Title

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Journal

Biological Psychiatry Cognitive Neuroscience and Neuroimaging, 5(1)

ISSN

2451-9022

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Publication Date

2020

DOI

10.1016/j.bpsc.2019.06.009

Peer reviewed

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2020 January ; 5(1): 10–22. doi:10.1016/j.bpsc.2019.06.009.

COMMON DATA ELEMENTS FOR NATIONAL INSTITUTE OF MENTAL HEALTH FUNDED TRANSLATIONAL EARLY PSYCHOSIS RESEARCH

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Abstract

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Conflict of Interest/Disclosure:
- Dr. Öngür served on a Scientific Advisory Board for Neurocrine Inc. in 12/2016.
- Dr. Tamminga has served as ad hoc consultant within the last 2 years to Sunovion, Astellas, Taisho and Intracellular Therapies; she is on the Clinical Advisory Board of Kynexis.
- The following authors were on the teams that developed some of the specific measures selected by the Working Group: Dr. Gur on the Computerized Neurocognitive Battery, Dr. Carter on the AX-Continuous Performance test and Relational and Item-Specific Encoding task, and Dr. Seidman on the Auditory Continuous Performance Test. In addition, the protocols for obtaining other specific measures have been provided by the following authors: Dr. Carter for functional MRI, and Dr. Öngür for Diffusion Tensor Imaging and Magnetic Resonance Spectrosopy. Note that these latter measures have been developed by large numbers of investigators in the field over decades.
- All other authors report no biomedical financial interests or potential conflicts of interest.

The National Institutes of Health has established the PhenX Toolkit as a web-based resource containing consensus measures freely available to the research community. The National Institute of Mental Health (NIMH) has introduced the Mental Health Research Core Collection as part of the PhenX Toolkit, and recently convened the PhenX Early Psychosis Working Group to generate the PhenX Early Psychosis Specialty Collection (EPSC). The Working Group consisted of two complementary panels for clinical and translational research. Here, we review the process, deliberations, and products of the translational research panel. The EPSC rationale for measure selection as well as additional information and protocols for obtaining each measure are available on the PhenX website (https://www.phenxtoolkit.org). The NIMH strongly encourages investigators to use instruments from the PhenX Mental Health Research Collections in NIMH-funded studies and discourages use of alternative measures to collect similar data without justification. We close by discussing some of the potential advances that can be achieved by collecting common data elements across large-scale longitudinal studies of early psychosis.

Keywords

PhenX; data element; early psychosis; schizophrenia; cognition; neuroimaging

BACKGROUND

The field of early intervention in psychiatry has seen an explosion of interest and activity in the past decade, as evidenced by the introduction of novel research and treatment approaches, a thriving international association, as well as the formation of journals devoted to the topic. The subspecialty field of psychotic disorders has benefited from and contributed to these developments. Expansion of early psychosis research and treatment has been accompanied by a growing diversity of tools and approaches. This diversity has created a challenge for effective communication between workers in the field and for progress in translational research that can provide novel insights into disease pathophysiology and provide leads for treatment development.

Psychiatry is not alone in this predicament; similar challenges have arisen in other fields of medicine. To address problems of standardization and communication in GWAS studies in particular, the National Human Genome Research Institute established the PhenX (consensus measures for **Phen**otypes and e**X**posures) Toolkit. The Toolkit is a web-based resource containing consensus measures freely available to the biomedical research community at (https://www.phenxtoolkit.org) (1). As part of the PhenX Toolkit, the NIMH introduced the Mental Health Research Core Collection for use in psychiatry research (2) and subsequently unveiled Specialty Collections in specific areas of research within psychiatry (see NOT-MH-15–009 and NOT-MH-15–031). The NIMH strongly encourages investigators to use instruments from the PhenX Mental Health Research Collections in NIMH-funded studies and discourages use of alternative measures to collect similar data without specific justification. Standard measures should foster measurement-based care as well as quality improvement efforts using aggregated data (3).

PHENX EARLY PSYCHOSIS SPECIALTY COLLECTION

Given the developments in the field of early intervention in psychiatry, the NIMH decided to add early psychosis research and clinical care to its growing list of Specialty Collections. The PhenX Early Psychosis Working Group was convened in early 2016 with the purpose of developing this collection. Members of the Working Group were selected based on the recommendations of the NIMH Project Scientists and their colleagues. An effort was made to have the combined expertise of working group members cover the scope of the domain, as well as provide diversity, e.g. regarding geography and institutions. Each had to commit their time to the effort, and demonstrated a willingness to contribute to a consensus-based effort. The working group included an individual with lived experience. In order to address the scope of the Early Psychosis domain, two complementary sub-panels focused on translational and clinical aspects. The entire Working Group first met together to develop a roadmap. This was followed by the two sub-panels meeting separately to develop their recommendations, and finally by a meeting of the entire Working Group to discuss all aspects of the work and to make joint final recommendations. The PhenX consensus process is described elsewhere (1). The charge for the Working Group was relatively narrow: selecting measures that can be used in research. We did not focus on other potential ways to improve early psychosis research, for example by providing a consensus definition of first episode psychosis itself. The process also included an outreach step subsequent to the Working Group meeting during which the preliminary list of measures was presented to research community for feedback and comment to strive for adequate representation of a diversity of views.

The measures included in the PhenX Early Psychosis Specialty Collection (EPSC) are listed in Table 1. The measures are organized roughly along a translational/clinical dichotomy where the first 7 measures listed are considered translational. Note that some measures cross this divide and provide relevant information in both contexts. The rationale for measure selection, additional information on the measure, and protocols for obtaining the measure are described on the PhenX website.

SPECIFIC CONSIDERATIONS FOR TRANSLATIONAL MEASURES

In the remainder of this article, we expand on the adoption of the translational research measures included in the EPSC. In a related contribution, Dixon and colleagues describe in greater detail the process for adoption of the collection’s clinical measures (4). These communications are intended to report on the work of the Early Psychosis Working Group to inform the early psychosis research and clinical community and to raise awareness regarding the availability of this resource. They do not provide a detailed discussion of how each measure was selected, or of scientific progress in this domain.

