NATIONAL FRAGILE X FOUNDATION

Consensus of the Fragile X Clinical & Research Consortium
May 2021

Assessment of Fragile X Syndrome for Clinicians

Detailed Recommendations for Clinicians, Providers and Other Professionals

Authors: David Hessl, Lisa Cordeiro, Adrienne Villagomez, Elizabeth Coan, Leonard Abbeduto, Anne Hoffman, Angela John Thurman, and Lauren Schmitt

Note: There is another version of this document designed for non-professionals — families, caretakers — that you may be interested in: An Introduction to Assessing Children with Fragile X Syndrome.

Assessment of individuals with fragile X syndrome (FXS) is challenging in numerous ways, ranging from choice and limitations of instruments, behavioral and emotional factors impacting the testing process, to scoring and interpretation. Fortunately, decades of research and clinical experience pertaining to assessment, including recent detailed studies of the performance of several measures as outcome measures for clinical trials, have provided very useful guidance.

This document first covers several important general considerations for the clinical assessment of people with FXS, including principles of measure selection, developmental considerations, preparation and approach to testing, and accommodations to the testing process that may yield more accurate results. Next, we cover the primary domains of

clinical assessment — cognition, language, adaptive behavior, academics, maladaptive behavior, motor, social functioning, and emotion — providing guidance on measure selection, application to the FXS phenotype, as well as limitations. We provide some examples and recommendations of tests in each domain of assessment. *Note that we only discuss published tests available to practitioners and have omitted experimental or laboratory-based tests from this summary.*

Clinical Assessment General Considerations

FXS Phenotype

A phenotype is a set of observable characteristic or traits of an individual resulting from the influences of genetics and the environment. All assessors should have an intimate understanding and awareness of the behavioral, social-emotional and cognitive phenotypes of FXS. This ensures that they will choose appropriate assessment tools, administer the assessment in ways that are sensitive to the common challenges of this population, recognize critical strengths and weaknesses when they are present, and interpret and report results in a manner that is both meaningful and accurate.

The FXS behavioral phenotype is characterized by problems with hyperactivity and impulsivity, inattentive behaviors, repetitive or stereotyped behavior and speech (which may be characterized as features of autism), social approach-avoidance (including prominent gaze avoidance), and social communication deficits (also may be characterized as autism), self-injury and irritable/aggressive behavior.

The cognitive phenotype includes relative weaknesses in sequential processing of information, various forms of attention (both auditory and visual), working memory, response inhibition, cognitive flexibility, and arithmetic reasoning. Each of these areas of cognitive weakness are usually in excess of the person's overall developmental level.

Indeed, one of the most important aspects of FXS that must be considered in the assessment process is developmental level.

Given that most males and a high proportion of females function in the intellectually disabled range, the person's developmental or mental age will be substantially below their chronological age. For example, an 18-year-old male with FXS with an IQ (intelligence quotient) in the low 40s may have a mental age of 3 years — that is, his overall cognitive functioning is similar to that of a typically developing 3-year-old child. Knowing a "developmental age estimate" prior to assessment (often based upon an initial interview with a caregiver and behavioral observations) will greatly aid the assessor in choice of instruments and starting points for objective tests.

The social-emotional phenotype includes prominent symptoms of anxiety (notably social anxiety and specific phobias), irritability or emotional lability, obsessive or perseverative thoughts, and poor coping mechanisms. These aspects are equally important, as effort must be made to ensure the assessor is allowing appropriate time for the individual to become comfortable in the testing environment and to develop appropriate rapport.

In summary, a thorough assessment of a person with FXS should cover the various domains described above. Language is delayed relative to age expectations in individuals with fragile X syndrome (particularly males), with some areas of language (e.g., pragmatics, or the social use of language, and expressive syntax) delayed even relative to nonverbal cognitive ability. At the same time, however, there is considerable variability among individuals with FXS in the degree and profile of language impairments, making a thorough assessment critical to planning intervention and to understanding the impact of language impairments on other aspects of an individual's functioning.

Measure Selection

There are several factors to consider when choosing a test or assessment instrument for a person with FXS.

First, a general rule of thumb is to select tools (i.e., tests, questionnaires, interviews, etc.) that have demonstrated the usual psychometric standards of reliability and validity as would be the case when establishing standards for assessments of any person. In addition, it is advisable to use tools that have established these properties in samples of individuals with FXS specifically. This provides added assurance that the tool is more likely to be feasible and interpretable. If these supportive FXS-specific data are not available, the next best option is to confirm that the tool is valid for persons with comparable disabilities who do not have FXS (e.g., general intellectual disability). As there is a range of abilities in FXS (i.e., among females or males with mosaicism), tools that are appropriate for those with FXS and ID may not be appropriate for all individuals with FXS.

Second, most standardized tests will show floor or ceiling effects when applied to FXS. All tests have maximum and minimum standard scores in the published range of possible scores. For example, the lowest possible score on many tests is about 3.5–4.0 standard deviations below average (e.g., IQ = 40). However, because the actual ability of many people with FXS falls below this level, the floored score may overestimate their actual ability. Also, a person's true ability or functioning in the area of interest may actually improve or worsen without being detected by usual standard scores, which can remain unchanged at floor level over repeated administrations. This should be appreciated in any person earning subtest scores at or near the floor of the standard score distribution, with interpretation of results taken with caution and explained in a summary.

Methods have been developed to correct this problem, one of which is currently available for the Stanford Binet Intelligence Scales, Fifth Edition (SB-5) [3]. This scoring correction is currently available for the SB-5 on the scoring program provided by the test publisher and will be automatically generated any time a person obtains one or more subtest floored scores.

Third, items on a given test or questionnaire may be inappropriate or invalid for people with FXS. For example, if a 10-year-old child is cognitively delayed and nonverbal, questions pertaining to verbal complaints (e.g., child says what they are worried about on an anxiety measure) or about ability to complete homework in school are not appropriate. Some cognitive tests may have too few items that the person can complete correctly to

accurately reflect their relative strengths and weaknesses. Conversely, tests or questionnaires that may be more developmentally appropriate, but given out of age range (e.g., giving CELF Preschool to a 16-year-old) does not provide valid scoring metrics except for raw scores and/or age equivalents.

Fourth, it is important to avoid choosing tests that are known to play to particular strengths or weaknesses that would skew the results in one direction or the other.

For example, in one study, when two different IQ tests, the SB-5 and Wechsler Scales, were administered to the same adults with intellectual disability (ID) (Down syndrome and other ID), the Wechsler IQ results were uniformly higher than the SB-5 in every case, with a mean difference of 16.7 IQ points (greater than 1 standard deviation from the mean) [4]. Thus, particular tests may unfairly over- or underestimate actual ability levels compared to the normal range. Likewise, assessments may require additional skills or processes than the primary domain is meant to address; thus, performance may be less specific and inappropriately lower due to a secondary problem. For example, cognitive tasks that require use of manipulatives may be especially challenging due to poor motor planning, not issues with problem solving. Similarly, “nonverbal” items that in fact rely on verbal instructions or requiring verbal responses may be unfairly impacted by language deficits.

Fifth, consider that most behavioral and emotional measures were developed using typically developing populations. As such, a measure of anxiety or hyperactivity is likely to yield scores that compare the individual with FXS to their age-peers, not to other people of the same developmental level. Although some of these measures (that were developed using typically developing populations) provide scores from a “clinical group,” because the questions describe behaviors of typically developing individuals the measure may still be inappropriate for use in FXS and may not depict how behavior and symptoms manifest within the FXS phenotype.

Last, assessments developed for older adolescents and adults, especially, may have materials and items less suited for individuals with FXS with lower mental/developmental ages, thus making it harder for this population to engage and participate. Thus, a measure

that can both reliably and validly assess an ability while still being engaging and holding their attention is an important consideration.

Assessment from Multiple Perspectives, Sources, and Settings

As with any assessment, collecting data from multiple sources, perspectives, and situations will provide a more reliable and accurate measurement. This may be especially critical for people with FXS who can show highly variable behaviors and abilities depending on mood states, social pressures, features of the environment (i.e., loud, crowded, or novel), timing of medications, or how comfortable and familiar they are with the assessor. It may be important to consider whether testing over one or multiple testing sessions is appropriate. Also, caregivers and other observers making judgments of behavior can be quite biased depending on their own experiences.

In the behavioral and emotional assessment domain, collecting observations and/or ratings from more than one caregiver and a rater outside the home, such as a teacher, is encouraged. In the cognitive domain, one should try to obtain records of prior testing, and include assessments of diverse areas of function including executive function, verbal comprehension, processing speed, memory, and arithmetic reasoning. Assessment in the social domain, including assessment of autism spectrum disorder (ASD) (discussed more thoroughly below), should include both direct assessment by the assessor as well as ratings and observations by multiple caregivers. Consideration of comorbid diagnoses will be relevant throughout, especially during cognitive and other performance-based measures.

In sum, the administration and interpretation of one assessment tool should never pass for a thorough evaluation. Instead, the combination of thorough record review, family interview and school/vocational placement report, performance on appropriate standardized measures, behavioral observation, and educated and thoughtful clinical judgment is necessary in comprehensive assessment.

Approaching Clinical Assessment: Test Prep and Accommodations

Many preparations, strategies, and accommodations can be used to maximize the chances for a successful and valid clinical assessment of a person with FXS. These considerations are described in more detail below.

Testing Preparations

Prior to the evaluation, one should obtain information from the caregiver about expected challenges and past experiences with testing, and to collect information about items or activities that may be especially motivating to use as rewards during the testing process. Some assessors utilize an extended checklist that can be sent ahead of time.

To minimize anxiety and increase rapport, one can send a friendly photo or a link to photos of the assessor and testing environment before the testing day. People with FXS are often remarkable in their ability to recall names and faces and this can be used to ease anxiety, as they will often recognize the assessor immediately upon introduction.

Prior to testing day, it will be important to communicate with the caregiver about what to expect of the testing environment and schedule. The examinee should be as rested as possible, adequately satiated (and prepared with snacks), equipped with any necessary vision correction (glasses, contacts) and/or communication devices, physically healthy, and following their typical medication protocol, to name a few considerations. The amount of time for testing may be either much shorter than usual for a typically developing person (if the person with FXS is unable to progress very far on test items), or it may be much longer than usual (if the person is agitated, needs many breaks, etc.) so it is best to schedule more time than typically expected if possible, and to be flexible regarding breaks and pauses in administration.

Prior to testing, it is important to establish whether the caregiver will be present in the testing room. Some younger children or especially anxious individuals may need this to even enter the testing room, and thus will require them to be present throughout. Others

will do much better without the parent present. Finally, a third group seems to do well with caregiver initially present and then excused.

Flexibility from the assessor is crucial, and the assessor may have to use different strategies throughout the process. For example, inclusion of the caregiver and multiple breaks may be successful at the beginning of testing, but the caregiver may later need to leave, and the assessor may need to reduce the numbers of breaks in order to maintain momentum so as not to lose attention and motivation.

Consideration of the testing environment itself is also imperative, as sensory sensitivities and hyperarousal can impact performance. Reducing the amount of light, closing blinds to eliminate visual distraction, positioning the assessor between the patient and the door, and decreasing auditory interruptions (announcements over a speaker, loud fans or clocks, etc.) will help to encourage the examinee's best effort related to focus and sustained attention.

Very young children with FXS are often quite hyperactive and may be better able to respond to test items if they are not confined to a chair; others will benefit from the added structure and confinement of a seated position. These young children often need many breaks, and all individuals with FXS may do best with testing divided across multiple days to minimize fatigue and frustration.

Testing Accommodations

A visual schedule can be quite helpful [5, 6], whereby the examinee can see tasks visually depicted in a sequence (using either photos or symbols) and allowing them to cross off completed tasks.

Although a warm-up period can be helpful, many assessors find it better to do this in the waiting area. Testing materials for initial, very easy items should be organized and already displayed for the examinee so that testing can commence immediately to generate successes right from the beginning. A detailed explanation of the testing process is often unhelpful and may increase anxiety.

Finally, many people with FXS respond well to humor or to comments about favorite interests, which can help reduce anxiety and improve rapport. Similarly, inserting breaks into testing, where access to favorite interests or preferred toys can be granted, may help support motivation. However, special consideration should be given to whether the examinee will be able to successfully transition back to structured activities if they are allowed access to one of their most preferred objects or interests.

