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Neuroimaging and Biosample Collection in the Toronto Adolescent and Youth Cohort Study: Rationale, Methods, and Early Data

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ABSTRACT

BACKGROUND: The Toronto Adolescent and Youth (TAY) Cohort Study will characterize the neurobiological trajectories of psychosis spectrum symptoms, functioning, and suicidality (i.e., suicidal thoughts and behaviors) in youth seeking mental health care. Here, we present the neuroimaging and biosample component of the protocol. We also present feasibility and quality control metrics for the baseline sample collected thus far.

METHODS: The current study includes youths (ages 11–24 years) who were referred to child and youth mental health services within a large tertiary care center in Toronto, Ontario, Canada, with target recruitment of 1500 participants. Participants were offered the opportunity to provide any or all of the following: 1) 1-hour magnetic resonance imaging (MRI) scan (electroencephalography if ineligible for or declined MRI), 2) blood sample for genomic and proteomic data (or saliva if blood collection was declined or not feasible) and urine sample, and 3) heart rate recording to assess respiratory sinus arrhythmia.

RESULTS: Of the first 417 participants who consented to participate between May 4, 2021, and February 2, 2023, 412 agreed to participate in the imaging and biosample protocol. Of these, 334 completed imaging, 341 provided a biosample, 338 completed respiratory sinus arrhythmia, and 316 completed all 3. Following quality control, data usability was high (MRI: T1-weighted 99%, diffusion-weighted imaging 99%, arterial spin labeling 90%, resting-state functional MRI 95%, task functional MRI 90%; electroencephalography: 83%; respiratory sinus arrhythmia: 99%).

CONCLUSIONS: The high consent rates, good completion rates, and high data usability reported here demonstrate the feasibility of collecting and using brain imaging and biosamples in a large clinical cohort of youths seeking mental health care.

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Epidemiological studies indicate that the presence of childhood psychiatric and neurodevelopmental disorders is associated with increased risk for psychosis spectrum symptoms (PSSs) and psychotic disorders (1–3). Biological changes at the molecular and neural-circuit levels linked with psychotic disorders in adulthood may be present in youth receiving mental health care before more severe clinical and functional impairments related to psychosis emerge (4,5). Therefore, a unique opportunity emerges to characterize molecular and brain circuit susceptibility pathways that may confer risk for psychosis, poor functional outcome, and suicidality in a large clinical cohort of youths presenting for mental health care.

Large-scale, cross-sectional neuroimaging studies of child and youth community samples, such as the Philadelphia Neurodevelopmental Cohort (PNC) (6) have helped identify biological circuits of relevance to mental illness. Dysfunction in cortico-striato-thalamo-cortical circuits supporting emotion, motivation, and cognition and a distributed corticolimbic circuit supporting threat processing have been associated with the pathogenesis of psychosis and related psychiatric conditions associated with heightened risk for PSSs (7–11). Risk is typically associated with cortico-striato-thalamo-cortical hyperconnectivity to sensory-motor cortical areas and hypoconnectivity to executive control regions (7,9), as well as

SEE COMMENTARY ON PAGE 247 AND COMPANION ARTICLES ON PAGES 253 AND 265

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age-dependent patterns of abnormal corticolimbic, especially amygdala under- or overconnectivity (12). These macroscale brain circuit abnormalities may be partly explained by dysregulation in molecular pathways supporting synaptic and immune function (13–16). Large-scale, longitudinal studies of youth, such as the Adolescent Brain Cognitive Development (ABCD) Study, will help define developmental trajectories of biological processes (17). However, as a population-based cohort, the large majority of its participants are not at elevated risk for clinically significant psychosis or associated outcomes and impairment. The Healthy Brain Network (HBN) (18), which is also a large-scale multimodal study, recruits from the community and through parents concerned about psychiatric symptoms in their children, thus broadening the heterogeneity and distribution of psychopathology. The Toronto Adolescent and Youth (TAY) Cohort Study that we present here is a large-scale clinical cohort recruited from tertiary care that will provide a complementary approach to general population cohorts to understand developmental trajectories of mental health risk and resilience pathways in youth already experiencing mental illness.