Historically, a rate limiting factor for many translational early psychosis research programs has been the difficulty in acquiring adequate samples for well-powered studies (see (5) for discussion). It takes long periods for single-site projects to enroll enough participants and methodological variations can create barriers to comparing findings or sharing data among laboratories. The PhenX EPSC addresses these limitations in a number of ways. For

example, the collection identifies several scientifically noteworthy measures that could be collected across all NIMH-funded early psychosis research clinics, thereby generating many thousands of data points each year. In our selections, we emphasized ease of implementation since we want as many clinics as possible to collect data along these lines. But data collection will inevitably take place in a research context, and not incorporated into clinical care workflows. These data will be stored in the NIMH Data Archive, harmonized, and made freely available to the scientific community for mega-analyses. Collecting and sharing research data in this manner will create new opportunities for collaborative science, and exciting possibilities for answering important questions in a timely and definitive manner.

The EPSC is not intended to solve scientific problems *per se*, but rather to standardize and improve the comparability of research data across the field. Representative topics that could be addressed with EPSC measures include: (1) large-scale psychometric projects to establish early psychosis population norms on translational measures; (2) collaborative neuroscience studies to chart cognitive function in early psychosis; (3) multi-site imaging research to explore relationships between symptom presentation and integrity of large-scale neuronal networks in the brain; and (4) efforts to examine the role of neuroinflammation in the pathophysiology of psychotic disorders. These measures are intended to be collected in well over one hundred coordinated specialty care clinics around the country where early psychosis patients are receiving care, as well as future EPINET clinics supported by NIMH. Thus, standardized data collection could be leveraged for longitudinal studies on the association of translational measures with clinical trajectories and treatment response. The assembly of longitudinal clinical and translational data obtained from a thousand or more individuals receiving care in such clinics each year would allow investigators to carry out analyses that have thus far remained out of reach. The value of such longitudinal multi-site studies has already been demonstrated in at-risk syndromes where cognitive profiles of at-risk individuals who convert to psychotic illness were defined (6, 7) and a calculator for risk of conversion to frank psychosis was developed (8).

With these opportunities in mind, the Translational Research panel identified several constructs for inclusion in the EPSC. The discussions focused on assessments of cognitive function, brain imaging modalities, and biochemical measures relevant to pathophysiology. For each construct, we considered protocols used by investigators in the field and evaluated each protocol from the point of view of scientific content, psychometric characteristics, ease of adoption, and likelihood of consistent implementation across research centers. In addition to a detailed description of how to collect the data, the protocol provides additional information, such as rationale, source, and specific instructions to enable Toolkit measures to effectively and consistently implement the measures across sites. In several instances, attractive instruments were found in other PhenX Toolkit Specialty Collections and Research Domains, e.g., the Assay for Cytokine Panel 12 that was added to the Toolkit by the Infectious Disease and Immunity domain work group (9). Measures included in the EPSC complement the existing content of the PhenX Toolkit. We encourage readers who notice gaps in topics covered by the EPSC to search the Toolkit more broadly as those constructs may be associated with a different research domain or specialty collection.

Cognitive Assessment

Cognitive impairment is common in psychotic disorders, can precede the onset of psychosis, and is strongly associated with adverse community functioning outcomes (10). The Working Group devoted significant attention to selecting common data elements for cognition research. A “global” cognitive measure was included (Measure #1) as well as theoretically motivated measures from cognitive neuroscience that probe specific, circuit-based cognitive functions. For the former, we selected a battery that is comprehensive, easily administered, and scalable in a variety of settings, including in digital format (11). This battery is available in the public domain and is based on functional neuroimaging studies (12). It has been applied across many settings and the “game like” tests are well tolerated across the age range of childhood to late adulthood (13). The total battery currently takes about one hour but covers the main domains of cognition including executive functions, episodic memory, complex cognition, social cognition and sensorimotor speed (14). Its modularity allows sampling of specific domains and repeated administrations (15). In addition, normative CNB data are available for males and females with different levels of education and from diverse populations. It has been translated to multiple languages and can be administered through remote connection on the web as well as in real-world settings including the military and resource limited hospitals and clinics globally (16). The development of the CNB and early applications have focused on early psychosis and psychosis risk. Furthermore, the CNB measures have established heritability in studies of schizophrenia spectrum disorders (17, 18). For the latter, we selected three measures (Measures #2–4). The context processing (AX CPT/DPX) and relational encoding and retrieval (RiSE) tasks engage frontal-parietal cognitive control and episodic memory related frontal-hippocampal circuitry, respectively (19, 20). We selected these tasks because impairments in cognitive control and episodic memory are core deficits in psychotic disorders, are present at or prior to the onset of psychotic illness, persist throughout the lifespan, and are also present in high risk groups, including first-degree relatives. Cognitive control is domain general and relevant for a broad range of cognitive deficits in psychosis, and in some cases for altered emotion processing as well (21, 22).

Both the AX CPT and RiSE were selected based upon recommendations of previous working groups including CNTRICS (23, 24). This initiative involved 7 meetings conducted over a 5-year period and was supported by an R13 from the NIMH. A diverse group of over 200 attendees from industry, academia (including basic cognitive neuroscientists and clinical investigators), and government participated in a consensus building process to identify constructs and paradigms to be targeted for development as biomarkers. Selection of paradigms for development as cognitive and imaging biomarkers was based upon rigorous objective criteria, including construct validity, sensitivity to deficits in schizophrenia, links to known neural systems and psychometrics and tolerability. The AX CPT was recommended as both a cognitive and imaging paradigm as reported in peer-reviewed publications (20, 25). In addition to being informed by the CNTRICS process, the AX CPT has undergone extensive optimization (for standardization of administration, length of task and subject tolerability), psychometric characterization and optimization and linkage to symptoms and functional measures over a 20-year period including most recently through the 5-site CNTRACS consortium. No other cognitive control task or imaging biomarker has

had the level of optimization for clinical research and this was the basis of its selection as a recommended behavioral and fMRI biomarker for the cognitive control construct. The AX CPT task has been downloaded from the CNTRACS web site by 156 labs across the world, both university and industry based (26, 27).

With regard to the AX CPT, both the letter and DPX version of the task are recommended as they are cognitively and functionally equivalent. The CNTRCS consortium validated the equivalence of these measures in a multisite fMRI study. This task engages frontal parietal networks supporting the goal maintenance function necessary for proactive cognitive control, a superordinate cognitive control system that regulates many other cognitive and emotional processing systems in the brain. Behavioral measures of AX CPT performance correlate with disorganization symptoms and impaired functioning, as does activation and functional connectivity of the dorsolateral prefrontal cortex during performance of the task. In schizophrenia patients, impairment on this task and altered DLPFC function are present at or prior to the onset of the illness, and remain as fixed deficits across various stages of the illness (28–32).