When utilizing accommodations or "breaks from standardization" during testing, the key concept to keep in mind is to provide adjustments to the testing process if doing so will allow the person with FXS to demonstrate their ability and knowledge (i.e., reduce barriers) without altering the construct being measured. For example, it may be necessary to provide more practice items or instructions to ensure understanding of a task. Or, the assessor may need to repeat an item if the person is distracted. However, one would not want to alter standard administration of an attention test by suggesting that the assessor direct the examinee's attention to stimuli. Instead, appropriate accommodations may include use of a token economy system (i.e., small rewards throughout testing leading to a bigger prize upon completion), using simplified instructions, allowing a fidget toy or other object, and offering encouraging praise for appropriate effort.

When using a token economy or other reward-based system, it is often important to find out from the caregiver beforehand what has worked with the individual in the past (e.g., sticker vs. goldfish snack) and, as mentioned previously, to consider whether certain rewards may be too distracting and disruptive (e.g., tablet). When possible, it may be extremely helpful for the individual to identify rewards from a "menu" to ensure cooperation and motivation. A useful reference with detailed accommodation possibilities and accepted guidelines for assessments of persons with intellectual disability, including FXS, can be found in Thompson et al. [7].

Cognition & Intelligence

IQ Testing

Cognitive assessments in persons with intellectual disability, including FXS, almost always include IQ testing. Results from IQ tests are used for curriculum planning and placement decisions, service eligibility, and providing input to caregivers regarding developmental level, degree of impairment, or transition planning, and guiding expectations for learning, socialization, and communication.

Many IQ tests are available, including the Wechsler Intelligence Scales, the SB-5, the Leiter International Performance Scale (Leiter-3), the Differential Ability Scales (DAS-2), and several others. Each test has different strengths and weaknesses. Each test generates standard IQ, index, or composite scores, which are almost always represented along a normal distribution where 100 is the average score in the general population.

It is important to recognize that tests use many different types of tasks to generate these overall IQ scores and cover different examinee age ranges. Also, some tests have been researched more thoroughly in individuals with FXS than others, including adjustments or accommodations in the administration or scoring that greatly improves their accuracy. As such, here we provide a brief overview of several options and recommendations for IQ test selection.

The Wechsler scales are widely used in research, clinical practice, and educational settings. Advantages include their widespread use, interpretability, and well-validated factors (e.g., processing speed, visual spatial reasoning). Disadvantages include the multiple versions required for different examinee ages (i.e., preschool, childhood, and adult versions), a bias toward overestimation of IQ in people with IDD (compared to the Stanford Binet) [4], and prominent floor effects in people with FXS or others with moderate to severe disability.

The multiple versions depending on age are a problem for lower-functioning persons because in order to derive scores, a version appropriate for chronological age must be used — therefore, a person with FXS with a mental age well below the lower limit of the test version is essentially untestable on this measure.

The SB-5 has been utilized extensively in people with FXS. It includes a very broad age range (2.5–89 years) and thereby includes items that are developmentally appropriate for both lower-functioning persons with FXS and also higher functioning (i.e., females or mosaic males). Although floor effects occur frequently in the standard use of the SB-5 (the test's lower IQ limit is 40), Sansone and colleagues [3], following from the work of Hessl et al. [8] developed a revised and validated scoring method that extends the range of subdomain and IQ scores well below the usual floor, allowing for detection of strengths and weaknesses in lower-functioning persons with IDD, including FXS.

These scores are well correlated with another cognitive battery (NIH Toolbox Cognitive Battery) [6], with no apparent over- or underestimation of ability. This revised method was adapted by the publisher of the test (Pro-Ed Inc.) and is generated by the test's scoring software when one or more subtests fall at the usual test floor. As a result of these scoring adaptations and its broad range, the SB-5 has been utilized in several ongoing FXS studies, including the CDC-funded Fragile X Online Registry With Accessible Research Database (FORWARD) project, which aims to capture the natural trajectory of cognitive development in individuals with FXS. The SB-5 also provides age equivalent scores (helpful for test interpretation to caregivers) and growth scores (potentially useful for tracking change over time).

The Leiter-3 is a nonverbal test, both in its administration (the assessor uses gestures and very limited language) and in examinee response (the person points or uses manipulatives such as blocks rather than speaking to answer). It provides growth scores, which may be helpful to detect cognitive change over time, and mental age equivalence scores. This test is relatively culture-free and useful in nonverbal or minimally verbal individuals with FXS. Limitations of the Leiter include floor and ceiling effects (lower limit = 30, scaled score upper limit = 12) and lack of information about verbal skills.

The *Differential Ability Scales, Second Edition* (DAS-2) is normed in ages 2:5–17:11. The subtests are organized into two versions based on age: early years and school age. The DAS-2 has not been used as often in FXS research. It has been shown to demonstrate good clinical utility, especially for individuals who may struggle with longer administrations as the core battery requires six subtests (less than the SB-5 or Wechsler scales), or who have lower expressive and/or receptive language skills.

Like the SB-5, the DAS-2 does require baseline skills of at least 2 1/2 years old, which may not be low enough for some younger individuals with FXS and significant developmental delays. For those with skills at or above the 2:6 age equivalent, the overlapping versions (lower and upper early years and school age) allow the assessment of individuals outside of their prescribed age range (i.e., dropping down to lower, out-of-level items for school-aged children when needed). Finally, the DAS-2 early years form is one of the few measures available in Spanish.

Other IQ tests, including *Kaufman Brief Intelligence Test* (KBIT-2), and *Woodcock-Johnson Test of Cognitive Abilities*, have been used less often in FXS. These tests generally have similar limitations to those outlined above, however there is generally less research documenting their psychometric properties in FXS. This makes it challenging to provide appropriate commentary on their suitability in this population, and thus we recommend assessors to exercise some caution with their use and interpretability.

Additional Areas of Cognitive Assessment of Importance for FXS

Executive Function

Assessment of cognitive function beyond IQ typically includes various neuropsychological domains such as executive function (attention, inhibitory control, cognitive flexibility, working memory), processing speed, other forms of memory, and visual perception. Based on the literature of prior studies examining cognitive function in FXS, it is clear that various aspects of executive function are areas of significant weakness (greater than

expected based on overall mental age), as described above. Therefore, for assessment and monitoring of progress or response to intervention, additional measures of executive function are recommended. Schmitt et al. [9] provide a useful academic summary that supports guidance of executive function assessment for FXS in applied settings, including numerous measures available for clinical practice or educational settings. Although standard scores on many of these tests will be at the floor in many people with FXS, research has documented that raw scores are sensitive to deficits and might be used to track clinical changes or progress.

Working Memory

Sentence, list, and digit/letter memory tasks, such as *Wechsler Digit Forward and Backward*, *SB-5 Sentence Memory*, *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS) *List Learning*, or *Woodcock-Johnson Test of Cognitive Abilities Memory for Word*s, can be utilized to evaluate verbal working memory. Consideration of receptive and expressive language skills is critical when administering such measures. Additionally, individuals with known echolalia may also be at an unfair advantage for certain, especially earlier, items.

Visual working memory can be assessed using tests such as *Leiter-R Spatial Memory* or *SB-5 Block Span*. These tests showed strong reliability and were sensitive to change in a cognitive training trial, however the more recent version of the *Leiter* (Leiter-3) no longer includes this subtest and has not been studied in FXS to date.

Inhibitory Control

Measures of prepotent response inhibition such as “Go/No-Go” tasks, have been sensitive to FXS deficits, e.g., Feasibility, reliability, and clinical validity of the *Test of Attentional Performance for Children (KiTAP) in Fragile X syndrome* (FXS)[10]), and are feasible in a fairly wide range of ability levels, however most clinically available instruments are too difficult or too long in duration for many individuals (e.g., *Conners Continuous Performance* tests). If an individual can perform such testing, however, outcomes can be a useful indicator of

changes in executive function [10]. Measures of interference control (or distractor interference), such as Flanker or Stroop tasks, also have been sensitive and feasible in FXS deficits. However, certain versions of Stroop should be cautioned as the majority require verbal responses as well as reading abilities. One of the cognitive measures described above (i.e., DAS-2) includes a diagnostic subtest of inhibition that may be feasible in some individuals with FXS as it allows for additional teaching trials and lower age-range extensions.

Cognitive Flexibility

Individuals with FXS tend to perseverate, both in their language and their thought patterns. This is often reflected in their problem-solving efforts, where they can become "stuck" on a particular response type and be unable to "shift gears" and think in a new way. Tasks requiring a dimensional change, whereby the individual matches two objects or symbols according to a rule and then must switch to matching by another dimension, clearly highlight cognitive flexibility weaknesses in FXS, however most tests are research-based (e.g., *Validation of the NIH Toolbox Cognitive Battery in intellectual disability*) [6]. The dimensional card sorting task from NIH Toolbox Cognitive Battery recently demonstrated feasibility and test-retest reliability in the majority of individuals with FXS (Hessl et al., 2016). Still, this and similar available tests in applied settings are too difficult for many with FXS as they often require additional cognitive processes like working memory (another cognitive weakness in FXS). If the assessor does not think it is feasible to assess cognitive flexibility through a standardized measure, often the assessor can observe cognitive flexibility deficits and perseverative responding during various cognitive tests and can relate these observations and their implications in test interpretations and summaries.

Attention

The construct of attention in human cognition includes components of selective attention (a focus on one thing at a time while filtering out distractions), divided attention (focus on

or process more than one thing at a time) and sustained attention (the ability to focus on a task over an extended period of time).

Although people with FXS tend to perform more poorly than their typically developing peers on all areas of attention, compared to mental age-matched peers, they have most difficulty with sustained attention (especially in the auditory domain) and divided attention.

Sustained attention can be evaluated using a continuous performance test, however in most cases an assessor would need to choose a version that is suited to the person's mental, not chronological, age. Flanker tasks are feasible for individuals with FXS and are especially sensitive to their weaknesses in attention and inhibitory control [*6*]. However, research has shown that even CPTs (cognitive performance tasks) designed for very young children can be too complex or long in duration for lower functioning persons with FXS.

Few, if any, clinical measures of divided attention are used in FXS, and those used in research, though sensitive to detect deficits in this population (e.g., *Test of Attentional Performance for Children* (KiTAP) *Divided Attention*) are probably too hard to be suitable for applied clinical use. Though selective attention appears to be a relative strength for people with FXS, it should be noted that multiple studies did find tendency for this population to perseverate on specific responses (responding multiple times for same item, using previous correct answer on next item). Thus, assessors should be diligent in identifying and noting such behavior, and it may be important to restate instructions when observed.

Planning

Considered a sub-domain of executive function, and sometimes considered its own cognitive domain requiring multiple facets of executive function, planning involves the ability to direct behavior based on current and future goals and is often an assay for general problem-solving abilities. Tower tasks like *NEPSY Tower* and *Tower of Hanoi* are most commonly used within clinical and research settings in typically developing individuals. Few studies have employed Tower tasks in FXS, and those readily indicate

prominent floor effects. Given the complexity of these tasks and the multiple component cognitive processes required, they are seldom suitable for the majority of people with FXS and may only be useful when other prerequisite skills are indicated (e.g., low average to average IQ, intact processing speed).

Assessment of Executive Function Using Caregiver Rating Scales

Executive function–related behaviors can be assessed using observer rating scales. For example, the *Behavior Rating Inventory of Executive Functions* (BRIEF) preschool and school-age versions (Gioia, Espy, & Isquith, 2003; Isquith, Guy, & Kenworthy, 2000) are an assessment system designed to gather information about how a person's executive function skills impact functioning at home, in school, and in the community. The two versions (preschool and school age) are designed to allow for developmentally sensitive items across relevant areas of attention and self-regulation. The BRIEF (and other similar measures such as *Conner's Parent Rating Scales and Swanson, Nolan, and Pelham Rating Scale* (SNAP-IV)) has been used in many studies of executive function in special populations, including autism, FXS, and Down syndrome. However, caution is needed in use of these types of measures because items that pertain to typically developing children may not apply to those with FXS who have substantial developmental delays. Also, some studies have failed to demonstrate correlations between caregiver report of executive function–related behavior and executive function measured on tests. Rating scales can certainly be helpful, so long as the assessor is aware of these and other potential limitations.

Cognitive Measures

Name/ Type	Time	Ages (Normed)	Translated to Other Languages	FXS- or ID-Specific Development or Scoring	Feasibility in FX	Floor Effect

Stanford Binet-5* Direct Assessment	20–45 min.	2.5–89 yrs.	No	FXS	Yes	Improved with z-deviation scoring; minimum mental age of 2:6 needed
DAS-2 Direct Assessment	20–45 min	2:6–17:11 yrs.	Yes	–	Yes	Mitigated by extension to other ages & additional teaching trials; minimum mental age of 2:6 needed
Wechsler Scales Direct Assessment	15–45 min	2:6–90:11 yrs.	Yes	–	Varies	Prominent & tasks are inappropriate for many with FXS
Leiter-3 Direct Assessment	15–45 min.	3–75+ yrs.	n/a	–	Yes	Present & as a nonverbal test does not provide info about verbal skills

**Recommended*

Language

Language abilities are critical to social functioning, as well as to learning about the world in both formal situations, such as school, and informal situations, such as interactions with peer models. Impairments in language can create a cascade in which many aspects of functioning are increasingly negatively affected. Assessment of language is thus important for guiding education, therapy, and even vocational training throughout the life course. There is an array of measurement tools to assess language in individuals with FXS, each with advantages and disadvantages.