In addition to the clinical (mental and physical health), health service, cognitive, and educational data collected in the TAY Cohort Study [as outlined in (19) and (20)], neuroimaging and biosamples are collected longitudinally to identify trajectories of neural circuit development, map relationships with PSSs and functioning, and characterize links with molecular markers. The protocol includes longitudinal multimodal neuroimaging, including structural and functional magnetic resonance imaging (fMRI) assessments harmonized with studies of normative development (most notably the ABCD Study) to enable integrated analyses that cut across clinical and normative samples; blood (or saliva) and urine to assess genomic, proteomic, and hormonal data; and respiratory sinus arrhythmia (RSA) and heart rate variability to assess markers of parasympathetic activity associated with psychosis risk (21–23). To provide novel mechanistic insight into biological pathways implicated in psychosis, a subsample of participants undergoes additional assessments, including positron emission tomography (PET) imaging of synaptic density and electroencephalography (EEG). The study has 3 main aims.

The first aim is to identify the trajectories of cortico-striato-thalamo-cortical development in this youth sample and the relationship with trajectories of PSSs, cognition, and functioning and also identify sex-specific effects and moderating effects of sex. The second aim is to identify genetic and proteomic underpinnings of circuit-specific PSS trajectory relationships. The third aim is to characterize effects of inflammation and stress on corticolimbic circuit development and map relationships with sex and gender identity, general psychopathology (including suicidality), and functioning.

Finally, we aim to integrate multilevel phenotyping to identify data-driven subtypes of youth and generate individually predictive models of key outcomes of interest (24). See the Supplement for more detailed aims and hypotheses. Here, we present the protocol consisting of imaging and biosample assessments. We have included characteristics and quality control (QC) metrics for participants recruited between May 4, 2021, and February 2, 2023, to demonstrate the feasibility of acquiring high-quality imaging and biosample data in a large clinical cohort.

METHODS AND MATERIALS

Study Design Overview

The TAY Cohort Study includes a detailed transdiagnostic assessment of mental and physical health as well as cognition and educational achievement in 1500 youths assessed longitudinally over 5 years (Figure 1), as outlined in the companion papers (19,20). All consenting participants are offered 1) a 1-hour MRI (or EEG if MRI was declined or contraindications were present); 2) biosample collection consisting of blood or saliva (if blood collection was declined or venipuncture was not feasible), and urine; and 3) a measure of cardiac parasympathetic tone (via RSA) completed at baseline and then repeated annually for 5 years, for a total of 6 assessments

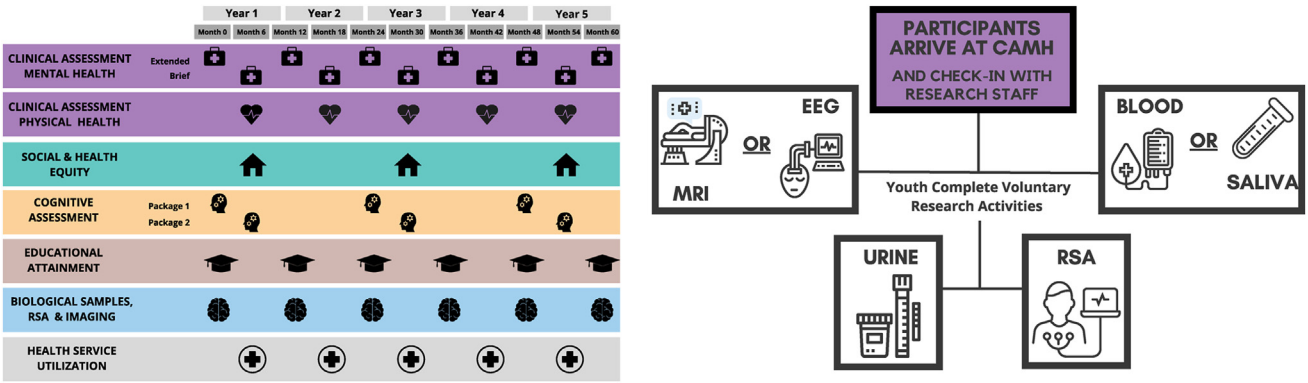

Figure 1. Depiction of Toronto Adolescent and Youth (TAY) Cohort Study longitudinal data collection timeline (top). Depiction of the participant procedures during the imaging and biosample protocol on-site visit. After the participant arrives on site, they confirm which samples they feel comfortable providing. Cognitive assessment [as per the cognition and educational achievement protocol; see (20)] is carried out on the same day as the imaging and biosample collection and is administered first. Imaging is completed afterward and prior to the end of the visit. Urine, blood, and respiratory sinus arrhythmia (RSA) collection times vary based on the availability of a research nurse and participant preference during the visit, with collection times recorded. CAMH, Centre for Addiction and Mental Health; EEG, electroencephalography; MRI, magnetic resonance imaging.