The RiSe task was designed by cognitive neuroscientists and schizophrenia researchers to isolate component processes of long term memory related to dissociable components of episodic memory encoding and retrieval that are linked to distinct frontal-medial temporal networks that are differentially affected in schizophrenia. It was identified as a promising measure through the CNTRICS consensus building process. It has undergone extensive development, validation and psychometric characterization via the CNTRACS consortium (33).

The third cognitive measure, auditory vigilance and working memory, has also proven sensitive to impairments in persons at clinical and familial risk for schizophrenia, and schizotypal personality disorder as well as in schizophrenia, allowing an analysis of cognitive competence or vulnerability at different loads, while also tapping into the fronto-parietal circuitry implicated in psychotic disorders (6, 34, 35). Complete longitudinal datasets from large numbers of early psychosis patients using these cognitive assessments will enable investigators to obtain new insights into the neurobiological evolution of psychotic disorders, the heterogeneity of cognitive function across patient populations, and how cognitive function early in illness is related to subsequent community outcomes. There have been promising advances in understanding the role of cognition in the evolution of illness from smaller single-site studies (36, 37) but we await definitive studies.

With regard to the cognitive assessments, as well as some of the other proposed measures, we note that not all early psychosis clinic sites will be able to collect all measures. In fact, we expect that the translational measures will most likely be collected at more research-oriented sites where there are resources and expertise for more complex procedures. The CNTRACS tasks were optimized for length of administration and subject tolerability. The CNTRACS consortium obtained formal tolerability ratings from a large sample of patients and controls for the experimental tasks that it developed as well as the MATRICS battery. Tolerability for the AX CPT and the RiSe were comparable to those of the MATRICS (27).

Neuroimaging

Among brain imaging modalities, we selected both anatomical and functional MRI measures (Measures #5 and 7, respectively). The oldest of in vivo neuroimaging modalities to be implemented in psychosis research, anatomical (or structural) imaging has uncovered significant brain pathology including reduced brain volume, enlarged cerebral ventricles, cortical thinning, and reduced hippocampal volume (38). Anatomical brain MRI measures are routinely implemented in all clinical MRI systems and multi-site studies are now commonplace in the field. Despite this wide availability, first episode psychosis research in this domain largely consists of single site studies with modest sample sizes, leading to concern for potential Type I error and poor generalizability. Therefore, broad implementation of standardized anatomical MRI imaging as a common data element across early psychosis clinics in the US can be transformative. Anatomical brain MRI data have been used to predict diagnostic (39), cognitive (40), and social outcomes (41) but systematic joint assessment of these issues in samples with good generalizability are lacking.

We also selected functional MRI (fMRI), a measure that has been a standard tool in use in cognitive and systems neuroscience for over 20 years. Functional MRI relies on measurement of the BOLD signal, which is coupled with neuronal activity and therefore provides a window onto brain function. Resting state fMRI captures brain activity in the absence of specific cognitive activity and is widely used for identification of large-scale neuronal networks consisting of brain regions with coupled activity profiles. Task fMRI, by contrast, provides unique data regarding activity and connectivity in discrete brain circuitry in relationship to individual differences in specific cognitive systems. Established methods exist for combining data in these modalities across sites, including those developed by the NIH-funded FBIRN consortium and further modified by the CNTRACS consortium (42). Functional MRI research has transformed the field of biological psychiatry over the past two decades (e.g.(43, 44). Although early psychosis research should have benefited as well and there is at least one ongoing multi-site early psychosis project that includes fMRI (45), the field has not reaped the benefits as much as it should. To maximize the impact of task fMRI in this battery, we selected tasks that were also used in the cognitive assessments. In settings where task fMRI is available, the participant can undergo the overlapping cognitive assessments only once in the scanner. In settings where task fMRI is not available, the cognitive assessments can be completed offline.

For both anatomical and functional MRI, harmonizing data collected across a large number of sites without sufficient technical expertise can be a challenge. The Working Group felt that it was still desirable to include these modalities in the EPSC for two reasons: sufficient progress has been made for both modalities such that multi-site studies are now commonplace; and the potential scientific utility of the data to be collected in a large sample of early psychosis patients is highly significant.

Biochemical Assays

Among biochemical measures, the C-reactive protein (CRP) in serum was included as part of the EPSC. CRP is a commonly used biomarker of inflammation and tissue damage. Elevated levels are common among people with chronic inflammatory conditions, but it is

also useful to measure an acute response. CRP is a nonspecific indicator but is of interest because of indications that peripheral markers of immune activation and inflammation may be predictive of a psychotic event (46).

Supplemental Information

The Translational Research panel considered additional constructs such as white matter integrity, chemical brain imaging, resting state and evoked brain electrophysiology and the glutathione serum biochemical measure in its deliberations. We concluded that measures for these constructs require a significant degree of expertise and access to specialized resources and equipment, and they are therefore not appropriate at this time for inclusion in the EPSC. Future advances and analyses may allow expansion in these directions. Nonetheless, these measures provide substantial scientific value if implemented in specialty research clinics. Therefore, these measures are included in the Supplemental Information portion of the collection (see Table 1) and would be considered valuable elements of any translational early psychosis dataset.

DISCUSSION

The translational segment of the EPSC provides a platform for the accrual of large longitudinal datasets using appropriate translational measures to support early psychosis research. These datasets will be collected and harmonized within the NIMH Data Archive and made broadly available to the scientific community. Ultimately, this effort will permit definitive well-powered analyses addressing major scientific questions in early psychosis research. We will discuss three potential examples here.