Standardized Tests

Standardized tests have the advantages of clearly specified procedures to ensure consistency in administration and allowing comparison of the performance of the individual with FXS to typically developing individuals of the same age to gauge the extent of delay in language for the individual with FXS. A disadvantage, however, is that standardized assessments are often not sensitive enough to measure subtle gains in language skills across time, particularly during adolescence and adulthood, or in response to treatment [1, 2].

Another disadvantage of such tests is that they measure language in situations very different from everyday social interactions, which means that performance on such a test may not always be a good indicator of how an individual with FXS actually uses and understands language in situations that are personally meaningful, such as school or on the job.

We describe below some useful and commonly used standardized tests. Note that similar to the choice of measures for other areas, the examiner should select a test based on the skills currently being displayed by the individual rather than strictly by chronological age.

Preschool Language Scales, *Fifth Edition* (PLS-5) [11] is a comprehensive developmental language assessment that is normed for use with children from birth to 7 years, 11 months of age. This test allows the use of caregiver report for earlier items, with later items requiring the child to actively complete both receptive and expressive language tasks. This assessment does not allow for separate analysis of specific language areas within receptive/expressive (e.g., vocabulary vs. syntax), but does provide general guidelines for overall global language ability and is most appropriate for children who are not yet using more complex language. PLS-5 has been used to describe language profiles and to track longitudinal language growth in FXS [12, 13].

The Clinical Evaluation of Language Fundamentals – Preschool, *Second Edition* (CELF-P2) [14] and *Clinical Evaluation of Language Fundamentals, Fifth Edition (CELF-5)* [15] are used extensively in research, clinical practice, and educational settings. These omnibus

assessments examine different areas of both receptive and expressive language (e.g., expressive vocabulary, comprehension of complex syntax). There is a significant floor effect for many individuals with FXS [16] and similar to the Wechsler scales, the two versions based on chronological age make valid assessment with these tools even more challenging for individuals with lower language ability.

The *CELF-Preschool-2* is meant for chronological ages of 3 to 6 years, but children who are still at the prelinguistic or single word stage are unlikely to receive valid scores. The CELF-5 is normed for ages 5 to 21 years and requires higher language skills. Both instruments frequently require the use of age equivalent scores or growth scale values (available only for the CELF-5) in order to track progress or make more accurate descriptions of language ability.

The Comprehensive Assessment of Spoken Language, *Second Edition* (CASL-2) [17] is another omnibus assessment that can be used to assess language in FXS. It has subtests examining semantics, syntax, and pragmatic language knowledge both receptively and expressively. This assessment contains multiple subtests normed for ages 3 to 21 years, increasing the likelihood of achieving a valid score although it is still limited in items at the lower language level. The CASL-2 has been used in research to assess language skills in FXS (e.g., [18, 19]).

Natural Communication Sampling

Natural communication sampling procedures involve collecting and analyzing audio or video recordings of samples of spoken language from an individual with FXS in one or more structured, but naturalistic, interactions with an examiner or adult care provider. These interactions can include play with a standard set of toys, conversation on a standard set of topics, narration of a story depicted in a picture book, and even pretending to be a talk show interviewer, with the choice of interaction determined by the age, developmental level, and interests of the individual being assessed [20].

Although natural communication sampling can be conducted in many different interactions — it is important that each interaction is structured and scripted so that it is

reasonably consistent every time the individual is assessed and is similar to that used with any normative comparison group [21]. When this consistency is ensured, natural communication samples can provide excellent measures of an individual's communication skills, including not only spoken language, but also the use of gestures and vocalization in prelinguistic or minimally verbal individuals [22].

The advantages of natural communication sampling relative to standardized tests include a wide range of applicability in terms of the age and developmental levels of the individuals to be assessed, and the closer correspondence of the assessment context to everyday social interaction. In addition, a sample can be analyzed to learn many things about the individual's linguistic and nonlinguistic communication skills, including the use of presymbolic and symbolic communication skills, breadth of vocabulary, difficulties with articulation, the ability to combine words in appropriate ways, the inclination to talk, and skills in using language to accomplish social goals.

Problematic language behaviors can also be assessed, such as perseveration on a topic or echolalia (repetition of others). The disadvantages of expressive language procedures are the time-consuming nature of the analysis, which often involves careful coding of communication acts and/or transcription of the talk prior to analysis and, of course, the fact it does not provide any insight into language comprehension, just expression. Normative comparisons are also not available for all types of interactions. In addition, natural communication sampling procedures are only now being evaluated for the same types of psychometric properties that have been established for standardized tests, such as test-retest reliability and construct validity; however, the studies to date have shown excellent psychometric properties for individuals with FXS specifically [1, 23, 24].

Other Measures

Parent/caregiver report is another important tool for the assessment of language and makes it possible to characterize language skills across settings. For earlier stages of language development, the *MacArthur Bates Communicative Development Inventories* (MB-CDIs) [25] allow tracking of current and emerging communication skills, although

obtaining standard scores is not possible for children over the age of 37 months. For children between the ages of 4 and 16 years who are using phrase speech (i.e., at least three word utterances), the *Children's Communication Checklist*, *Version 2* (CCC-2) (Bishop, 2003) [26] uses parent report to compare different areas of language, as well as assess social communication areas linked to ASD.

Adaptive Behavior

Adaptive behavior is a term used to refer to an individual's daily living skills. The terms "daily living skills," "adaptive skills," "functional skills," and "adaptive functioning," are often used interchangeably to refer to adaptive behavior. Adaptive behavior encompasses multiple areas of functioning separated into three domains: conceptual skills, social skills, and practical skills [27]. Among other skills within each of these domains, communication and socialization, personal self-care skills, and domestic and community living skills are emphasized. Fine and gross motor skills are also assessed, more often at younger ages, but may extend into later ages among those with ID.

Adaptive behavior is age-related, modifiable, and considered within the social context [28]. As a result, the daily living skills that are expected by an individual change with age in order to meet environmental demands [29]. Importantly, adaptive behavior is defined by an individual's usual performance of a skill, rather than the ability to complete that behavior independently. In other words, adaptive behavior is a measure of what an individual consistently does do, and not solely on what the individual can do.

Measuring an individual's adaptive behavior is a critical component in the assessment and diagnosis of developmental disabilities, such as intellectual disability and autism spectrum disorder [27, 30]. Over the last several years, adaptive behavior is increasingly emphasized as an important criterion for defining intellectual disability [27]. Furthermore, severity of intellectual disability is now characterized by deficits in adaptive behavior and not IQ in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) [30]. In addition to aiding in diagnosis, results from adaptive behavior measures are also used to determine special education eligibility, to plan and implement intervention and rehabilitation

services, and to track and monitor progress. Given the reliance on measures of adaptive behavior, reliable and valid standardized assessment is increasingly important [31].

Developmental Trajectory

Research on the developmental trajectory of adaptive behavior in FXS is mixed. Differences in findings are often attributed to factors such as gender, age, and number of times that skills were measured [29]. Additionally, the types of scores used, such as age-equivalents and standard scores, also contribute to mixed findings. A number of research studies suggest general declines in adaptive behavior over time [32-35]. Additionally, steady increases of adaptive behavior for individuals with FXS are often seen until 10 to 12 years of age before skills plateau or decline [32, 36-38]. Both males and females with FXS show a skill acquisition rate that slows over time [35]. In a longitudinal study with individuals followed through 18 years of age, males with FXS shows significant declines in their standardized scores across all adaptive behavior domains and females with FXS showed significant declines only in communication [35]. Given declines in raw scores observed in over half (56%) of children with FXS at or before 10 years of age, middle childhood is considered pivotal for adaptive behavior development [29].

Measures

Adaptive behavior can be measured in several ways, including through use of questionnaires or rating scales, standardized interviews, and direct assessment. Most commonly questionnaires and interviews are completed by caregivers, such as parents and other family members. It is important to note that these forms may also be completed by a variety of other caregivers, including job coaches, teachers, and residential counselors, provided the caregiver is familiar with and knowledgeable of the individual's daily living skills that are being assessed. In some cases, individuals may report on their own adaptive behavior through self-report measures. However, given the nature of adaptive behavior — the breadth of skills, and the emphasis on consistent performance over ability — caregiver report through questionnaires and interviews is considered a more suitable approach than self-report measures and direct assessments [28].

While many measures of adaptive behavior exist, only four standardized instruments are considered to have sufficient psychometric properties to be used clinically to determine intellectual disability [31]. The *Vineland Scales of Adaptive Behavior* (VABS), *Adaptive Behavior Assessment System* (ABAS), and *Scales of Independent Behavior – Revised* (SIB-R) are among these measures as well as the *Adaptive Behavior Scale – School, Second Edition* (ABS-S: 2).

The most popular measures include the *Vineland Adaptive Behavior Scales, Third Edition* (VABS-3) [28], and the *Adaptive Behavior Assessment System, Third Edition* (ABAS-3) (Harrison & Oakland, 2015). The *Vineland* is consistently utilized in large-scale, national research efforts, and tracks reasonably well with IQ [6]. This popularity of the Vineland across multi-site research studies and clinical trials suggests general consensus around use of the *Vineland* interview form in the field of FXS. The *Vineland-3* includes four primary domains: communication, socialization, daily living skills, and motor skills, with subscales within each.

All domains except motor skills are included in an overall score, referred to as the *Adaptive Behavior Composite* (ABC). The motor skills domain is optional and normed for individuals 9 years and younger but may be administered to older individuals to obtain age equivalents, especially when motor concerns remain relevant for that individual.

In comparison, other standardized measures are used less frequently, given certain limitations. For instance, the *Scales of Independent Behavior – Revised* (SIB-R), (Bruininks, Woodcock, Weatherman, & Hill, 1996), which is a set of questionnaires that are similar to the VABS and ABAS series, is limited by outdated item content and norms (the sample of individuals that were included in the development of the measure). The *Pediatric Evaluation of Disability Inventory* (PEDI) (Haley et al., 1992), is also a measure of adaptive behavior that is used less often given limitations in age range, efficiency, and item content (Dumas et al., 2010). The revised version of the *PEDI* is now a computer adaptive test called the *PEDI-CAT* for ages birth to 20 years old, with a recently updated ASD version. Research of this measure in FXS is ongoing.

It is important to note that during an evaluation or assessment, the measure chosen by the clinician is often determined on an individual basis and based on a number of logistical factors. Within this context, there is stronger empirical evidence for some measures than others. Specifically, the *Vineland-3 Comprehensive Interview Form* is described as "the most widely used" and well researched measure of adaptive behavior.

Assessment Considerations

Assessment considerations for adaptive behavior in FXS primarily focus around determining whether an interview or questionnaire format is more appropriate for a family to complete.

There are several advantages to an interview format instead of a parent-questionnaire format, including opportunities for a clinician to gain more in-depth information. An interview format to assess adaptive behavior is also generally considered the "gold standard" as it is designed to correct for inaccuracies or biases that may occur in questionnaires.

There are several advantages to an interview format instead of a parent-questionnaire format, including opportunities for a clinician to gain more in-depth information. An interview format to assess adaptive behavior is also generally considered the "gold standard" as it is designed to correct for inaccuracies or biases that may occur in questionnaires.

In a comprehensive review the National Research Council concluded that "structured and semi-structured interviews… appear to be the best available safeguard against threats to the reliability and the validity of adaptive behavior assessment." A common mistake among interviewers is the failure to adhere to standardized item administration and scoring, such as failing to appreciate the critical concepts of particular behaviors or skills completed without help or reminders. Also, scoring according to what the caregiver reports that the person with FXS can do rather than what they actually do is a common error.

Assessor drift often occurs with this instrument — assessors may administer the Vineland correctly initially, but as years pass they may drift away from accurate administration and scoring. As such, periodic checks on assessor drift are recommended.

Alternatively, feasibility is a primary advantage to using a questionnaire format. When utilizing a questionnaire in lieu of an interview format, it is important for providers to review the response style and follow up with caregivers regarding any potential inconsistencies or misunderstandings of specific items or domains. Another difficulty with use of the questionnaire form of the *Vineland-3*, specifically, is establishing appropriate start and stop points for caregivers to reduce burden while simultaneously gathering necessary information. Despite parallel content between parent-report and survey-interview versions of the *Vineland 3*, most correlations across all domains are moderate between these two versions.