(Figure 1). These assessments are administered in person and are typically paired with the baseline cognitive/educational assessment (20). Participants who are ≥16 years and have completed MRI are offered to participate in the longitudinal PET imaging substudy (to assess synaptic density, projected target n = 100).

Participants

Participants ages 11 to 24 years and of any race, ethnicity, sex assigned at birth, or gender identity and who are currently seeking and/or accessing mental health services at the Centre for Addiction and Mental Health (CAMH) are eligible. Youth with psychotic disorders are not actively recruited because a key goal of the study is to identify factors associated with psychosis risk. Exclusion criteria include any youth who does not provide informed consent (for those with the capacity to consent) or assent (for those who lack the capacity to consent), individuals who are nonverbal, and individuals who do not speak English. For individuals who lack the capacity to consent, the inability of the legal guardian to provide informed consent for the youth is also an exclusion criterion. While youth participants are encouraged to involve a caregiver to participate in the TAY Cohort Study, the imaging and biosample protocol is completed only by youth. All procedures were approved by the CAMH Research Ethics Board and comply with the World Medical Association Declaration of Helsinki.

Screening, Training, and Support Prior to and During Imaging and Biosample Visit. Efforts to engage participants in the imaging and biosample protocol were codeveloped with youth and family advisers with lived/living experience of mental illness. During the initial TAY Cohort Study consent discussion, research staff explain protocol procedures using accessible infographics. Research visit confirmations include links to videos introducing the research team, a virtual walk-through of the imaging facility, and information about what to expect (https://www.taycohort.ca/). Individuals who consent to neuroimaging but are not eligible for, are not interested in, or are unable to complete MRI are offered participation in EEG. Imaging and biosample visits are often booked in the afternoon and evening (3–8 PM) on weekdays and all day on Saturdays to accommodate youth and caregiver schedules. Youth participants and accompanying caregiver/support people are offered snacks, beverages, and meals during in-person visits; transportation support; remuneration for each imaging and biosample assessment provided (cash or gift cards); or volunteer hours for participation time. Youth who participate in MRI can choose to receive a 3-dimensional printed brain model or their printed brain image on paper or a t-shirt. For the approach to the sequence of assessments, see the Supplement.

Imaging Samples

Magnetic Resonance Imaging. MR images are acquired on a 3T GE Discovery MR750 Scanner with a Nova medical 32-channel coil at the CAMH. The 1-hour protocol includes a fixed order of sequences that begin with a localizer, T1-weighted (T1w) structural image, diffusion-weighted imaging (DWI), two resting-state fMRI sequences (5 min, 13 seconds each), the ABCD Study emotional n-back fMRI task, and arterial spin labeling (ASL). T1w, DWI, and fMRI sequences are harmonized with the protocol currently being implemented in the ABCD Study (17) and optimized for high-quality acquisition, including multiband acquisitions for echo-planar imaging (blood oxygen level–dependent fMRI and DWI). The emotional n-back fMRI task was chosen because it is widely used (25), developmentally appropriate (25,26), and known to engage working memory (26) and the fronto-amygdala circuitry (27,28). Full acquisition parameters are presented in Table S1. For participant preparation and comfort measures, see the Supplement.

All MRI DICOM images are transferred to a neuroimaging database, XNAT, within the CAMH Neuroinformatics Platform. DICOM images are converted to NIfTI (Neuroimaging Informatics Technology Initiative) images and organized locally following the BIDS (Brain Imaging Data Structure) convention. A web-based dashboard (https://github.com/TIGRLab/datman-dashboard) is used locally for monitoring data and visual QC processes for early identification of major issues (i.e., missing scans and major artifacts). MR images are preprocessed using open reproducible pipelines (BIDSapps) (29) that generate visual pipeline QC images for important preprocessing steps, as well as the quantitative metrics of data quality. T1w and fMRI data are processed with MRIQC, version 0.16.1 (30), to generate QC metrics. In preparation for planned cortical surface–based analyses, T1w and fMRI data are also preprocessed using fMRIPREP (31) and CIFTIFY (32). To generate QC metrics for DWI and ASL, QSIPREP, version 0.16.0RC3 (33), and ASLPREP, version 0.2.8 (34) are used, respectively. Quantitative assessment (i.e., derived QC metrics) from MRIQC, ASLPREP, and QSIPREP are described further in Table S2.