First, trajectories of recovery from a first episode of psychosis are diverse. Overall rates of symptomatic and functional recovery are higher than what might be expected from clinical experience, but only a minority of patients recover and the odds are by no means encouraging (47–51). Multiple groups have examined predictors of recovery in clinical cohorts they follow. The typical prediction study relies on measurement of a series of baseline variables and examination of symptomatic and functional improvements over time using multivariate analyses or hypothesis-driven analyses of specific baseline variables. Some highlight the role of positive and negative symptoms of psychosis in predicting subsequent recovery, especially if symptom reduction is sustained for some time (52, 53). Others find a mixture of symptom and neurocognitive function effects on recovery (54). The role of demographic variables such as age and gender has been debated with evidence both pro (55) and con (56). One review of seventy-five studies of early onset psychosis found that the most replicated predictors of outcome were premorbid difficulties, duration of untreated psychosis, and severity of negative symptoms at baseline (56). Thus, study of the most easily accessible clinical and demographic factors has provided modest return, not sufficient for use in meaningful clinical prediction. Biological predictors of outcome, requiring greater participant and investigator commitment and cost, have been studied much less intensively, and none have been replicated. There is debate about their utility (57). Studies to date have had low to moderate success in predicting outcome in FEP, usually explaining between a quarter and half of the variance (53, 57–60). Almost all studies to date have examined

relatively low number of patients (often 100 or lower) typically in single centers, a particular problem when many variables are being collected and analyzed. Some have advocated for development of models based on time-varying multimodal data to predict trajectories following a FEP (61) but this approach has not been fully deployed to date. The PhenX EPSC provides a platform that can elevate prediction research in early psychosis. The products of this line of research have immediate clinical import, since clinicians can use prediction tools to deploy scarce resources where they are most needed (with future poor outcome patients).

Second, early psychosis patients have variable treatment response. Patients with first episode psychosis respond well to one or another of commonly deployed treatment modalities such as antipsychotic medications, cognitive behavioral therapy for psychosis, cognitive remediation, or even electroconvulsive therapy. Randomized clinical trials (62) and naturalistic studies (63) often highlight this heterogeneity in treatment response. It is reasonable to assume that measurable patient-specific factors must underlie this heterogeneity but these factors have not yet been uncovered. Note that treatment response is to some extent related to long-term outcomes as discussed above. There is likely to be overlap in the mechanisms of treatment response and community functioning. However, there is value in differentiating the two concepts because patient response to antipsychotic medication is not a good predictor of long-term functional outcomes (42). Standardized multimodal longitudinal data collection in large numbers of patients using the PhenX EPSC will facilitate studies of treatment response heterogeneity. This approach would ultimately provide algorithms of treatment selection based on translational measures obtained at baseline.

Third, large standardized datasets with cognitive, imaging, and CRP data that can be generated using the EPSC would also facilitate a deeper understanding of the disease process and outcome trajectories. In other words, these datasets may offer valuable mechanistic insights that are not easily available from smaller single-site studies. Such datasets would also permit the field to apply state-of-the-art computational analytic methods that may open new avenues of discovery. This optimism can be tempered by the possibility of selection bias: the poor outcome patients whose data would be the most valuable may also be the ones who refuse to participate in data collection in research studies.

In addition to these sample research questions, a potential benefit of the EPSC is to improve communication and collaboration between translational researchers and community-based clinics that offer specialized care for persons with early psychosis. Common approaches for defining cases, assessing moderators, and measuring outcomes could facilitate new opportunities for practice-based research, potentially bringing many thousands of service users and family members into studies that address questions of common interest.

Conclusions

There is great unmet need for improving outcomes in psychotic disorders. The early phase of psychosis is a critical period for making a positive impact on patient trajectories. Recent developments in research and clinical care delivery in early psychosis point to a promising

future. We hope that the PhenX EPSC will provide a vital new set of tools that will assist the early psychosis research and clinical care communities in this mission.

Acknowledgments

Funding for the PhenX Toolkit was provided by National Institutes of Health, National Human Genome Research Institute (via Cooperative Agreement U41 HG007050) with co-funding from the National Institute on Drug Abuse. The Early Psychosis Administrative Supplement to the PhenX U41 was supported with funding from the National Institute of Mental Health (3U41HG007050-03S1).

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Table 1.

Early Psychosis Measures for the PhenX Toolkit

Measure	Age Range	Description of Protocol	Source	Completion Time (min)	Healthy Norms
1. Global Cognitive Functioning	**Ages 8 & older**	The Computerized Neurocognitive Battery (CNB) is a series of tests developed at the University of Pennsylvania and used in neuroimaging studies that are formatted like computer games and puzzles and that are administered by study investigators in a specific order using clickable icons on a computer. Test results are uploaded to a data repository via an automated script. Results are scored by a program and evaluated by a neuropsychologist.	Gur, R. C., Richard J., Hughett, P., Calkins, M. E., Macy, L., Bilker, W. B.,… Gur, R. E. (2010). A cognitive neuroscience based computerized battery for efficient measurement of individual differences: Standardization and initial construct validation. Journal of Neuroscience Methods, 187(2), 254–262. (11)	60	Y
2. Context Processing	**Ages 18 & older**	The AX-Continuous Performance Test (AX-CPT) is a computerized test, implemented in Eprime by the Cognitive Neuroscience Test Reliability and Clinical applications for Schizophrenia (CNTRACS) consortium that evaluates goal maintenance in working memory. During AX-CPT, the subject views a series of cues and probe sequences (one at a time) and performs a button press indicating if the stimulus is the target or non-target.	MacDonald, A. W., III, Pogue-Geile, M. F., Johnson, M. K., &Carter, C. S. (2003). A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. Archives of General Psychiatry, 60(1), 57–65. (64)	<15	Y
3. Relational Encoding and Retrieval	**Ages 18 & older**	The Relational and Item-Specific Encoding Task (RiSE) is a computerized test, developed in Eprime by the Cognitive Neuroscience Test Reliability and Clinical applications for Schizophrenia (CNTRACS) consortium that evaluates item-specific encoding and relational encoding. The subject views visual objects (pictures) and responds yes/no to whether the objects are “living” (item-specific encoding).	Ragland, J. D., Ranganath, C., Barch, D. M., Gold, J. M., Haley, B., MacDonald, A. W., III, Silverstein, S. M., Strauss, M. E., Yonelinas, A. P., & Carter, C. S. (2012). Relational and Item-Specific Encoding (RISE): Task Development and psychometric characteristics. Schizophrenia Bulletin, 38(1), 114–124. (19)	<20	Y
4. Auditory Vigilance	**Ages 12 & older**	The Auditory Continuous Performance Test (ACPT) battery is a compilation of four auditory vigilance tests designed to measure the cognitive functions of working memory and interference control. Each subsequent version increases the cognitive load on the subject, allowing the investigator to ascertain processing susceptibilities. The tests are administered and scored using a computer.	Seidman, L. J., Meyer, E. C., Giuliano, A. J., Breiter, H. C., Goldstein, J. M., Kremen, W. S.,… Faraone, S. V. (2012). Auditory working memory impairments in individuals at familial high risk for schizophrenia. Neuropsychology, 26(3), 288–303. (35)	<15	Y
5. Brain Anatomical Imaging	**Ages 12 & older**	The Three-Dimensional (3D) Magnetization-Prepared RApid Gradient Echo (MP-RAGE) is an image that captures the high tissue contrast in the brain and provides high spatial resolution of the whole brain in a short scan time. Images collected with the sequence are used to detect pathological changes of the brain, estimate regional brain volume abnormalities associated with brain functions, assess brain development, and evaluate treatment or therapeutic responses.	Han, X., Jovicich, J., Salat, D., Kouwe, A. V., Quinn, B., Czanner, S.,… Fischl, B. (2006). Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer. *NeuroImage, 32*(1), 180–194. (65)	6:03	Y
6. C-Reactive Protein in Serum	**Ages 3 & older**	This protocol details technical and analytical procedures for the quantification of C-reactive protein (CRP) from serum. It includes the application of mouse monoclonal anti-CRP antibody-bound polystyrene particles to a diluted serum sample. CRP in the sample forms an antigenantibody complex with the latex particles that are then quantified by measuring light scatter in a nephelometer. CRP concentrations are calculated using a calibration curve.	National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes/index.htm)	1	Y
7. Brain Activation and Connectivity	**Ages 12 & older**	This protocol recommends technical and analytical procedures for the collection of task functional magnetic resonance imaging (fMRI) data based on methods for assessment during cognitive functioning testing. These procedures include key MRI acquisition parameters, critical elements of data preprocessing, and interpretational issues.	Ragland, J. D., Ranganath, C., Harms, M. P, Barch, D. M., Gold, J. M., Layher, E.,… Carter, C. S. (2015). Functional and neuroanatomic specificity of episodic memory dysfunction in schizophrenia: A functional magnetic resonance	6	Y

