

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

Supplementary Materials

Phase 2A - Supplementary Methods

Concept Elicitation Interviews. Participants completed a 45-minute semi-structured concept elicitation interview during which they answered questions about their neurocognitive symptoms. For each symptom endorsed, participants were asked 1) to describe their experiences with the symptom, 2) how often they experience it, 3) if anything triggers the symptom, 4) how severe the symptom is, 5) how it affects their daily life, relationships, and/or work/school, 6) how bothersome the symptom is to them, 7) if the symptom had changed over the last 6 months, and 8) if it changes based on their PKU treatment adherence and/or blood Phe level. Participants were also asked if they experience any symptoms not explicitly asked about and whether or not others in their lives (e.g., family, friends, doctors) have told them they struggle with certain symptoms due to their PKU. Each spontaneously generated symptom was followed up by the same series of eight questions outlined above. Prototypical examples of symptom-level experiences identified by participants are documented in Supplementary Table S1.

Cognitive Interviews. After completing the EASSI, participants completed a semi-structured cognitive interview with study staff in which they answered a series of questions about each item. For each item, participants were asked 1) what the statement means in their own words, 2) whether or not it was easy or difficult to understand, 3) if difficult, what would make it clearer, 4) why they selected the response they did, 5) whether the activity/experience described in the item changes based on their Phe level or treatment adherence, 6) what response options (relative to their selected choice) would represent a meaningful improvement and a worsening in the activity/experience described, 7) why the aforementioned changes would be meaningful, 8) how far back they were thinking when selecting their response, and 9) if they have suggestions for how to improve the item. Participants were also asked to describe what the overall measure instructions were asking them to do, whether or not they were easy to understand, and how they could be improved. At the end of the interview, participants were asked a series of general questions probing 1) the ideal number of items for the EASSI, 2) how long the measure should take to complete, 3) if the items on the measure were relevant to their experience with PKU, 4) if anything was missing from the measure, 5) if anything about the measure was confusing, 6) if there were any items on the measure irrelevant to their experience with PKU, and 7) if there were any items they were uncomfortable answering. All participants were given regular breaks throughout the study session.

Table S1.

Phase 2A Results: Prototypical examples of symptom-level experiences identified by participants

EASSI Domain	Participant Excerpts
Processing Speed	<i>“It's like, if there's a pause in the conversation, somebody else is jumping in, even though I have a thought, I just can't get it –you know by the time I realize there's a break in the conversation for me to get a word in, somebody else has already started talking type thing. So, it's always that I'm like a half beat behind.”</i>
Hyperactivity/Impulsivity	<i>“I guess my family have noticed that. unless I –I'm either moving or I'm asleep. And it's no there's no there's no between and that's unique to me, like no one else in my family is really like that.”</i>
Cognitive Flexibility	<i>“I'm very bad at transitioning tasks. Okay, once I am started on a task, I kind of fixate on it a little bit as long as it's like a task that I am wanting to fixate it on, or like, once I get moving on that task, I want to continue to. But if its –yeah, I think transitioning tasks is very difficult for me.”</i>
Organization/Initiation	<i>“For a lot of tasks, especially if I don't want to do them or have a tough time figuring out how I'm going to do them, I will obsess over the most efficient way to get it done instead of doing the thing.”</i>
Attention-Working Memory	<i>“I guess the other thing that I've noticed and it's definitely correlated with Phe levels is I can't focus that kind of focusing, holding a thoughts to act on it, especially when my Phe level is high. I kind of compare it to being on those game shows. We're in the tube with all the money flying around. You're trying to grab as many, you know, dollar bills as you can. It's like I'm trying to grab and hold on to these thoughts, but I can't grab a hold on to them long enough to –to do anything with them. And that is definitely a Phe level related thing.”</i>
Emotion Regulation	<i>“Internally, I feel manic. I feel like every little thing is just like constant friction inside of me. And I feel like reactively angsty about it. And it could be something simple. It could be something that's, you know a normal part of my everyday life. But for some reason it's just irritating me to –to an extreme extent.”</i>

Table S2*Correlations between Scores for the 60-Item and 36-Item Versions of the PKU-EASSI*