Scoring and Interpretation

Adaptive behavior measures may be useful tools for progress monitoring daily living skills for individuals with FXS over time. Given what research shows about patterns of adaptive behavior in FXS, it can be beneficial for providers to include growth scale values (GSVs) data in order to track progress, rather than only reporting standard scores and age equivalents. The inclusion of GSV data can allow for interpretation of whether individuals with FXS are exhibiting true declines in daily living skills versus developing skills at a slower rate. Moreover, when adaptive behavior scales are used to monitor progress over time, GSV scores, rather than age-equivalent scores and standard scores, are recommended because individuals with IDD do not show an increase in skills at the same rate as typically developing peers and raw scores can show changes in actual skills over time [39]. Because standard scores are relative to typically developing peers, these scores are more likely to show decline due to not keeping up with same-aged peers, despite possible increase in skills (Kover et al., 2013; Mervis & Klien-Tasman, 2004). Given indications of plateaus and declines in adaptive behavior as early as middle childhood, annual assessment of adaptive behavior is recommended [29]. This is especially important in order to target and potentially remediate areas of true decline.

Limitations

The primary limitation in measuring adaptive behavior is specific to the use of questionnaires and rating scales given that they are more susceptible to inaccurate ratings by caregivers. Specifically, when a provider is unable to administer an interview, a lack of familiarity with the items and limited support from the provider to answer clarifying questions can lead to under- or overreporting on questionnaires. This limitation is a primary reason why an interview format, such as the *Vineland-3 Survey Interview* form, is considered best practice and recommended for assessment in FXS.

Academic Skills

The assessment of academic skills, also referred to as educational testing, is important for educational and vocational planning.

Academic skills pertain specifically to reading, writing, and math skills. Obtaining information about current levels of academic functioning is essential for identifying learning goals, selecting appropriate curriculum materials, informing objectives for instruction, and determining the need for additional intervention and related services (e.g., assistive technology, occupational therapy, and environmental modifications). Often academic testing is used to develop or update an individualized education plan (IEP) in school, which provides accommodations and modifications to a curriculum to meet the unique needs of a student (see General Educational Guidelines for Students with Fragile X Syndrome in the Consensus of the Fragile X Clinical & Research Consortium on Clinical Practice series for additional information).

Academic skills are assessed using standardized measures that are norm-referenced and provide similar types of scores as IQ tests. Qualitative measures, such as curriculum-based assessments, that are based on academic content specifically taught in the classroom may also be used. For children with FXS, it is often important to supplement the results of standardized testing with informal assessment and work samples.

Phenotype

Children with FXS often outperform predictions of academic functioning made based on IQ test scores [40]. However, academic achievement and IQ are highly correlated and academic skills are ultimately influenced by intellectual ability. As such, we would expect academic skills to be more on par with a child's developmental level than their chronological age if they are identified as having an intellectual disability. For example, a second grader may not be reading words at a second-grade level and instead may be showing some school readiness skills, such as letter identification. In addition to IQ, academic functioning is easily influenced by environmental factors (e.g., intervention), as well as changes in behavior, executive function, and language ability. Additionally, the presence of autistic behaviors also impacts acquisition of academic skills in FXS [41].

For boys with FXS, academic skills are shown to increase during early childhood before the rate of academic growth plateaus in adolescence or adulthood [41]. Boys with FXS show relative strengths in broad-based academic skills that are gained through experience [41]. In comparison, they show greater difficulty with core reading, writing, and math skills. Although phonological awareness is an area of relative weakness for boys with FXS [42, 43], one study concluded that despite these difficulties, boys with FXS are able to attain reading skills commensurate with their developmental level [42]. In adolescence and adulthood, many males with FXS show a range of functional academic skills including identifying numbers, familiar signs, words, writing their name, copying, and notions of time and money [44].

For girls with FXS, academic achievement scores generally fall below typically developing peers, though this is less than the discrepancy seen in IQ [40]. Girls with FXS have relative strengths in reading skills and weakness in math skills [45, 46]. Risk for difficulties in math may be apparent as early as kindergarten or first grade [47]. For example, difficulty with counting seen in kindergarten often continues into third grade for girls with FXS [48]. Another study extended this finding to late elementary school, showing that girls with FXS had difficulty with number sense (e.g., counting), and incomplete mastery of math

calculation skills compared to IQ-matched peers [45]. Given strengths in long-term memory, girls with FXS often benefit from repeated exposure to academic material [49].

Measures

There are a number of well-known academic measures, namely the *Wechsler Individual Achievement Test-II (WIAT-III)*, the *Woodcock-Johnson Tests of Achievement-III* (WJ-III Tests of Achievement), and the *Kaufman Test of Educational Achievement*, *Second Edition* (KTEA-II), each of which consist of a battery of subtests to assess various components of reading, writing, and math skills.

In addition to these comprehensive measures, school psychologists and learning specialists also utilize measures that focus on specific skills (e.g., listening comprehension) with tests such as the *Oral and Written Language Scales*, *Second Edition* (OWLS-II). Basic concepts related to school readiness (e.g., colors, letters, numbers) may be assessed by the *Bracken School Readiness Assessment*, *Third Edition*, as well as on the diagnostic subtests of the DAS-2. These school readiness tasks more often utilize receptive responding (i.e., pointing) and may be an important first step in academic assessment of individuals with FXS with ID of all ages.

At this time, while well-known and widely accepted measures of academic skills, such as the WJ-III and WIAT-III, have good reliability and some validity studies on clinical populations, the validity within the FXS population remains unknown [50]. When selecting measures, it is important to capitalize on the evidence that children with FXS learn and perform better when material is presented in a holistic rather than a sequential manner, and with a structured rather than an open-ended format.

Choosing measures that use simple instruction, allow for a simple response style (e.g., pointing), are highly structured, and utilize familiar structure and format will likely provide the most valid estimate of academic skills. For example, reading comprehension can be assessed a number of ways. Children with FXS will likely be more successful in demonstrating their understanding on a task that provides pictures cues, utilizes a cloze procedure (fill in the blank), or allows for recognition through a multiple-choice format (if

skills are beyond an emergent level). To assess mathematics, consider tasks that include visual cues and picture-supported items that require only pointing to a response (e.g., *Math Concepts and Applications on the KTEA-II*). Assessment of writing skills can be supported by using measures that incorporate familiar tasks, such as writing their name, copying words, and labeling pictures, e.g., *Oral and Written Language Scales* (OWLS) and the KTEA-II assess emergent and more advanced writing skills in familiar and structured formats.

Assessment Strategies

Following standardized administration of academic testing, testing the limits may provide valuable qualitative information around learning deficits, problem-solving skills, and response to different teaching strategies. Strategies to consider include breaking down tasks and changing the presentation of instruction in a stepwise fashion, using visuals (e.g., to assess math concepts), and using additional cues to support how a student approaches a task. The guidelines and accommodations set out in the aforementioned paper by Thompson and colleagues may also be helpful [7].

Academic Measures

Name/ Type	Time	Ages (Normed)	Translated to Other Languages	FXS- or ID-Specific Development or Scoring	Feasibility in FX	Floor Effect
Bracken-3* Direct Assessment	10–15 min.	3–6 yrs.	Yes	–	Yes	Mitigated by task expectations (pointing only) & assessing foundational skills

WIAT-III Direct Assessment	Varies	4–50 yrs.	No	–	Varies	Present
WJ-III Direct Assessment	Varies	2–90 yrs.	Yes	–	Varies	Present
KTEA-II: Math Concepts & Applications Direct Assessment	15–85 min.	4–25 yrs.	No	–	Yes	Present, but tasks use visual cues and responses are non-verbal (i.e. pointing)
OWLS-II Writing Direct Assessment	10–60 min.	3–21 yrs.	No	–	No	Present, but tasks may be familiar (copying, writing name, labeling pictures)
DAS-2 Subtests Direct Assessment	10–20 min.	3:6–6:11 yrs.	Yes	–	Yes	Mitigated by extension to other ages & additional teaching trials

**Recommended*

Anxiety

Phenotype

The presence of both anxiety symptoms and disorders are pervasive in FXS and have been previously documented at rates higher than other ID populations. In a national survey of 1,492 individuals with FXS, parents reported that 70% of males and 56% of females with FXS had been treated for anxiety symptoms or received a formal anxiety diagnosis [51].

In a study of 100 individuals with FXS administered standardized caregiver interviews, 86.2% of males and 76.9% of females met DSM criteria for at least one anxiety disorder [52], compared to a rate of 10.5% in individuals with ID [53]. Similar rates have been reported in other DSM-based studies [54].

While anxiety disorders are typically considered more common in females in the general population [55–57], they are equally prominent in FXS regardless of gender. The higher rates of anxiety in FXS compared to general ID suggests that the FMR1 full mutation that causes FXS presents an increased risk for these disorders and has been found to be independent of other clinical factors (i.e., ID, autism diagnosis, gender, age, etc.). As such, a thorough clinical assessment and treatment of anxiety should be included in the FXS standard of care.

Measures

The clinical assessment of anxiety in individuals with ID, including those with FXS, can be particularly difficult. In recent years, there has been considerable progress made to move away from mostly parent-report measures and/or measures that had not been validated for use in ID, i.e., *Behavior Assessment System for Children* (BASC), *Child Behavior Checklist* (CBCL), etc., to using DSM-based measures and/or those normed for ID populations.

Anxiety Disorders Interview Schedule-Parent (ADIS-P): This is a semi-structured interview designed to diagnose a variety of anxiety disorders and allows the rater (the parent) to make dimensional ratings of disorder features [58]. These ratings indicate either the degree of distress or interference the item presents in a person's functioning (none = 0, very severe = 8). There is a recently published ADIS with *Autism Spectrum Addendum* (ADIS/ASA) [59, 60]. The ADIS/ASA offers a series of additional clinical guidelines and queries that are woven into the semi-structured format of the ADIS-P for the specific phobia, social phobia, OCD (obsessive-compulsive disorder), GAD (generalized anxiety disorder), and SAD (social anxiety disorder) sections. These guidelines may be useful for those with FXS and comorbid ASD. The ADIS-P has been validated in FXS with another parent-report questionnaire developed for ID called the *Anxiety, Depression and Mood Scale* (ADAMS) [52]. The ADIS has been used in both FXS and autism populations with specific adjustments for ID and has also been validated against other measures normed for ID.

Anxiety, Depression and Mood Scale (ADAMS): This is a 28-item questionnaire used to screen for psychiatric disorders in persons with ID [61]. Behaviors are rated on a four-point Likert scale ranging from 0 ("not a problem") to 3 ("severe problem"). The ADAMS yields five subscale scores: general anxiety, social avoidance, depression, manic/hyperactive, and obsessive/compulsive behavior. It was psychometrically evaluated and normed using 265 individuals and validated with 129 psychiatric patients with ID [61] and used in FXS and other neurodevelopmental disorders, as well as clinical trials [52, 62-64]. The ADAMS was developed for use in ID to measure numerous psychiatric symptoms and validated with other measures.

Pediatric Anxiety Rating Scale – Revised (PARS-R): This is a clinician-rated instrument for assessing the severity of anxiety symptoms associated with common DSM-IV anxiety disorders (social phobia, separation anxiety disorder, and generalized anxiety disorder) in children [11], although it has been validated and used in groups of adolescents and young adults with FXS as well [65]. The PARS-R has 61 symptom items and seven severity/ impairment items. This symptom checklist is grouped into the following categories: social interactions or performance situations, separation, generalized, specific phobia, panic

symptoms/physical signs, obsessive-compulsive, health/illness concerns, and other. The PARS-R offers more detailed assessment of anxiety symptomology than other parent-report measures but takes less time than a structured interview. Reports suggest it is useful for treatment monitoring [11, 66] and is able to discriminate between those children with depression or anxiety [67] and can be adopted for use in adults with FXS [64, 65].

Scoring and Interpretation

As all the above-mentioned measures of anxiety rely upon caregiver report, either via questionnaire or interview, it is important to consider accepted adjustments to diagnostic criteria for ID. For example, a common adjustment is to not require that the individual verbalize their "worry" and to consider other observable indicators of anxiety (i.e., repetitive questioning, pacing, avoidance, avoiding eye-contact, etc.).