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Measure	Age Range	Description of Protocol	Source	Completion Time (min)	Healthy Norms
			imaging study of the relational and item-specific encoding task. JAMA Psychiatry, 72(9), 909–916. (42)		
8. Family History of Mental Illness	**Ages 18 & older**	The Family Interview for Genetic Studies (FIGS) was developed through the National Institute of Mental Health (NIMH) Schizophrenia and Bipolar Disorder Genetics Initiatives and with the help of NIMH extramural program staff. FIGS is a tool used by a trained interviewer to collect information about biological relatives of the subject who has a mental disorder. The interview is conducted with the relatives themselves and not through the subject.	National Institute of Mental Health (NIMH), Center for Collaborative Genomics Research on Mental Disorders. (1999, February 11). Family Interview for Genetic Studies (FIGS). St. Louis. MO: Department of Psychiatry, Washington University School of Medicine. (https://www.nimhgenetics.org/interviews/figs/)		
	Ages 18 & older	This abbreviated version of the FIGS includes only a Symptom Checklist for psychosis.	National Institute of Mental Health (NIMH), Center for Collaborative Genomics Research on Mental Disorders. (1999, February 11). Family Interview for Genetic Studies (FIGS). St. Louis. MO: Department of Psychiatry, Washington University School of Medicine. (https://www.nimhgenetics.org/interviews/figs/)		
9. Premorbid Adjustment in Psychosis	**Ages 11 & older**	The Modified Cannon-Spoor Premorbid Adjustment Scale (PAS) is an interviewer-administered rating scale that assesses functioning levels in four major areas of the subject's life: social accessibility-isolation, peer relationships, ability to function outside the nuclear family, and capacity to form intimate socio-sexual ties. The scale is divided into four life periods and includes a scoring guide.	van Mastrigt, S., & Addington, J. (2002). Assessment of premorbid function in first-episode schizophrenia: Modifications to the Premorbid Adjustment Scale. Journal of Psychiatry and Neuroscience, 27(2), 92–101. (66)		
10. Psychiatric Symptoms - Frequency	**Ages 18 & older**	The modified Colorado Symptom Index (CSI) is a 14-item, self-report scale designed to assess frequency of positive mood and cognitive symptoms. Items are rated on a 5-point Likert-style scale (Not at all, Once during the month, Several times during the month, Several times a week, at least every day). Each item is scored on a 0–4 scale (not at all = 0; at least every day = 4) and added together to give a score between 0 and 56, with higher scores indicating greater emotional distress.	Conrad, K. J., Yagelka, J. R., Matters, M. D., Rich, A. R., Williams, V., & Buchanan, M. (2001). Reliability and validity of a modified Colorado Symptom Index in a national homeless sample. Mental Health Services Research, 3(3), 141–153. (67)		
11. Global Psychopathology Rating Scale	**Ages 18 & older**	The Brief Psychiatric Rating Scale (BPRS) is a clinician-administered rating scale for assessing the positive, negative, and affective symptoms of individuals who have psychotic disorders, especially schizophrenia. The version of the BPRS included here only includes the 18 items associated with positive symptoms, negative symptoms, and mood. For each item, the rater enters a number ranging from 1 (not present) to 7 (extremely severe). The BPRS is scored by adding together the scores from the individual items, with higher scores indicating more severe pathology.	Ventura, J., Lukoff, D., Nuechterlein, K. H., Liberman, R. P., Green, M., & Shaner, A. (1993). Appendix 1: Brief Psychiatric Rating Scale (BPRS) Expanded version (4.0) scales, anchor points and administration manual. International Journal of Methods in Psychiatric Research, 3, 227–244. (68)		
	Ages 18 & older	**The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia is a 30-item interviewer-administered questionnaire. The PANSS includes 7 positive symptoms (delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness/persecution, and hostility), 7 negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking) and 16 general psychopathology items (somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor**	Kay SR, Fiszbein A, Opler LA. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin, 13(2), 261–276. (69)		