	60-Item Version						
	Global Composite	Cognitive Flexibility	Emotional Regulation	Hyperactive / Impulsivity	Organization / Initiation	Processing Speed	Attention/ Working Memory
36-Item Version							
Global Composite	0.993	0.881	0.812	0.863	0.821	0.894	0.921
Cognitive Flexibility	0.879	0.993	0.733	0.690	0.611	0.762	0.829
Emotional Regulation	0.843	0.736	0.979	0.739	0.519	0.657	0.687
Hyperactive/Impulsivity	0.870	0.694	0.730	0.979	0.658	0.672	0.782
Organization/Initiation	0.833	0.643	0.541	0.679	0.989	0.799	0.740
Processing Speed	0.864	0.742	0.613	0.641	0.764	0.979	0.820
Attention/Working Memory	0.907	0.803	0.663	0.796	0.710	0.815	0.970

Note. All correlations were significant at the $p < .001$ level

Table S3*Concurrent Validity: Correlations Between PKU-EASSI and Individual PGI Item Scores*

	EASSI						
	Global Composite	Cognitive Flexibility	Emotional Regulation	Hyperactive/ Impulsivity	Organization/ Initiation	Processing Speed	Attention/ Working Memory
PGI							
Global Item	0.703						
Cognitive Flexibility		0.623					
Emotional Control			0.620				
Hyperactivity				0.670			
Impulsivity				0.665			
Organization					0.816		
Initiation					0.616		
Processing Speed						0.553	
Attention							0.616
Working Memory							0.734

Note. All correlations were significant at the $p < .001$ level

Table S4*Reliability & Concurrent Validity of EASSI with Missing Data*

Variable	Cronbach's Alpha (α)	Test-Retest Correlation	BRIEF-A GEC Correlation
Global Composite	0.951	0.894	0.847
Cognitive Flexibility	0.828	0.828	0.684
Emotional Regulation	0.811	0.899	0.628
Hyperactive/Impulsivity	0.771	0.877	0.761
Organization/Initiation	0.865	0.835	0.811
Processing Speed	0.756	0.815	0.711
Attention/Working Memory	0.789	0.843	0.733

Note. Phase 3 data were used to simulate random missing data under the established data completeness and scoring validity criteria (For calculation of domain scores: one item missing within a given domain; For calculation of global composite score: up to six items missing overall, with no more than two missing from any single domain). Reliability and validity statistics were computed, and the process was repeated for 1,000 iterations. The mean output values are reported in the table.

Table S5*Sensitivity and Specificity Metrics for PKU-EASSI Predicting Group (PKU, non-PKU)*

	SENS	SPEC	PPV	NPV	TCA
Global Composite	0.80	0.54	0.75	0.62	0.71
Cognitive Flexibility	0.78	0.54	0.74	0.59	0.69
Emotional Regulation	0.85	0.54	0.76	0.68	0.74
Hyperactive/Impulsivity	0.85	0.50	0.74	0.67	0.72
Organization/Initiation	0.83	0.46	0.72	0.61	0.69
Processing Speed	0.78	0.63	0.78	0.63	0.72
Attention/Working Memory	0.85	0.54	0.76	0.68	0.74

Note: SENS = sensitivity. SPEC = specificity. PPV = positive predictive value. NPV = negative predictive value. TCA = total classification accuracy.

Table S6*Inter-Measure Correlations between EASSI Composite and Domain Scores*

	Global Composite	Cognitive Flexibility	Emotional Regulation	Hyperactive/Impulsivity	Organization/Initiation	Processing Speed	Attention/Working Memory
Global Composite	---	0.888	0.811	0.874	0.848	0.891	0.919
Cognitive Flexibility	0.888	---	0.735	0.708	0.639	0.758	0.812
Emotional Regulation	0.811	0.735	---	0.727	0.539	0.619	0.631
Hyperactive/Impulsivity	0.874	0.708	0.727	---	0.68	0.669	0.799
Organization/Initiation	0.848	0.639	0.539	0.68	---	0.794	0.744
Processing Speed	0.891	0.758	0.619	0.669	0.794	---	0.832
Attention/Working Memory	0.919	0.812	0.631	0.799	0.744	0.832	---

Note. All correlations were significant at the $p < .001$ level.

INITIAL ADOLESCENT VALIDATION STUDY (PHASE 2D)

Following phase 2C, a small sample of teens with PKU were recruited to ensure that the 60-item draft of the EASSI was easily comprehensible to an adolescent population.