Assessment Strategies

Clinicians will often observe that individuals with FXS will exhibit heightened anxiety symptoms when initially meeting an individual or in a new situation. As such, it is important to probe about and/or allow time for the individual to become more comfortable in order to assess how their behavior may change with time. Additional probes regarding whether preparation for an event or situation helps or hinders an individual's success, frequency of avoidance and withdrawal, as well as discussion of the sequence of events leading up to aggressive or hyperarousal episodes will help elucidate possible anxiety-provoking scenarios (see Functional Behavior Assessment below).

Limitations

While there are tools available for the assessment of anxiety in ID, the use of inappropriate tools, i.e., *Behavior Assessment System for Children* (BASC), *Child Behavior Checklist* (CBCL), etc., among those with ID remains a concern. Any tools that have not

been developed for ID and/or that rely on verbal expression of anxiety symptoms will limit their appropriateness in the full range of the FXS phenotype.

Anxiety Measures

Name/ Type	Time	Ages (Normed)	Translated to Other Languages	FXS- or ID-Specific Development or Scoring	Feasibility in FX	Floor Effect
ADIS-P & ADIS-ASA Clinician-rated Caregiver Interview	10–15 min.	5+ yrs.	No	FXS, ID	Yes	Used in FXS & autism, DSM-based
ADAMS Caregiver Questionnaire	5–10 min.	10+ yrs.	Yes	FXS, ID	Yes	Validated with a DSM-based anxiety interview in FXS
PARS-R Clinician-rated Caregiver Interview	15–30 min.	6–17 yrs.	No	FXS	Yes	May be adapted to use in older ages; Reported to be sensitive to change over time
RCMAS-2 Caregiver Questionnaire	15–45 min.	6–19 yrs.	No	–	Yes	Present, but tasks use visual cues and responses are non-verbal

	(i.e., pointing)

*Recommended

Autism

Phenotype

The presence of both anxiety symptoms and disorders are pervasive in FXS and have been previously documented at rates higher than other ID populations.

FXS is the most common, known genetic cause of autism spectrum disorder. While FXS accounts for an estimated 1% to 6% of all ASD cases, many individuals with FXS are co-diagnosed with ASD. Depending on the criteria used for the diagnosis of ASD, studies have reported that 30% to 54% of males with FXS meet diagnostic criteria for autism by various assessments including the *Autism Diagnostic Observation Scales* (ADOS), the *Autism Diagnostic Interview – Revised* (ADI-R), or DSM checklists, and 46% met criteria based on parent report. For females, 16% to 20% met diagnostic criteria for autism, or were assigned by parent report [12, 13, 52, 69-73].

Though there is symptom overlap, professionals believe that the presentation of autism in FXS is often different than in idiopathic autism. Specifically, individuals with ASD and FXS often show relatively more prominent social withdrawal, higher levels of anxiety, and less intense simple and complex repetitive and restricted behaviors as measured by ASD diagnostic instruments [71, 73, 74]. However, individuals with FXS and ASD also tend to exhibit a more pronounced degree of social motivation, in that they often initiate simple social exchange, and seek out specific social praise and approval.

Individuals with FXS and ASD have a higher prevalence of seizures (20.7% vs 7.6%), persistence of sleep problems later in childhood, increased behavior problems (especially

aggressive/disruptive behavior), and higher use of medications compared to those individuals with FXS (without ASD) [72]. Possible features differentiating ASD in FXS from idiopathic ASD include lower verbal-IQ, receptive language and theory of mind performance [75], and more significant behavior problems [76]. Among young children with FXS, adaptive behavior, cognition, and repetitive behaviors were not found to differ between those with and without autism [77].

Autism and FXS are typically diagnosed at separate times. When evaluation for autism occurs before genetic testing for FXS, it is commonly attributable to the presence of universal screening for ASD. Due to existing standards of care implemented by the American Academy of Pediatrics [78], which recommends genetic testing (including a specific fragile x panel) for all new diagnoses of ASD, a child's initial ASD diagnosis often leads to a genetic work-up where the subsequent diagnosis of FXS can be made if present. However, there are some individuals with FXS who receive their FXS diagnosis early due to clear developmental delays or a known FXS family history, and then pursue ASD testing and evaluation due to heightened awareness of the symptom overlap, increased risk for ASD, and the need for intervention services.

Measures

ASD is a behavioral diagnosis defined by the presence of specific behavioral criteria, and as such assessment for ASD typically includes a combination of symptom checklists and in-person behavioral observation.

AUTISM DIAGNOSTIC OBSERVATION SCHEDULE, Second EDITION

In a comprehensive developmental assessment for ASD, the *Autism Diagnostic Observation Schedule*, *Second Edition* (ADOS-2), is administered. The ADOS-2 is a semi-structured assessment designed to help determine whether an individual's behavioral presentation is consistent with a medical diagnosis of ASD [79]. It captures samples of behavior that align with the areas of concern for ASD, including social communication and interaction, play and imagination, and restricted and repetitive behaviors. The ADOS-2 has five separate

modules that consist of different activities and tasks. The ADOS-2 module selected is based on a child's age and expressive language level so that behaviors can be compared to expectations for a child at a similar language level. Although the ADOS-2 is a standard test measure, it does not provide standardized or normative scores. As such the scores for the ADOS-2 are used to direct clinical diagnoses and are not intended to predict or describe functioning relative to others.

OBSERVATIONAL SCREENERS

Over the years, additional measures have been developed to provide alternatives to the *ADOS-2*, which typically takes about an hour to administer, and requires several years of advanced training to be administered. This includes measures such as the *Screening Tool for Autism in Two-Year-Olds* (STAT) and the *Autism Screening Instrument for Educational Planning, Third Edition* (ASIEP-3). Benefits to such measures include shorter administration time, and less training required for administration and scoring. In addition, a recent paper has highlighted specific evidence to support the use of the ASIEP within the FXS population due to these conveniences, as well as its unique ability to track social progress over time [80].

PARENT REPORT MEASURES

Documentation of symptoms is typically reported through extended clinical interview as well as parent-report inventories, of which there are many. Popular measures to capture parent report of symptoms include the *Autism Diagnostic Interview, Revised* (ADI-R), *Social Communication Questionnaire* (SCQ), *Social Responsiveness Scale, Second Edition* (SRS-2), *Gilliam Autism Rating Scale* (GARS), *Childhood Autism Rating Scale* (CARS), to name a few.

In addition, a recent publication sought to update some of these parent-report questionnaires (SRS-2, SCQ) in an effort to create measures that are more sensitive to autism in the FXS population. These methods improved the sensitivity and/or specificity of the SCQ and SRS-2 but has not addressed all of the larger issues related to diagnostic accuracy of ASD in FXS [81].

Assessment Strategies

For those that are first diagnosed with FXS, pursuing autism specific assessment often calls for a different approach to evaluation and intervention, primarily due to the presence of relative strengths in social interest and motivation, as well as increased symptoms of hyperarousal and anxiety. Often these increased symptoms of hyperarousal and anxiety may manifest as extremely difficult externalizing behaviors, such as complete withdrawal from social interaction, task refusal, or severe aggressive or self-injurious behaviors. As such, additional considerations need to be made when approaching autism specific assessment.

The role of hyperarousal and anxiety is especially crucial to understand and plan for when preparing to assess for the presence of autism. Waiting to administer the ADOS-2 until later in an assessment session, for instance, may help to alleviate anxiety symptoms that are more pronounced in the beginning of a visit. In addition, though the ADOS-2, STAT, or ASIEP-3 are designed to elicit and capture symptoms of autism based on a standardized protocol, good behavioral observation throughout the assessment process should always be integrated into final diagnostic conclusions. For instance, difficulties following adult instructions on a cognitive or developmental measure, or repetitive motor behaviors while watching a favorite video on the tablet may not be the standardized activities in which we look for autism symptoms, but if such symptoms are present, they should always be noted and incorporated into the overall clinical picture.

Because the ADOS-2 module choice is based on language level not chronological age, it is also important to consider whether certain tasks/items presented are appropriate. The ADOS-2 manual indicates certain modifications are acceptable in cases where there is a large mismatch between language ability and age. For instance, action figures instead of dolls and high fives instead of tickles may be more suitable for a nonverbal 30-year-old male. Recently, the *Adapted-ADOS* (A-ADOS) [82] has demonstrated initial validity and reliability of assessing adults with minimally verbal skills (modules 1 and 2); however, it has not yet been validated for specific use in FXS.

Scoring and Interpretation/Limitations

Special consideration needs to be made in how the symptoms inherent to many with FXS may falsely inflate scores and over-identify autism on these measures. Specifically, males with FXS who meet diagnostic criteria for intellectual disability will clearly exhibit social communication delays when compared to their same-aged peers. In addition, the significant anxiety presentation seen across males and females with FXS can contribute to social withdrawal, deficits in social reciprocity and social communication (i.e., lack of eye contact, limited speech), as well as increases in behavioral rigidity or repetitive behaviors.

Though the ADOS-2 is considered the gold standard instrument in the field for assessing for the presence of autism spectrum disorder, studies have revealed that the ADOS-2 does not reliably differentiate autism from intellectual disability, especially in younger children (i.e., children with ID often exceed the cutoff for autism on the ADOS-2 [82-85]. In addition, as parent report of symptoms may endorse behaviors that are commonly seen in individuals with ASD, many individuals with FXS may engage in behavior that appear to meet criteria for autism, when these may actually be behavioral manifestations of other, FXS-specific symptoms (i.e., low verbal abilities, intellectual disability, hyperarousal, anxiety). Experienced assessors must be very familiar with the behavioral presentations of both FXS and ASD to appropriately understand the complexity of these overlapping symptoms. As such, the diagnosis of ASD in the person with FXS is ultimately determined based on the DSM-5 criteria for ASD determined by clinical judgment using all available information including direct assessment, caregiver and other reports, ratings scales, and developmental history.

Maladaptive Behaviors & Emotions

Maladaptive behaviors are actions or tendencies that do not allow an individual to adjust well to certain situations. They are typically disruptive, dysfunctional, and can range from mild to severe.

Maladaptive behaviors may be attempts at reducing discomfort, anxiety, and hyperarousal, but are typically not effective and can even make the original symptoms worse as they are a poor adaptation of behavior. Measurement of behavior symptoms is a critical component of clinical assessment in FXS — it can aid in tracking response to treatment, as well as in identifying targets for intervention and possible obstacles to learning.

Phenotype

Aggression, self-injurious behavior (SIB), restricted and repetitive behaviors (RRBs), or stereotypic behaviors are significant problems for at least 50% of males with FXS [86, 87].

Aggression may be directed at others and/or property and expressed as tantrums, defiance, hitting, and kicking [88]. A survey of over 700 caregivers found that almost all of their children with FXS — 92% of males and 83% of females — engaged in at least one aggressive act in the last 12 months [88]. A study of 50 males with FXS using both the mother and father report of the *Behavior Problems Inventory* (BPI) [89] reported that aggressive and SIBs occurred among ~75% of participants on a weekly basis, whereas stereotypic behaviors occurred in 98% of the sample on a daily basis. The most common reported behaviors were hitting (49%) and kicking (30%) others, self-hitting (50%) and self-biting (50%), and repetitive hand and arm movements (~50%). In a more recent study of 154 individuals with FXS using a different parent-report measure, the *Restricted Behavior Scale – Revised (RBS-R)*, FXS caregivers rated resisting changes in activities/difficulty with transitions and hand/finger mannerisms as the most problematic followed by fascination with one subject or activity, strong attachment to one specific object, and sensory repetitive behaviors [90].

From the standpoint of many clinicians and parents, aggressive outbursts, SIBs, and stereotypic behaviors are often precipitated by sensory stimuli or unexpected changes in the physical or social environment that the patient is overwhelmed by, leading to hyperarousal [91] (Hessl, 2006 #93; Wheeler, 2016 #408).

Measures

As with selection of measures used to assess aspects of mental health (i.e., anxiety or depression), consideration of the content and wording of behavior checklists requiring verbalization or description of situations that do not apply to the individual with ID will improve this portion of a clinical evaluation.

Aberrant Behavior Checklist – Community, Second Edition (ABC-C-2) / ABC-Fragile X (ABC-CFX): The ABC-C-2 is a 58-item rating scale of maladaptive behaviors evaluated on a four-point Likert scale ranging from 0 (not at all a problem) to 3 (the problem is severe in degree). The ABC-C was developed with five original dimensions or subscales: irritability, hyperactivity, lethargy/withdrawal, stereotypy, and inappropriate speech to be used with individuals with developmental disabilities [92, 93]. A factor analysis of the *ABC-C specifically in FXS* (ABC-FXS) generated a 6-factor structure: irritability, lethargy, stereotypy, hyperactivity, inappropriate speech, and social avoidance [94]. Therefore, while the items and response choices do not differ between the two versions, there are two scoring options, with the ABC-FXS being somewhat better supported by factor analysis studies and used in several FXS clinical trials.