Measure	Age Range	Description of Protocol	Source	Completion Time (min)	Healthy Norms
		impulse control, preoccupation, and active social avoidance). Each item is rated on a 7-point scale (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate-severe, 6=severe, 7=extreme) that captures psychopathology in the past week. All items include full definitions and detailed anchoring criteria for all seven rating points.			
12. Psychosis Recovery Assessment	**Ages 18 & older**	The Questionnaire about the Process of Recovery (QPR) is a 15-item, self-administered rating scale that captures a patient's viewpoint about recovery from psychosis. The QPR should be completed in proximity to another professional or person to discuss any questions or issues. Each item is rated on a 5-point scale (0 = disagree strongly, 1 = disagree, 2 = neither agree nor disagree, 3 = agree, 4 = agree strongly), and items are added together to give a total recovery score, with higher scores indicating greater recovery.	Neil, S. T., Kilbride, M., Pitt, L., Nothard, S., Welford, M., Sellwood, W., & Morrison, A. P. (2009). The Questionnaire about the Process of Recovery (QPR): A measurement tool developed in collaboration with service users. Psychosis: Psychological, Social and Integrative Approaches, 1(2), 145–155. (70)		
13. Social and Role Dysfunction in Psychosis and Schizophrenia	**Ages 18 & older**	Global Functioning: Social and Global Functioning: Role scales are seven social-scale prompts and four-item clinician-administered interviews that include detailed anchors for prodromal problems relevant for the typical age range for the prodromal phase. Each question is scored on a 10-point scale (10 = superior function; 1 = extreme dysfunction) and captures current functioning, lowest functioning over the past year, and highest functioning over the past year. Example prompts/questions are included.	Cornblatt, B. A., Auther, A. M., Niendam, T., Smith, C. W., Zinberg, J., Bearden, C. E., & Cannon, T. D. (2007). Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. Schizophrenia Bulletin, 33(3), 688–702. (71)		
14. Personal Wellbeing	**Ages 18 & older**	The Personal Wellbeing Index-Adult (PWI-A) is a seven-item, self-administered scale that measures satisfaction with the following life domains: standard of living, health, life achievement, personal relationships, personal safety, community connectedness, and future security. Each item is rated on a 0-to-10 scale (0 = No satisfaction at all; 10 = Very satisfied). Items can be scored individually to derive a score for the corresponding domain, or all the scores for all items can be summed and averaged to form the Personal Wellbeing Index (PWI).	International Wellbeing Group (2013). Personal Wellbeing Index (5th Ed.). Melbourne, Australia: Australian Centre on Quality of Life, Deakin University. (72)		
	Ages 11–20	The Personal Wellbeing Index-School Children (PWI-SC) is a self-administered scale that includes seven items of happiness corresponding to seven life domains: standard of living, health, life achievement, personal relationships, personal safety, community connectedness, and future security. Each item is rated on a 0-to-10 scale (0 = Very Sad; 10 = Very Happy). Items can be scored individually to derive a score for the corresponding domain or all the scores for all items can be summed and averaged to form the Personal Wellbeing Index (PWI). To create scores that can be compared with one another, the ratings can be converted to a 0-to-100 scale by shifting the decimal point one place to the right (e.g., a score of 6.5 becomes 65%).	International Wellbeing Group (2013). Personal Wellbeing Index (5th Ed.). Melbourne, Australia: Australian Centre on Quality of Life, Deakin University. (72)		
15. Mental Health Services Satisfaction	**Ages 13–18**	The Mental Health Statistics Improvement Program (MHSIP) Youth Services Survey (YSS) is a 25-item, self-administered rating scale that captures a patient's viewpoint about service satisfaction. The YSS should be completed in proximity to another professional or person to discuss any questions or issues. Each item is rated on a 5-point scale (1 = Strongly Disagree, 2 = Disagree, 3 = Undecided, Agree = 4, Strongly Agree = 5). Ratings from the individual items can be added together to yield a total score, with higher scores indicating greater satisfaction.	Brunk, M., Koch, J. R., & McCall, B. (2000). Report on parent satisfaction with services at community services boards. Richmond, VA: Virginia Department of Mental Health, Mental Retardation, and Substance Abuse Services. (73)		
16. Perception of Recovery Orientation and Care Quality of	**Ages 18 & older**	The Recovery Self-Assessment (RSA) administrator/manager version is a 36-item, provider-completed rating scale that focuses on perceptions of recovery principles and overall quality of services, including determination, staff helpfulness, and staff responsiveness. The RSA includes six subscales: life	O'Connell, M., Tondora, J., Croog, G., Evans, A., & Davidson, L. (2005). From rhetoric to routine: Assessing perceptions of recovery-oriented practices in a state mental health and addiction		