Procedure. Participants included four adolescents aged 14 (3F) to 15 (1M) who were recruited via PKU advocacy group email list servs. Participants were considered eligible if they were diagnosed with and began treatment for PKU within the first 30 days of life, were English speaking, and had no history of neurologic problems unrelated to PKU. Participants and their caregivers reported good historical and present dietary control ($\text{Phe} < 360 \mu\text{mol/L}$). Following consent and assent, participants completed the 60-item draft of the EASSI, which took approximately 10-15 minutes. The instructions and each item were read aloud by study staff to ensure adequate attention. Afterward, participants completed a semi-structured cognitive interview with study staff about the measure. They were first asked what the instructions of the measure asked them to do, whether they were easy or difficult to understand, and if they could be made clearer. For items that were misinterpreted, study staff queried as to why participants interpreted the item(s) the way they did. Participants were then asked a series of questions about the response options of the measure, specifically whether or not they were sufficient to respond to the items and if they were easy or difficult to respond with. The bulk of the interview consisted of a series of questions that participants answered about each item on the EASSI and included 1) whether the statement in the item was easy or difficult to understand, 2) what the statement means in their own words, and 3) if anything could make it clearer. Finally, participants answered a series of questions assessing the overall relevance of the items on the measure to their PKU experience, if anything important was missing from the measure, if any items were uncomfortable to answer, and if anything not yet addressed was confusing about the measure. In total, interviews lasted approximately 90 minutes and participants were given 5-minute breaks every 45 minutes as well as by request.

Analysis & Results.

Cognitive interviews. Content of cognitive interviews from the adolescent sample phase were coded and analyzed in Microsoft Excel. All participants were able to correctly restate the EASSI instructions in their own words, rated them as easy to understand, and did not believe that anything could be changed to make them clearer. When asked about response options on the measure, all participants rated both the frequency and impact response options as sufficient and easy to respond with. Two participants incorrectly restated one item each (different items); otherwise all other items were correctly restated by all participants. One item was rated as difficult to understand by one participant; otherwise all items were rated as easy to understand by all participants. When asked, three of four participants stated that the EASSI was relevant to their experiences with PKU, and one stated that it was more relevant to their everyday (non-PKU) experiences. Only one participant felt that something was missing from the questionnaire, but the experience identified (i.e., headaches) was out of the scope of the EASSI. All participants felt that no items were irrelevant to their experiences with PKU and no items were uncomfortable to answer.

PATIENT GLOBAL IMPRESSION (PGI) SCALE

- 1.) Rate how much difficulty that you have had during the past 7 days with your cognitive and thinking skills.
 - ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 2.) Rate how much difficulty that you have had during the past 7 days with working memory (i.e., the ability to hold information in mind and recall it later).
 - ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 3.) Rate how much difficulty that you have had during the past 7 days with your ability to focus attention and concentrate.
 - ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 4.) Rate how much difficulty that you have had during the past 7 days with your ability to control your emotional actions and reactions.
 - ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 5.) Rate how much difficulty that you have had during the past 7 days with cognitive flexibility (i.e., the ability to adapt to new situations by changing your thinking or behavior).
 - ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much

- 6.) Rate how much difficulty that you have had during the past 7 days with feelings of restlessness and difficulty quieting your mind.
- ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 7.) Rate how much difficulty that you have had during the past 7 days due to poor organization and planning.
- ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 8.) Rate how much difficulty that you have had during the past 7 days with processing speed (i.e., how quickly you are able to take in information, make sense of it, and then respond).
- ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 9.) Rate how much difficulty that you have had during the past 7 days with impulsivity (i.e., saying or doing things without first thinking them through).
- ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 10.) Rate how much difficulty that you have had during the past 7 days due to procrastination or trouble starting new tasks.
- ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much
- 11.) Rate how much difficulty that you have had during the past 7 days with understanding the perspectives or actions of others.
- ☐ Not at all
 - ☐ A little bit
 - ☐ Somewhat
 - ☐ Quite a bit
 - ☐ Very much

12.) Rate how much difficulty that you have had during the past 7 days with fine motor coordination (i.e., performing tasks such as tying your shoes or typing on keyboard that require finger speed and control).

- ☐ Not at all
- ☐ A little bit
- ☐ Somewhat
- ☐ Quite a bit
- ☐ Very much