Behavior Problems Inventory (BPI): This is a parent-report questionnaires used to assess SIB, stereotyped behavior, and aggression/destruction over the past 2 months [89]. Each item is scored on a five-point frequency scale (from never = 0, to hourly = 4), and a four-point severity scale (from no problem = 0, to severe problem = 3). The BPI is a reliable instrument and has been validated against the *Aberrant Behavior Checklist* (ABC-C) and *Diagnostic Assessment for the Severely Handicapped-II* (DISC-II) [89]. There are some reports of the BPI being used as an interview, as well. The BPI was developed for use in ID and has been cross validated with other measures.

Restricted and Repetitive Behavior Scale-Revised (RBS-R): This is a parent-report questionnaire comprised of 43 items that measure restricted and repetitive behaviors (RRBs) and is normed on individuals with ID. Items are rated on a four-point Likert scale: behavior does not occur = 0, behavior occurs and is a mild problem = 1, behavior occurs

and is a moderate problem = 2, behavior occurs and is a severe problem = 3. Items are grouped into six subscales: stereotyped behavior, self-injurious behavior, compulsive behavior, ritualistic behavior, sameness behavior, and restricted behavior. Two scores can be derived from the subscales, one based on the summed scores for each subscale, and one based on the number of items endorsed for each subscale. The RBS-R was developed for use in ID and has also been used and cross-validated with other measures in FXS.

Vineland Adaptive Behavior Scales, Third Edition (VABS-3) Maladaptive Behavior domain: This is available as either a semi-structured interview or a parent-caregiver survey, but the most reliable method is the interview. The maladaptive domain is one component of a larger interview. It measures internalizing, externalizing, and critical behaviors. internalizing and externalizing sections yield a v-scale score with a mean of 15 and standard deviation of 3. The critical items section does not generate a scaled score. Items are rated as occurring often, sometimes, or rarely/never.

Scoring and Interpretation

Diagnostic over-shadowing can occur in FXS. Diagnostic overshadowing occurs when symptoms are seen as attributable to intellectual disability and not regarded as a co-occurring issue or condition in a patient with ID. In FXS, this can occur when RRBs or gaze aversion are attributed to the existence of autism and not appreciated as a possible sign of anxiety, for example. The overlap of maladaptive behaviors, mental health (especially anxiety), autism, and hyperarousal symptoms in FXS can make interpretation of behavior difficult. A comprehensive assessment in FXS must evaluate all of these aspects in order to best classify and treat overlapping symptom presentation.

Assessment Strategies

The importance of and reliance upon caregiver report in maladaptive behavior assessment cannot be understated. As such, an important step in administration of questionnaires is to review the purpose and response choices with respondents before asking them to fill them out. For example, making a clear distinction as to whether they are

making ratings as compared to other individuals their son or daughter's age or compared to other individuals with FXS/ID, which ideally is guided by standardized instructions. Similarly, clarifying the time period for reporting and helping the parent to anchor that time frame (i.e., discuss what was going on in the household 30 days ago) and providing examples when specific behaviors are not described in the questionnaire or interview can help to improve the accuracy of ratings.

Direct observations of the individual's behavior, especially in the environments in which maladaptive behaviors occur, provides the opportunity to identify what is occurring before (also referred to as antecedents) the act of aggression, SIB, or RRBs.

Functional behavior assessments (FBAs) are an in-person observation and data-collection tool that can also be very useful in determining why certain behaviors may be occurring. These assessments can help to determine if certain behaviors are specific to certain environments, which can help to inform the overall diagnostic picture. For instance, if a child engages in increased self-injurious behaviors in the school environment, it could be that they are experiencing increased anxiety when in that setting. FBA's can also help to track behavioral change over time, which may help to identify shifts in an individual's behavior that may be suggestive of an underlying concern. For instance, for an individual who typically engages in many social initiations in the classroom and suddenly is engaging in far less, this might indicate the onset of depression.

Limitations

The reliance upon caregiver questionnaires for assessment of behavior is a limitation, as various forms of bias and limited recollection of behaviors can affect results. Additionally, the majority of measures have no way of accounting for the level of disruption to the individuals, their family, or others. This is especially important when considering treatment intervention and prioritization, as a self-harm behavior occurring only once a day is different than a relatively harmless repetitive behavior like stimming or perseverative questioning.

Name/ Type	Time	Ages (Normed)	Translated to Other Languages	FXS- or ID-Specific Development or Scoring	Feasibility in FX	Floor Effect
ABC-2* Caregiver Questionnaire	10–15 min.	5+ yrs.	Yes	FXS, ID	Yes	ABC-FXS scoring used in many FXS clinical trials
ADAMS* Caregiver Questionnaire	5–10 min.	10+ yrs.	Yes	FXS, ID	Yes	Validated with other measures (ABC, BPI, etc.)
BPI* Caregiver Questionnaire	15–25 min.	14–91 yrs.	Yes	FXS, ID	Yes	Long (52 items) & short (30 items) forms available online
RBS-R* Caregiver Questionnaire	15–25 min.	All ages	Yes	ID	Yes	Early childhood version recently developed
Vineland-3* Caregiver Interview	n/a	0–9 yrs.	Yes	–	Yes	Used in older individuals for age equivalents
BASC-2 Caregiver, Teacher & Self-Report	15–45 min./td>	6–21 yrs.	Yes	–	Varies	May be useful among those without ID

Questionnaires						
CBCL Caregiver, Teacher & Self-Report Questionnaires	10–15 min./td>	1:6–18 yrs.	Yes	–	Varies	May be useful among those without ID

**Recommended*

Neuromotor Functioning

Neuromotor development and functioning includes many domains such as general strength and motor skills, as well as motor speed/response time, dexterity, precision, balance, and coordination. Neuromotor skills are integral to the development of many other skills including adaptive, cognitive, and language domains.

Phenotype

Children and adults with FXS have neuromotor deficits and these are considered a core aspect of the FXS phenotype [86]. Neuromotor deficits are an important part of the early presentation of an ongoing area requiring treatment in FXS. Some of the common, presenting early symptoms include hypotonia, delayed motor milestones, motor skill, and coordination deficits. These early symptoms may be the first presenting signs that lead to FXS testing and diagnosis. Occupational and/or physical therapy are recommended as part of a comprehensive treatment plan for most individuals with FXS to improve motor skills affecting daily living skills in areas of self-help, academic, work, and play/social activities.

Measures

Neuromotor assessments evaluate motor functions through the age at which a skill is expected to be mastered. Therefore, most of the available instruments are normed in age ranges insufficient for the protracted developmental trajectories in disability populations. Neuromotor assessments are likely to be useful beyond the age of standardized scoring.

Many comprehensive developmental tests include the domain of motor, especially for infants and toddlers (e.g., *Bayley Scales of Infant and Toddler Development*).

Movement Assessment Battery for Children, *Second Edition* (MABC-2)*:* The MABC-2 is a norm-based assessment of fine and gross motor performance for children ages 3 through 16 years [95]. It evaluates skills in three component areas: manual dexterity, aiming and catching, and balance. It also yields an overall test score.

There are three forms (or age bands) of the MABC-2 with slightly different items and/or administration instructions for ages 3–6, 7–,10 and 11–16 years old. Standard scores are generated for each item, as well as each of the three component areas. The MABC-2 covers a range of neuromotor skills and offers three age bands that can be considered for use with older individuals with FXS.

Quick Neurological Screening Test, Third Edition (QNST-3): is a norm-referenced assessment of the development of motor coordination and sensory integration seen as neurological soft signs (NSSs), such as poor coordination, sensory perceptual changes, and difficulty sequencing complex motor tasks [96]. The presence of NSSs is often considered an indication of learning difficulties.

The QNST-3 includes tasks used in traditional neurologic exams, including hand skill, figure recognition and production, palm form recognition, eye tracking, sound patterns, finger to nose, thumb and finger circle, rapidly reversing repetitive hand movements, arm and leg extension, tandem walk, stand on one leg, skipping, left-right discrimination, and behavioral irregularities.

A unique feature of the QNST-3 is the scoring method — scores are "earned" for errors in response or qualitative performance deficits, thereby allowing a broader range of individuals to feasibly complete the measure. The QNST-3 offers a broad age range (5–80 years old), requires minimal supplies for administration, measures a variety of neuromotor functions (vs. just neuromotor skills), and its scoring increases utility across the FXS phenotype.

Vineland Adaptive Behavior Scales, Third Edition (VABS-3) Motor Skills domain: This is available as either a semi-structured interview or a parent-caregiver survey, but the most reliable method is the interview. The motor skills domain is one component of a larger interview (see Adaptive Behavior above for more information). It measures gross and fine motor skills. A motor skills domain standard score (mean of 100, standard deviation of 15), as well as gross and fine motor v-scale scores (mean of 15 and standard deviation of 3) are generated. The motor skills domain is normed through age 9 years but is often administered beyond this age range in FXS as age equivalents and growth scale values are available. Items are rated as occurring usually, sometimes, or rarely/never.

NIH Toolbox motor batteries: This brief battery assesses a variety of gross and fine motor skills including dexterity, grip strength, standing balance, gait speed, and endurance across four to five tasks (dependent upon age).

Additionally, a more recent addition of the NIH Toolbox Early Childhood Motor Battery for children 3–6 years has been made available. Because the battery is available across a wide age range it may be suitable for the majority of individuals with FXS. Still, there is limited available data regarding its use and suitability for this population. It includes some tasks (i.e., pegboard) that can be difficult to administer across the phenotypic range in FXS, but does offer objective data of sway during balance if it is feasible for the participant to wear a device around their waist.

Scoring and Interpretation

As most neuromotor tests evaluate the expected and typical maturation of neuromotor skills over time, i.e., MABC-2 or *Bruininks-Oseretsky Test of Motor Proficiency* (BOT-2), the

age range for standardized scores is limited, leading to floor effects. Although some tests such as the *McCarron Assessment of Neuromuscular Development* (MAND) offer normative scores for special populations, the feasibility was weak in a pilot study of FXS. Similar to academic and cognitive domains, neuromotor assessment scores must be interpreted cautiously. The use of raw scores and tests outside of their standardized age range should be considered. Neuromotor tests that score the response quality and/or error types, i.e., QNST-3, *Berg's Balance Scale*, *or Pediatric Balance Scale* (PBS), will provide more meaningful information.

Assessment Strategies

There are helpful strategies to consider when directly assessing neuromotor functioning in FXS. As it relates to standardized administration, verbal instructions may need to be adjusted to better match the language abilities of the individual. For example, pointing and saying, "leg up," while demonstrating on the mirrored side (i.e., examiner's right leg for examinee's left leg) instead of "lift your left leg up." More teaching or demonstration trials should be provided as motor planning and processing time can be impacted in FXS. Finally, prompting should move from least intrusive (i.e., gesture or verbal, depending on task) to most intrusive (i.e., hand over hand) to provide the individual with the opportunity to perform the skill in the most independent manner possible. Also, this successive prompt approach can provide the clinician information as to what type of supports may lead to success in intervention and therapies.

A unique component of the FXS phenotype is hyperarousal and sensitivity to sensory experiences. It is critical to consider this during neuromotor testing. Prolonged eye-contact, touch, unexpected noise, as well as the fatigue that may come with performing physically difficult tasks, can all lead to increased hyperarousal. Paying attention to signs such as increased perspiration (especially in the palms), redness in cheeks, rapid breathing, increased gaze avoidance, or attempts to avoid the task with conversation (often in higher functioning or more verbal individuals) can help the clinician/assessor intervene earlier (i.e., drop eye contact, side conversations, breaks, rewards, etc.) to reduce hyperarousal. Some individuals with FXS are particularly averse

to fine motor tasks such as pencil and paper tasks. In a comprehensive clinical assessment, neuromotor tasks can be interspersed in the evaluation as movement breaks.

Presenting tasks with clear verbal and visual supports that denote beginning and end can be particularly useful when assessing individuals with FXS. For example, empty boxes that are crossed off (or filled with a sticker of their choice) after the completion of a task or demonstrating the end of the task (not just demonstrating how to do it or start it) is when "all the coins are in the box" or counting together to 10.

Limitations

As mentioned above, a limitation of many neuromotor assessments is the age-to-maturation of skills assumption. By using tests beyond their standardized age range, the protracted development of skills over time in FXS can be tracked. Further, consideration of both skills (being able to run, jump, or write using a pencil) and functions (tracking an object with their eyes, tactile sensation or strength) in neuromotor assessment provides the most accurate prognostic information.