Measure	Age Range	Description of Protocol	Source	Completion Time (min)	Healthy Norms
Mental Health Services		goals, consumer involvement, diversity of treatment options, consumer choice, individually tailored services, and inviting environment. Each item is rated on a 5-point scale (1 = Strongly Disagree; 5 = Strongly Agree). Ratings from the individual items can be added together to yield a total score, with the higher scores indicating greater quality care.	system. Psychiatric Rehabilitation Journal, 28(4), 378–386. (74)		
	Ages 18 & older	The Recovery Self-Assessment (RSA) family member/significant other version is a 40-item, proxy-administered rating scale that focuses on perceptions of recovery principles and overall quality of services, including determination, staff helpfulness, and staff responsiveness. The RSA includes six subscales: life goals, consumer involvement, diversity of treatment options, consumer choice, individually tailored services, and inviting environment. Each item is rated on a 5-point scale (1 = Strongly Disagree; 5 = Strongly Agree). Ratings from the individual items can be added together to yield a total score, with the higher scores indicating greater quality care.	O'Connell, M., Tondora, J., Croog, G., Evans, A., & Davidson, L. (2005). From rhetoric to routine: Assessing perceptions of recovery-oriented practices in a state mental health and addiction system. Psychiatric Rehabilitation Journal, 28(4), 378–386. (74)		
	Ages 18 & older	The Recovery Self-Assessment (RSA) is a 32-item, self-administered rating scale that focuses on perceptions of recovery principles and overall quality of services, including determination, staff helpfulness, and staff responsiveness. The RSA includes six subscales: life goals, consumer involvement, diversity of treatment options, consumer choice, individually tailored services, and inviting environment. Each item is rated on a 5-point scale (1 = Strongly Disagree; 5 = Strongly Agree). Ratings from the individual items can be added together to yield a total score, with the higher scores indicating greater quality care.	O'Connell, M., Tondora, J., Croog, G., Evans, A., & Davidson, L. (2005). From rhetoric to routine: Assessing perceptions of recovery-oriented practices in a state mental health and addiction system. Psychiatric Rehabilitation Journal, 28(4), 378–386. (74)		
	Ages 18 & older	The Recovery Self-Assessment (RSA) provider version is a 32-item, provider-completed rating scale that focuses on perceptions of recovery principles and overall quality of services, including determination, staff helpfulness, and staff responsiveness. The RSA includes six subscales: life goals, consumer involvement, diversity of treatment options, consumer choice, individually tailored services, and inviting environment. Each item is rated on a 5-point scale (1 = Strongly Disagree; 5 = Strongly Agree). Ratings from the individual items can be added together to yield a total score, with the higher scores indicating greater quality care.	O'Connell, M., Tondora, J., Croog, G., Evans, A., & Davidson, L. (2005). From rhetoric to routine: Assessing perceptions of recovery-oriented practices in a state mental health and addiction system. Psychiatric Rehabilitation Journal, 28(4), 378–386. (74)		
17. Antipsychotic Medication Extrapyramidal Side Effects	**Ages 18 & older**	The Extrapyramidal Symptom Rating Scale (ESRS) is a clinician-administered rating scale that includes four subscales and four Clinical Global Impression Severity (CGI-S) scales. The four subscales include drug-induced movement disorders (12-item questionnaire rated on a 4-point scale), parkinsonism and akathisia (seven-item examination rated on a 7-point scale), dystonia (10-item examination rated on a 7-point scale), and dyskinesia (seven-item examination rated on a 7-point scale). The four clinical global impression severity scales capture tardive dyskinesia, parkinsonism, dystonia, and akathisia and are rated according to the clinician's experience using an 8-point rating scale.	Chouinard, G., & Margolese, H. C. (2005). Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophrenia Research, 76(2–3), 247–265. (75)		
18. Multi-dimensional Assessment of Antipsychotic Medication Side Effects	**Ages 18 & older**	The Glasgow Antipsychotic Side-effect Scale (GASS) is a 22-item, self-administered checklist that captures a patient's viewpoint about suffering from excessive side effects from the antipsychotic medication. Questions 1–20 relate to the previous week, and questions 21–22 relate to the last 3 months. For questions 1–20, "never" = 0 points, "once" = 1 points, "a few times" = 2 points, and "every day" = 3 points. For questions 21–22, "yes" = 3 points and "no" = 0 points. All items are added together to give a total score, and higher scores reflect more frequent experience of side effects.	Waddell, L., & Taylor, M. (2008). A new self-rating scale for detecting atypical or second-generation antipsychotic side effects. Journal of Psychopharmacology, 22(3), 238–243. (76)		

Measure	Age Range	Description of Protocol	Source	Completion Time (min)	Healthy Norms
19. Antipsychotic Medication Adherence	**Ages 18 & older**	The Brief Adherence Rating Scale (BARS) is a four-item, clinician-administered rating scale that captures a patient's intake of the antipsychotic medications.	Byerly, M. J., Nakonezny, P. A., & Rush, A. J. (2008). The Brief Adherence Rating Scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder. Schizophrenia Research, 100, 60–69. (77)		
20. Physical Activity	**Ages 15 & older**	The International Physical Activity Questionnaire (IPAQ) is a seven-item, self-administered questionnaire that captures a subject's physical activity over the last seven days.	Lee. P. H., Macfarlane, D. J., Lam, T. H., & Stewart, S. M. (2011). Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): A systematic review. International Journal of Behavioral Nutrition and Physical Activity, 8, 115. (78)		
21. Family Expressed Emotion Toward Relatives with Psychosis and Schizophrenia	**Ages 18 & older**	The Family Questionnaire (FQ) is a 20-item, self-administered questionnaire that measures expressed emotion status (criticism and emotional over involvement [EOI]) of family members toward patients with mental illness. The FQ has two subscales: critical comments, and EOI. Each item is rated on a 4-point scale (1 = never/very rarely; 4 = very often). The FQ is scored by adding together the ratings from the individual items, with higher scores indicating greater levels of expressed emotion.	Wiedemann, G., Rayki, O., Feinstein, E., & Hahlweg, K. (2002). Family Questionnaire: Development and validation of a new self-report scale for assessing expressed emotion. Psychiatry Research, 109, 265–279. (79)		
22. Family Function	**Ages 12 & older**	The 15-item Systematic Clinical Outcome Routine Evaluation (SCORE-15) Index of Family Functioning and Change is a 15-item, self-administered instrument that assesses family problems and includes subscales for family strengths, family difficulties, and family communication. Each item is rated on a 5-point scale, where 1 = Describes us: Very well and 5 = Describes us: Not at all. The scores from all individual items can be added together into a total family problem score. Subscale scores are derived by adding the questions for each of the dimensions: Strengths and Adaptability (questions 1, 3, 6, 10, 15); Overwhelmed by Difficulties (questions 5, 7, 9, 11, 14); and Disrupted Communication (questions 2, 4, 8, 12, 13).	Stratton, P., Bland, J., Janes, E., Lask, J. (2010). Developing an indicator of family function and a practicable outcome measure for systemic family and couple therapy: the SCORE. *Journal of Family Therapy, 32(11)*(3): 232–258. (80)		
23. Family Burden of Mental Illness	**Ages 18 & older**	The Burden Assessment Scale (BAS) is a 19-item, self-administered scale to assess the burden on families with a seriously mentally ill family member. Items 1–10 assess objective consequences, including financial problems, limitations on personal activity, and household disruptions. Items 11–19 measure subjective consequences, including shame, stigma, guilt, and resentment. Each item is rated on a 4-point scale (1 = not at all; 4 = a lot). To score the BAS, ratings from each item are added together to give a total score, with higher scores indicating greater levels of caregiver burden.	Reinhard, S.C., Gubman, G.D., Horwitz, A.V., & Minsky, S. (1994). Burden assessment scale for families of the seriously mentally ill. Evaluation and Program Planning, 17(3): 261–269. (81)		
24. Shared Decision Making in Clinical Encounters	**Ages 18 & older**	The CollaboRATE questionnaire is a three-item, self-administered questionnaire that measures the shared decision-making process. Each item is scored on a 5-point Likert-type scale (0 = no effort was made; 4 = every effort was made). The scores of the individual items are added together to give a total score, with higher scores indicating greater shared decision-making.	Elwyn, G., Barr, P. J., Grande, S. W., Thompson, R., Walsh, T., & Ozanne, E. M. (2013). Developing CollaboRATE: A fast and frugal patient-reported measure of shared decision making in clinical encounters. Patient Education and Counseling, 93(1), 102–107. (82)		
25. Incarceration	**Ages 12–17**	This protocol includes two self-administered questions about time spent in juvenile detention centers from the Youth Mental Health Service Utilization section of the National Survey on Drug Use and Health (NSDUH) 2014 Questionnaire.	National Survey on Drug Use and Health (https://nsduhweb.rti.org/respweb/homepage.cfm)		

