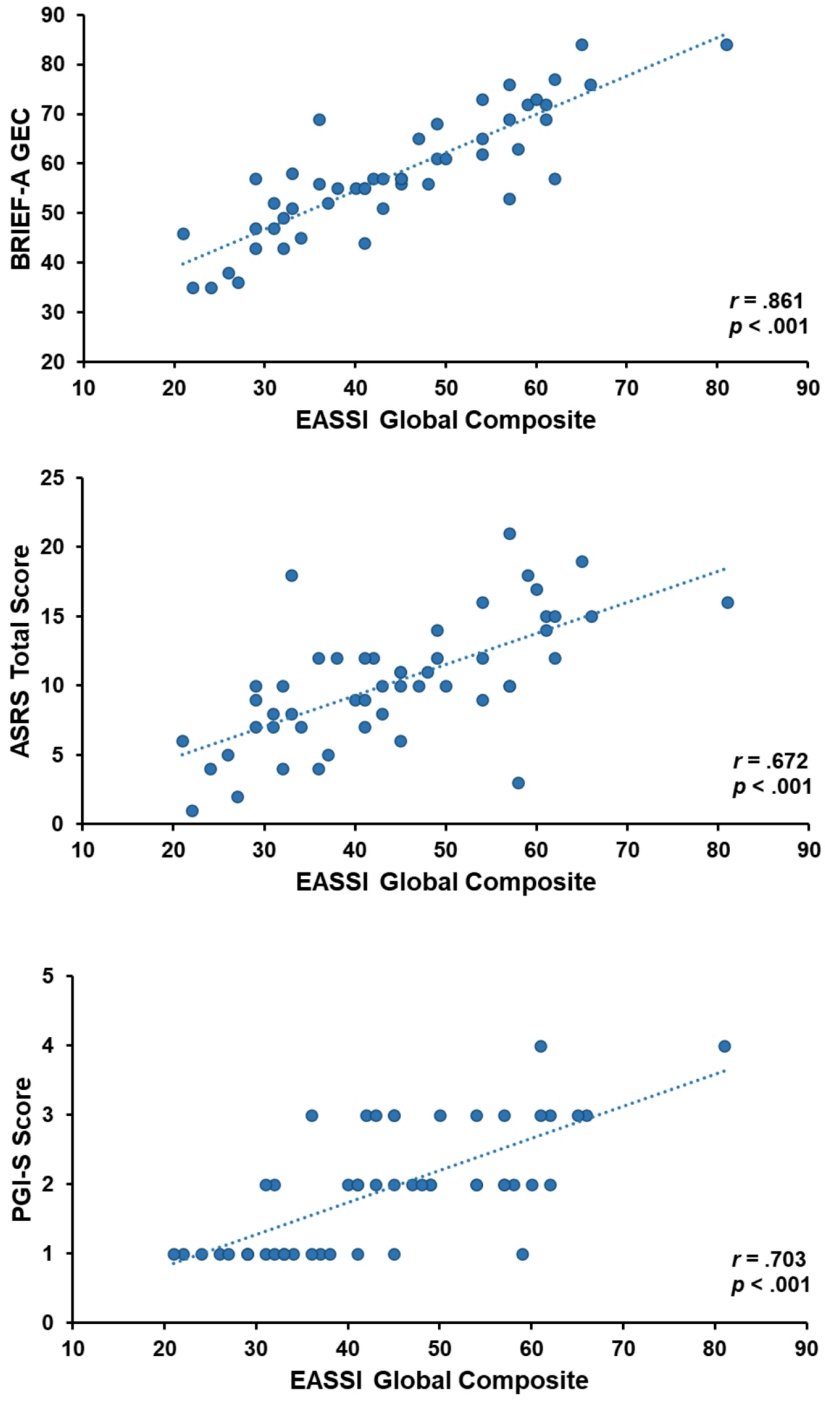


Figure 4

Scatterplot graphs illustrating the relationship between EASSI Global Composite scores and BRIEF-A Global Executive Composite (top panel), ASRS Total Score (middle panel), and PGI-S scores (bottom panel). BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version; ASRS = Adult ADHD Self-Report Scale; PGI-S = Patient Global Impression Severity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- EASSIDevelopmentSupplementalMaterials.pdf