Electroencephalography. Participants are asked not to apply hair products prior to EEG. They can wear their own clothing and keep piercings in during scanning. Continuous EEG data are collected at a sampling rate of 512 Hz using a Biosemi system with 64 scalp electrodes during 20 minutes of rest. Resting EEG is followed by an auditory mismatch negativity (MMN) task (20 minutes). The MMN task provides a difference potential between responses to unpredictable stimuli (deviants) and predictable stimuli (standards). This task was chosen because MMN is substantially reduced in individuals with schizophrenia (35) and has been used to predict future psychosis risk in vulnerable youth populations (36). See the Supplement for further details on specific MMN task administration, QC, and EEG acquisition considerations.

Positron Emission Tomography. Recruitment for the PET protocol began on Jun 25, 2022, following regulatory approval. Eligible TAY Cohort Study participants are offered to participate in annual PET scans with [^{18}F]SynVesT-1 (also known as [F-18]SDM8) (up to 3 total, depending on age at entry). [^{18}F]SynVesT-1 was chosen for its ability to image synaptic density in vivo based on the longstanding hypothesis that the emergence of psychosis is linked with excessive synaptic pruning (37). PET scans are performed using the GE Discovery MI 5 ring PET/computed tomography (GE Revolution EVO). See the Supplement for further details on PET procedures.

Biosamples

Blood/Saliva/Urine. All participants are given the option to provide a blood or saliva sample. While blood samples are indicated to participants as preferred to allow for full assessment, saliva is offered as an alternative if participants do not wish to or are unable to complete blood draw. Blood samples are collected by antecubital venipuncture. Two EDTA and 2 serum tubes totaling 26 mL of blood are collected at baseline and annually. After initial processing, aliquots of plasma-EDTA, buffy coat, and serum are stored anonymized at −80 °C. One EDTA tube is used for DNA extraction, after which DNA is stored for genotyping and methylation analyses. The plasma and serum aliquots allow for the assessment of a wide variety of biomarkers, including circulating plasma proteins and mitochondrial DNA, immune markers, and hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes hormones. Saliva samples are used only for DNA extraction and genotyping. Samples are collected using Oragene kits (DNA Genotek Inc.) in agreement with manufacturer's guidelines. Multipolygenic risk score approaches (38) reflecting risk across multiple related phenotypes and based on multiethnic reference samples (39) will be prioritized to optimize predictive power and generalizability. Urine samples are collected at baseline and annual time points to record/confirm medications and substances detected on the day of imaging and biosample collection. Samples are sent to our hospital clinical laboratory for immunoassay drug screen, synthetic cannabinoid urine screen, and full broad spectrum drug screen. Results are entered into our research database.

Respiratory Sinus Arrhythmia. RSA and heart rate variability are recorded using BioLab version 3.4.1 software (MindWare) following a procedure similar to that previously described (40,41) in which cardiac data are recorded over 4 minutes while participants are in a seated position. Electrocardiogram data are collected using 3 disposable electrodes with a modified lead II (right collarbone and lower left and right ribs). The heart rate signal is digitized at a sampling rate of 500 Hz. Interbeat intervals are determined from the R waves and stored for later analyses. See the Supplement for further details.

Statistical Analyses

Statistical Power. Due to the paucity of published data on PSSs in treatment-seeking youth populations, effect size assumptions were largely based on cross-sectional studies of youth at clinical high risk for psychosis and adults diagnosed with schizophrenia showing small-to-medium effect sizes (Cohen's *d*: 0.22–0.58) for structural and fMRI phenotypes (42,43) and peripheral blood levels of inflammatory cytokines and growth factors (44). We conducted mixed model–based simulations using a Monte-Carlo method given the expected sample sizes across baseline and 4 follow-up time points. We observed 80% power to detect a correlation as low as 0.25 between biomarkers and repeatedly measured PSSs, (odds ratio = 1.50 for binary PSS, per 1 SD change in biomarker). Accounting for multiple testing, the minimum detectable correlation increases to 0.34 (odds ratio = 1.7, e.g., for 25 biomarker panel). For whole-person data integration analyses to identify subtypes across data types collected, formal power calculations were not performed. Our sample size exceeds those recommended for a variety of clustering approaches, including high-dimensional methods (45,46).