Measure	Age Range	Description of Protocol	Source	Completion Time (min)	Healthy Norms
	Ages 18 & older	This protocol includes four self-administered questions that capture total number of arrests and also number of arrests and time spent on probation or parole in the last 12 months from the National Survey on Drug Use and Health (NSDUH) 2014 Questionnaire.	National Survey on Drug Use and Health (https://nsduhweb.rti.org/respweb/homepage.cfm)		
26. Clinician-Administered Psychiatric Assessment	**Ages 12 & older**	The Structured Clinical Interview for DSM-5® Disorders-Clinician Version (SCID-5-CV) is a clinician-administered, semi-structured interview guide for making diagnoses using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).	First, M. B., Williams, J. B., Karg, R. S., & Spitzer, R. L. (2015). *Structured Clinical Interview for DSM-5® Disorders–Clinician Version* (SCID-5-CV) Washington, DC: American Psychiatric Association. (83)		
Early Psychosis Measures for the PhenX Supplemental Information					
Measure	**Age Range**	**Description of Protocol**	**Source**		
1. White Matter Integrity	**Ages 12 & older**	This protocol details the recommended sequence for performing a Diffusion Tensor Imaging (DTI) brain scan on a 3T or higher field-strength magnetic resonance (MR) scanner. Microstructural imaging probes white matter integrity based on the pattern of diffusion of water molecules.	Magnetic resonance imaging (MRI) diffusion tensor imaging (DTI) parameters courtesy of Dr. Ongur and colleagues, McLean Hospital/Harvard Medical School, 115 Mill St., Belmont, MA 02478.		
2. Chemical Brain Imaging	**Ages 12 & older**	This protocol details the collection of chemical brain imaging by application of 1H magnetic resonance spectroscopy (MRS) technical and analytical procedures with a 3T or higher field-strength magnetic resonance (MR) scanner.	Du, F., Cooper, A. J., Thida, T., Shinn, A. K., Cohen, B. M., & Öngür, D. (2013). Myelin and axon abnormalities in schizophrenia measured with magnetic resonance imaging techniques. Biological Psychiatry, 74(6), 451–457. (84)		
3. Glutathione	**Ages 3 & older**	The protocol includes basic instructions for measuring the total glutathione (GSH) (the sum of GSH and glutathione disulfide [GSSG]) in plasma using glutathione reductase. Because there are many comparable assays based on the Tieze method for measuring total GSH, the protocol also provides basic guidelines to aid comparability among different studies.	Baker, M. A., Cerniglia, G. J., & Zaman, A. (1990). Microtiter plate assay for the measurement of glutathione and glutathione disulfide in large numbers of biological samples. Analytical Biochemistry, 190(2), 360–365. (85) Eyer, P., & Podhradsky, D. (1986). Evaluation of the micromethod for determination of glutathione using enzymatic cycling and Ellman's reagent. Analytical Biochemistry, 153(1), 57–66. (86) Tietze, F. (1969). Enzymic method for quantitative determination of nanogram amounts of total and oxidized glutathione: Applications to mammalian blood and other tissues. Analytical Biochemistry, 27(3), 502–522. (87)		
4. Prodromal Psychosis Symptoms	**Ages 18 & older**	The Structured Interview of Psychosis-risk Syndromes (SIPS) is a structured interview for diagnosing a clinical high risk (CHR) syndrome for psychosis and cases of first-episode psychosis. It contains a severity rating scale (the Scale of Psychosis-risk Symptoms [SOPS]); a well-anchored Global Assessment of Functioning (GAF); the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), schizotypal personality disorder checklist; a brief assessment of the family history of psychosis; and the Criteria of Psychosis-risk Syndromes (COPS), Presence of Psychosis Scale (POPS), and DSM-5 Attenuated Psychosis Syndrome (APS) criterion sets.	Woods, S. W., Walsh, B. C., Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Heinssen, R., Perkins, D. O., Seidman, L. J., Tarbox, S. I., Tsuang, M., Walker, E. F., & McGlashan, T. H. (2014). Current status specifiers for patients at clinical high risk for psychosis. Schizophrenia Research, 158, 69–75. (88)		
5. Clinician-Administered	**Ages 18 & older**	The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a structured diagnostic interview for making Diagnostic and Statistical Manual of Mental	The M.I.N.I. International Neuropsychiatric Interview is a proprietary instrument and		

Measure	Age Range	Description of Protocol	Source	Completion Time (min)	Healthy Norms
Neuropsychiatric Interview		Disorders, 4th edition (DSM-IV), and International Classification of Diseases, version 10 (ICD-10), diagnoses.	administration requires a license from Dr. David V. Sheehan: (http://www.medical-outcomes.com/index/minifororganizations)		
6. Negative Psychosis Symptoms	**Ages 18 & older**	The four-item Negative Symptom Assessment (NSA-4) is a clinician-administered instrument that rates behaviors including restricted speech and reduced emotion, social drive, and interests. Each item is rated on a 7-point scale: 1 = Behavior is not reduced compared with a healthy young person; 2 = Behavior is minimally reduced; significance is questionable; 3 = Behavior is mildly reduced, 4 = Behavior is moderately reduced; 5 = Behavior is markedly reduced and definitely interferes with subject's functioning; 6 = Behavior is severely reduced or entirely absent; it is glaring and markedly interferes with functioning; and 9 = behavior not ratable. The ratings from the individual items can be added together to yield a global score for negative symptoms, with a higher score indicating more severe symptoms.	Alphs, L., Morlock, R., Coon, C., Van Willigenburg, A., & Panagides J. (2010). The 4-item Negative Symptom Assessment (NSA-4) instrument: A simple tool for evaluating negative symptoms in schizophrenia following brief training. *Psychiatry (Edgemont), 7*(7), 26–32. (89)		