Neuromotor Measures

Name/ Type	Time	Ages (Normed)	Translated to Other Languages	FXS- or ID-Specific Development or Scoring	Feasibility in FX	Floor Effect
MABC Age Band 1 Direct Assessment	20–30 min.	3–16 yrs.	Yes	–	Yes	Reduced when using Age Band 1 with older individuals
QNST-3* Direct Assessment	15–30 min.	5–80 yrs.	No	ID	Yes	Minimal due to scoring method

Pediatric and Berg Balance Scales* Direct Assessment	15–20 min.	5+ yrs.	Yes	Currently being studied	Yes	Minimal due to scoring method & with adjustments to verbal instructions
Vineland-3 Motor* Caregiver Interview	10–15 min.	3–7 yrs.	Yes	–	Yes	Somewhat improved due to lower limit (SS=20) and v-scale scores

**Recommended*

Infant and Toddler Development

FXS is a developmental disability, and as such, early identification is important to ensure that the individual is getting the support and intervention they need to show their best skills and continue to progress. This early identification initiative is supported by publicly funded early intervention programs across all 50 states. These programs, as well as guidelines related to early childhood development and education, are discussed in specific detail in Early Childhood Developmental and Educational Guidelines for Children with Fragile X Syndrome and Early Intervention for Infants and Toddlers with Fragile X Syndrome.

Assessment of developmental delays is recommended to occur as soon as differences are noted and/or a diagnosis of FXS is made, and repeat testing is often an integral part of an individual's treatment plan. Frequent reevaluation of an individual's skills is needed to inform treatment and education plans, and to track progress over time. When FXS is identified prenatally or early in a child's life, it is often encouraged for these children to be

seen every three to six months before the age of 2, and at least yearly following their second birthday.

Measures

Comprehensive developmental measures assess skills across domains including early cognitive skills (i.e., problem solving), language skills (receptive and expressive), and motor skills (fine and gross). While developmental measures do not directly assess social skills and play as a unique domain, these skills are often captured across items in the cognitive and language domains. For example, participation in social routines (e.g., peekaboo), attending to nursery rhymes, and engaging in back-and-forth play are assessed in the language domain, whereas functional and pretend play skills are assessed in the cognitive domain. In addition, a child's general approach to structured adult-led tasks can also be observed and informally assessed during developmental testing, which may hint to additional concerns such as behavioral rigidity, a tendency to be self-led, or other differences in social responsiveness.

The *Bayley Scales of Infant and Toddler Development, Fourth Edition* (Bayley-4) is a widely used comprehensive developmental assessment for children age 16 days to 42 months old. The Bayley-4 has high internal consistency, test-retest reliability and validity, as well as recently updated norms in 2019. The Bayley has long been used in research and clinical care in FXS [97]. While another developmental measure, the Mullen Scales of Early Learning, continues to be used in clinical and research settings given several benefits including a wider age range (birth to 68 months), the norms and materials are outdated and as such this measure is not recommended for clinical use.

The Bayley allows for adaptation across the lifespan when necessary. For instance, for individuals who may be chronologically older than the given age range, but exhibit significant deficits across most developmental areas, these tools can be administered to estimate age equivalents (and GSVs to track change via the Bayley-4) for their skills. This is especially beneficial in cases of severe to profound intellectual disability when other standardized measures (i.e., cognitive or intellectual assessments) have basal age cut-offs

that are higher than the individual's developmental level. Care must be taken, however, to ensure that lack of engagement in certain developmentally younger test materials does not interfere in the testing process or interpretation of results.

Scoring and Interpretation

Standardized developmental measures are important for monitoring and identifying developmental delay in infants and toddlers with FXS. Developmental measures may also be carefully considered for older children with FXS who are unable to participate meaningfully in traditional cognitive (IQ) testing. In these cases, however, standard scores are not obtained and instead age equivalents can be used to provide information about a child's approximate developmental functioning.

It is important to note that results from developmental assessments provide estimates of current functioning and are not predictive of future ability for young children. This is an important distinction to IQ testing, in which scores are considered stable as children get older.

Assessment Strategies

There are several considerations for administration and scoring of developmental testing for young children with FXS. Without violating standardized administration, children with FXS may benefit from multiple opportunities to demonstrate skills when inattention interferes or there are other difficulties engaging. It is especially important for clinicians to pair performance on developmental measures with parent report given that these assessments often cannot completely capture a child's full range of skills.

Relatedly, reporting on skills that are observed during an evaluation but outside of the developmental test may also provide a more complete picture of a child's functioning. For example, a clinician might consider observing and giving credit for receptive and expressive language skills that are observed throughout an evaluation (e.g., during informal behavior observations) rather than exclusively including only what is seen during administration of a given item. When this occurs, it is important for clinicians to note this

shift from standardization. This is a unique difference from other standardized assessment measures, including cognitive/intellectual testing, academic testing, and performance on the *Autism Diagnostic Observation Schedule, Second Edition* (ADOS-2), which have more strict rules about scoring the child's in-the-moment response to a specific item or press. The newest version of the Bayley includes explicit guidance about scoring based on parent report and/or observations outside of testing.

Lastly, children with FXS will likely benefit from clinicians moving between developmental domains to administer items. For instance, shifting between cognitive items (e.g., administering a puzzle item) and language items (e.g., identifying pictures in a book), often maintains engagement more effectively than requiring or expecting a child to complete all items in the language domain in consecutive order. Again, these are expectations that are typically required by standardized testing administered to older children, such as cognitive or intellectual assessment. Such flexibility allows for the assessor to follow a child's lead, encourage sustained motivation and attention, and improves overall rapport.

Limitations

One of the primary limitations of developmental testing in young children is that results represent only a snapshot of a child's full skillset. It is often difficult for clinicians to fully capture the range of skills a child has based on a measure that is typically completed in 45–60 minutes, especially if there are additional behavioral considerations (self-harm, aggression, tantrums). As a result, developmental testing will often underestimate true abilities and thus it is especially important to pair results from developmental testing with caregiver report. For example, the Vineland-3 would provide caregiver report on similar skills, (e.g., receptive and expressive language skills, play skills, fine motor skills) that are assessed on the Bayley-4. Alternatively, a clinician may score the Bayley-4 based on what was observed during testing and add parent report qualitatively.

Summary

Taken together, the clinical assessment of individuals with FXS must be comprehensive, accommodate the unique aspects and range of the FXS phenotype, and utilize tools that are appropriate (feasible, scorable, and valid) for use in FXS and commensurate with their developmental level. The field is actively engaging in projects to better guide the selection of the most appropriate measures in FXS and recommendations will be updated accordingly. Individuals with FXS possess numerous strengths such as humor, engagement, social interest, sensitivity to others, and visual memory that can be recognized as part of a positive assessment.

References

1. Berry-Kravis, E., et al., ***Development of an expressive language sampling procedure in fragile X syndrome: a pilot study***. J Dev Behav Pediatr, 2013. 34(4): p. 245-51.

2. Casenhiser, D.M., et al., ***Measuring and supporting language function for children with autism: evidence from a randomized control trial of a social-interaction-based therapy***. J Autism Dev Disord, 2015. 45(3): p. 846-57.

3. Sansone, S.M., et al., ***Improving IQ measurement in intellectual disabilities using true deviation from population norms***. J Neurodev Disord, 2014. 6(1): p. 16.

4. Silverman, W., et al., ***Stanford-Binet & WAIS IQ Differences and Their Implications for Adults with Intellectual Disability (aka Mental Retardation)***. Intelligence, 2010. 38(2): p. 242-248.

5. Hessl, D., et al., ***The NIH Toolbox Cognitive Battery for intellectual disabilities: three preliminary studies and future directions***. J Neurodev Disord, 2016. 8(1): p. 35.

6. Shields, R.H., et al., ***Validation of the NIH Toolbox Cognitive Battery in intellectual disability***. Neurology, 2020. 94(12): p. e1229-e1240.

7. Thompson, T., et al., ***Standardized Assessment Accommodations for Individuals with Intellectual Disability***. Contemporary School Psychology, 2018. 22(4): p. 443-457.

8. Hessl, D., et al., ***A solution to limitations of cognitive testing in children with intellectual disabilities: the case of fragile X syndrome***. J Neurodev Disord, 2009. 1(1): p. 33-45.

9. Schmitt, L.M., et al., ***Executive Function in Fragile X Syndrome: A Systematic Review***. Brain Sci, 2019. 9(1).

10. Knox, A., et al., ***Feasibility, reliability, and clinical validity of the Test of Attentional Performance for Children (KiTAP) in Fragile X syndrome (FXS)***. J Neurodev Disord, 2012. 4(1): p. 2.

11. ***The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties***. J Am Acad Child Adolesc Psychiatry, 2002. 41(9): p. 1061-9.

12. Hernandez, R.N., et al., ***Autism spectrum disorder in fragile X syndrome: a longitudinal evaluation***. Am J Med Genet A, 2009. 149A(6): p. 1125-37.

13. Kaufmann, W.E., et al., ***Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors***. American Journal of Medical Genetics Part A, 2004. 129(3): p. 225-234.

14. Semel, E., E. Wig, and W. Secord, ***The Clinical Evaluation of Language Fundamentals: Preschool-2***. 2004: Psychological Corporation.

15. Wiig, E.H., W.A. Secord, and E. Semel, ***Clinical Evaluation of Language Fundamentals: Fifth Edition***. 2013: Pearson.

16. Hoffmann, A., et al., ***Language across the Lifespan in Fragile X Syndrome: Characteristics and Considerations for Assessment***. Brain Sci, 2020. 10(4).

17. Carrow-Woolfolk, E., ***(CASL-2) Comprehensive Assessment of Spoken Language, Second Edition.*** 2017: Western Psychological Services.

18. Martin, G.E., et al., ***Longitudinal profiles of expressive vocabulary, syntax and pragmatic language in boys with fragile X syndrome or Down syndrome***. Int J Lang Commun Disord, 2013. 48(4): p. 432-43.

19. Turkstra, L.S., L. Abbeduto, and P. Meulenbroek, ***Social cognition in adolescent girls with fragile x syndrome***. Am J Intellect Dev Disabil, 2014. 119(4): p. 319-39.

20. Barokova, M. and H. Tager-Flusberg, ***Commentary: Measuring Language Change Through Natural Language Samples***. J Autism Dev Disord, 2020. 50(7): p. 2287-2306.

21. Abbeduto, L., et al., ***Effects of sampling context on the expressive language of children and adolescents with mental retardation***. Ment Retard, 1995. 33(5): p. 279-88.

22. Tager-Flusberg, H., et al., ***Defining spoken language benchmarks and selecting measures of expressive language development for young children with autism spectrum disorders***. J Speech Lang Hear Res, 2009. 52(3): p. 643-52.

23. Abbeduto, L., et al., ***Expressive language sampling as a source of outcome measures for treatment studies in fragile X syndrome: feasibility, practice effects, test-retest reliability, and construct validity***. J Neurodev Disord, 2020. 12(1): p. 10.

24. Channell, M.M., et al., ***Narrative Language Sampling in Typical Development: Implications for Clinical Trials***. Am J Speech Lang Pathol, 2018. 27(1): p. 123-135.

25. Fenson, L., ***MacArthur-Bates Communicative Development Inventories***. 2007: Paul H. Brookes Publishing Company.

26. Bishop, D.V.M., ***The Children's Communication Checklist version 2 (CCC-2)***. 2003: Psychological Corporation.

27. Schalock, R.L., M.A. Verdugo, and L.E. Gomez, ***Evidence-based practices in the field of intellectual and developmental disabilities: an international consensus approach***. Eval Program Plann, 2011. 34(3): p. 273-82.

28. Sparrow, S., D. Cicchetti, and C. Saulnier, ***Vineland Adaptive Behavior Scales–Third Edition (Vineland-3)***. 2016, San Antonio, TX: Pearson.

29. Hahn, L.J., et al., ***Do children with fragile X syndrome show declines or plateaus in adaptive behavior?*** American journal on intellectual and developmental disabilities, 2015. 120(5): p. 412-432.

30. Association, A.P., ***Diagnostic and statistical manual of mental disorders***. 2013: American Psychiatric Association.

31. Tasse, M.J., et al., ***Development and Standardization of the Diagnostic Adaptive Behavior Scale: Application of Item Response Theory to the Assessment of Adaptive Behavior***. Am J Intellect Dev Disabil, 2016. 121(2): p. 79-94.

32. Fisch, G.S., et al., ***Longitudinal changes in cognitive and adaptive behavior in fragile X females: A prospective multicenter analysis.*** American Journal of Medical Genetics, 1999. 83(4): p. 308-312.

33. Fisch, G.S., R.J. Simensen, and R. Schroer, ***Longitudinal changes in cognitive and adaptive behavior scores in children and adolescents with the fragile X mutation or autism***. Journal of autism and developmental disorders, 2002. 32(2): p. 107-114.

34. Freund, L.S., et al., ***Preliminary report on cognitive and adaptive behaviors of preschool-aged males with fragile X***. Developmental Brain Dysfunction, 1995.

35. Klaiman, C., et al., ***Longitudinal profiles of adaptive behavior in fragile X syndrome***. Pediatrics, 2014. 134(2): p. 315-24.

36. Dykens, E., et al., ***Trajectories and profiles of adaptive behavior in males with fragile X syndrome: multicenter studies***. J Autism Dev Disord, 1996. 26(3): p. 287-301.

37. Dykens, E.M., et al., ***Trajectories and profiles of adaptive behavior in males with fragile X syndrome***. Journal of Autism and Developmental Disorders, 1993. 23(1): p. 135-145.

38. Hatton, D.D., et al., ***Adaptive behavior in children with fragile X syndrome***. Am J Ment Retard, 2003. 108(6): p. 373-90.

39. Warren, S.F., et al., ***The Longitudinal Effects of Parenting on Adaptive Behavior in Children with Fragile X Syndrome***. J Autism Dev Disord, 2017. 47(3): p. 768-784.

40. Cornish, K., V. Sudhalter, and J. Turk, ***Attention and language in fragile X***. Ment Retard Dev Disabil Res Rev, 2004. 10(1): p. 11-6.

41. Roberts, J.E., et al., ***Academic skills of boys with fragile X syndrome: profiles and predictors***. Am J Ment Retard, 2005. 110(2): p. 107-20.

42. Klusek, J., et al., ***Reading and phonological skills in boys with fragile X syndrome***. J Autism Dev Disord, 2015. 45(6): p. 1699-711.

43. Adlof, S.M., et al., ***Phonological awareness and reading in boys with fragile X syndrome***. J Child Psychol Psychiatry, 2015. 56(1): p. 30-9.

44. Raspa, M., et al., ***A comparison of functional academic and daily living skills in males with fragile X syndrome with and without autism***. Res Dev Disabil, 2018. 78: p. 1-14.

45. Murphy, M.M. and M.M. Mazzocco, ***Mathematics learning disabilities in girls with fragile X or Turner syndrome during late elementary school***. J Learn Disabil, 2008. 41(1): p. 29-46.

46. Bartholomay, K.L., et al., ***Closing the Gender Gap in Fragile X Syndrome: Review on Females with FXS and Preliminary Research Findings***. Brain Sci, 2019. 9(1).

47. Mazzocco, M.M., ***Math learning disability and math LD subtypes: evidence from studies of Turner syndrome, fragile X syndrome, and neurofibromatosis type 1***. J Learn Disabil, 2001. 34(6): p. 520-33.

48. Murphy, M.M., et al., ***Mathematics learning disability in girls with Turner syndrome or fragile X syndrome***. Brain Cogn, 2006. 61(2): p. 195-210.

49. Braden, M., ***Classroom adaptations,*** in ***Educating Children with Fragile X Syndrome: A Multi-Professional View***, D. Dew-Highes, Editor. 2004, Routeledge.

50. Berry-Kravis, E., et al., ***Outcome measures for clinical trials in fragile X syndrome***. J Dev Behav Pediatr, 2013. 34(7): p. 508-22.

51. Bailey, D.B., Jr., et al., ***Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey***. Am J Med Genet A, 2008. 146A(16): p. 2060-9.

52. Cordeiro, L., et al., ***Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: prevalence and characterization***. Journal of neurodevelopmental disorders, 2011. 3(1): p. 57.

53. Dekker, M.C. and H.M. Koot, ***DSM-IV disorders in children with borderline to moderate intellectual disability. I: prevalence and impact***. J Am Acad Child Adolesc Psychiatry, 2003. 42(8): p. 915-22.

54. Ezell, J., et al., ***Prevalence and Predictors of Anxiety Disorders in Adolescent and Adult Males with Autism Spectrum Disorder and Fragile X Syndrome***. J Autism Dev Disord, 2019. 49(3): p. 1131-1141.

55. Fergusson, D.M., L.J. Horwood, and M.T. Lynskey, ***Prevalence and comorbidity of DSM-III-R diagnoses in a birth cohort of 15 year olds.*** J Am Acad Child Adolesc Psychiatry, 1993. 32(6): p. 1127-34.

56. McGee, R., et al., ***DSM-III disorders in a large sample of adolescents***. J Am Acad Child Adolesc Psychiatry, 1990. 29(4): p. 611-9.

57. Costello, E.J., et al., ***Prevalence and development of psychiatric disorders in childhood and adolescence***. Arch Gen Psychiatry, 2003. 60(8): p. 837-44.

58. Silverman, W.K. and W.B. Nelles, ***The anxiety disorders interview schedule for children***. Journal of the American Academy of Child & Adolescent Psychiatry, 1988. 27(6): p. 772-778.

59. Kerns, C.M., et al., ***Anxiety Disorders Interview Schedule-Autism Addendum: Reliability and Validity in Children With Autism Spectrum Disorder***. J Clin Child Adolesc Psychol, 2017. 46(1): p. 88-100.

60. Kerns, C.M., et al., ***The autism spectrum addendum to the anxiety disorders interview schedule***. Unpublished manual, 2015.

61. Esbensen, A.J., et al., ***Reliability and validity of an assessment instrument for anxiety, depression, and mood among individuals with mental retardation***. J Autism Dev Disord, 2003. 33(6): p. 617-29.

62. Shaffer, R.C., et al., ***The Relationship between Expressive Language Sampling and Clinical Measures in Fragile X Syndrome and Typical Development***. Brain Sci, 2020. 10(2).

63. Royston, R., et al., ***The Profiles and Correlates of Psychopathology in Adolescents and Adults with Williams, Fragile X and Prader-Willi Syndromes***. J Autism Dev Disord, 2020. 50(3): p. 893-903.

64. Heussler, H., et al., ***A phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal cannabidiol (ZYN002) for the treatment of pediatric fragile X syndrome***. J Neurodev Disord, 2019. 11(1): p. 16.

65. Russo-Ponsaran, N.M., et al., ***Feasibility, reproducibility, and clinical validity of the pediatric anxiety rating scale-revised for fragile X syndrome***. Am J Intellect Dev Disabil, 2014. 119(1): p. 1-16.

66. Kim, S.K., et al., ***Assessing treatment efficacy by examining relationships between age groups of children with autism spectrum disorder and clinical anxiety symptoms: Prediction by correspondence analysis***. J Affect Disord, 2020. 265: p. 645-650.

67. Ginsburg, G.S., et al., ***The Utility of Clinicians Ratings of Anxiety Using the Pediatric Anxiety Rating Scale (PARS)***. Child & Youth Care Forum, 2011. 40(2): p. 93-105.

68. Clifford, S., et al., ***Autism spectrum phenotype in males and females with fragile X full mutation and premutation***. J Autism Dev Disord, 2007. 37(4): p. 738-47.

69. Hall, S.S., A.A. Lightbody, and A.L. Reiss, ***Compulsive, self-injurious, and autistic behavior in children and adolescents with fragile X syndrome***. Am J Ment Retard, 2008. 113(1): p. 44-53.

70. Harris, S.W., et al., ***Autism profiles of males with fragile X syndrome***. Am J Ment Retard, 2008. 113(6): p. 427-38.

71. Budimirovic, D.B., et al., ***Autism spectrum disorder in Fragile X syndrome: differential contribution of adaptive socialization and social withdrawal***. Am J Med Genet A, 2006. 140A(17): p. 1814-26.

72. Kaufmann, W.E., et al., ***Autism Spectrum Disorder in Fragile X Syndrome: Cooccurring Conditions and Current Treatment***. Pediatrics, 2017. 139(Suppl 3): p. S194-S206.

73. Boyle, L. and W.E. Kaufmann, ***The behavioral phenotype of FMR1 mutations***. Am J Med Genet C Semin Med Genet, 2010. 154C(4): p. 469-76.

74. Talisa, V.B., et al., ***Autism and anxiety in males with fragile X syndrome: an exploratory analysis of neurobehavioral profiles from a parent survey***. Am J Med Genet A, 2014. 164A(5): p. 1198-203.

75. Lewis, P., et al., ***Cognitive, language and social-cognitive skills of individuals with fragile X syndrome with and without autism***. J Intellect Disabil Res, 2006. 50(Pt 7): p. 532-45.

76. Niu, M., et al., ***Autism Symptoms in Fragile X Syndrome***. J Child Neurol, 2017. 32(10): p. 903-909.

77. Hogan, A.L., et al., ***Autism Spectrum Disorder Symptoms in Infants with Fragile X Syndrome: A Prospective Case Series***. J Autism Dev Disord, 2017. 47(6): p. 1628-1644.

78. Hyman, S.L., et al., ***Identification, Evaluation, and Management of Children With Autism Spectrum Disorder***. Pediatrics, 2020. 145(1).

79. Lord, C.a.R., M., ***Autism Diagnostic Observation Scales-2nd Edition (ADOS-2)***. 2012, Torrance, CA: Western Psychological Services.

80. Cordeiro, L., et al., ***Evaluating Social Interactions Using the Autism Screening Instrument for Education Planning-3rd Edition (ASIEP-3): Interaction Assessment in Children and Adults with Fragile X Syndrome***. Brain Sci, 2020. 10(4).

81. Kidd, S.A., et al., ***Improving the Diagnosis of Autism Spectrum Disorder in Fragile X Syndrome by Adapting the Social Communication Questionnaire and the Social Responsiveness Scale-2***. J Autism Dev Disord, 2019.

82. Bal, V.H., et al., ***The Adapted ADOS: A New Module Set for the Assessment of Minimally Verbal Adolescents and Adults***. J Autism Dev Disord, 2020. 50(3): p. 719-729.

83. Sappok, T., et al., ***Diagnosing autism in a clinical sample of adults with intellectual disabilities: how useful are the ADOS and the ADI-R?*** Res Dev Disabil, 2013. 34(5): p. 1642-55.

84. Thurm, A., et al., ***State of the Field: Differentiating Intellectual Disability From Autism Spectrum Disorder***. Front Psychiatry, 2019. 10: p. 526.

85. Pedersen, A.L., et al., ***DSM Criteria that Best Differentiate Intellectual Disability from Autism Spectrum Disorder***. Child Psychiatry Hum Dev, 2017. 48(4): p. 537-545.

86. Hagerman, R.J. and P.J. Hagerman, ***Fragile X syndrome: diagnosis, treatment, and research***. 2002, Baltimore: Johns Hopkins University Press.

87. Symons, F.J., et al., ***Self-injurious behavior in young boys with fragile X syndrome***. Am J Med Genet A, 2003. 118A(2): p. 115-21.

88. Wheeler, A.C., et al., ***Aggression in fragile X syndrome***. J Intellect Disabil Res, 2016. 60(2): p. 113-25.

89. Rojahn, J., et al., ***The Behavior Problems Inventory: an instrument for the assessment of self-injury, stereotyped behavior, and aggression/destruction in individuals with developmental disabilities***. J Autism Dev Disord, 2001. 31(6): p. 577-88.

90. Reisinger, D.L., et al., ***Delineating Repetitive Behavior Profiles across the Lifespan in Fragile X Syndrome***. Brain Sci, 2020. 10(4).

91. Miller, L.J., et al., ***Electrodermal responses to sensory stimuli in individuals with fragile X syndrome: a preliminary report***. Am J Med Genet, 1999. 83(4): p. 268-79.

92. Aman, M.G., et al., ***The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects***. Am J Ment Defic, 1985. 89(5): p. 485-91.

93. Aman, M.G., et al., ***Psychometric characteristics of the aberrant behavior checklist***. Am J Ment Defic, 1985. 89(5): p. 492-502.

94. Sansone, S.M., et al., ***Psychometric study of the Aberrant Behavior Checklist in Fragile X Syndrome and implications for targeted treatment***. J Autism Dev Disord, 2012. 42(7): p. 1377-92.

95. Henderson, S.E., Sugden, D.A., and Barnett, A., ***Movement Assessment Battery for Children-Second Edition (MABC-2)***. 2007: Pearson Assessments.

96. Mutti, M., Martin, N.A., Sterling, H.M. and Spalding, N.V., ***Quick Neurological Screening Test-Third Edition Revised (QNST-3R)***. 2017: WPS.

97. Budimirovic, D.B., et al., ***Updated report on tools to measure outcomes of clinical trials in fragile X syndrome***. J Neurodev Disord, 2017. 9: p. 14.