RESULTS

Of the 417 participants who consented to participate in the overall TAY Cohort Study before February 2, 2023, 98% agreed to neuroimaging (MRI or EEG), and 98.5% agreed to biosample collection. A CONSORT (Consolidated Standards of Reporting Trials) diagram of study completion is presented in Figure 2. Of those who agreed to participate in the imaging and biosample assessments (*n* = 412), 334 completed imaging (281 MRI, 53 EEG), 341 provided a biosample (*n* = 191 blood, *n* = 146 saliva, *n* = 300 urine, *n* = 338 RSA). As detailed in Figure 2, the gap from 412 to 334, 341, or 338 is mainly due to participants either changing their minds about the study in general or these assessments in particular or not showing up for their study visit. The average interval between completion of the mental and physical health assessments (19) and the imaging and biosample in-person visit was 32 days (range 0–144 days). Demographic characteristics of participants who completed at least 1 imaging and biosample assessment are presented in Table S3. Participants who did not complete any imaging and

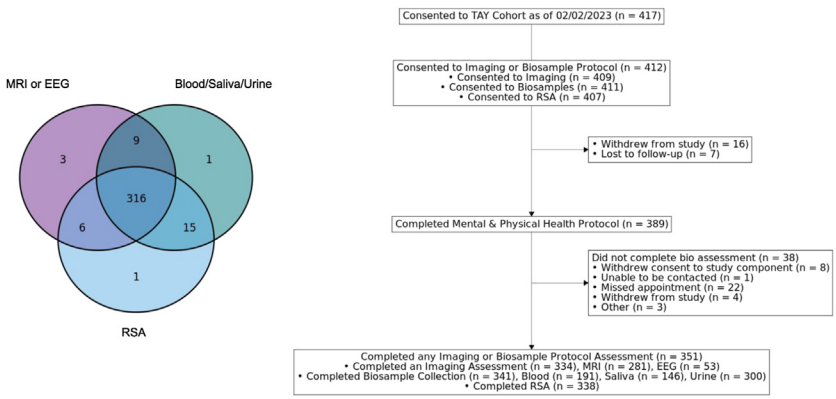

Figure 2. (Left) Venn diagram showing completion of components for the imaging and biosample protocol (*n* = 351). (right) CONSORT (Consolidated Standards for Reporting Trials) flow-style depiction of completion/incompletion of the imaging and biosample protocol for 417 participants who consented and were assessed between May 4, 2021, and February 2, 2023. EEG, electroencephalography; MRI, magnetic resonance imaging; RSA, respiratory sinus arrhythmia; TAY, Toronto Adolescent and Youth.

biosample assessments were older (mean age = 19.6, SD = 3.08) on average than completers (mean age = 18.1, SD = 3.77) based on the nonparametric Mann-Whitney test (p = .001). Overall, the demographic characteristics of participants who completed imaging and biosample assessments did not differ from the demographic characteristics of participants who completed the mental and physical health assessments [see (19); also see Table S3]. Participants' psychiatric diagnoses were also representative of the overall sample (see Table S4); median number of mental health diagnoses met per participant was 3.5, and 49% met a pre-established threshold for PSSs [as defined in (19,47)].

Imaging

A total of 409 participants agreed to participate in EEG or MRI, and 334 participants completed imaging (n = 281 MRI, n = 53 EEG). Reasons for not participating in MRI/EEG (for those who participated in other biosample or RSA assessments, n = 17) included not consenting to imaging (n = 4), technical issues with the EEG equipment (n = 5), anxious/uncomfortable/claustrophobic feeling during the MRI scan (n = 4), braces or piercings (n = 3), and missed appointments (n = 1).

MRI Completion and Data Quality. A total of 281 participants completed T1w MRI. See Figure 3 for a Venn diagram of available scans by sequence and quantitative metrics of MRI image quality. See Figures S1–S4 for CONSORT diagrams noting issues tracked by MRI modality. Additional MRI quality metrics are plotted in Figure S5. After visual and quantitative QC of T1w scans with MRIQC (30), 280 (99.6%) passed QC checks. Of the 281 participants who completed DWI, 278 (99%) of DWI data passed QC checks. A total of 261 participants (93% of those with T1w scans) completed the ASL scan, and 255 (97% of ASL scans, 90% of those with T1w) passed ASL QC checks. A total of 280 participants completed at least 1 of the 2 resting-state fMRI runs, and 266 (95%) passed QC

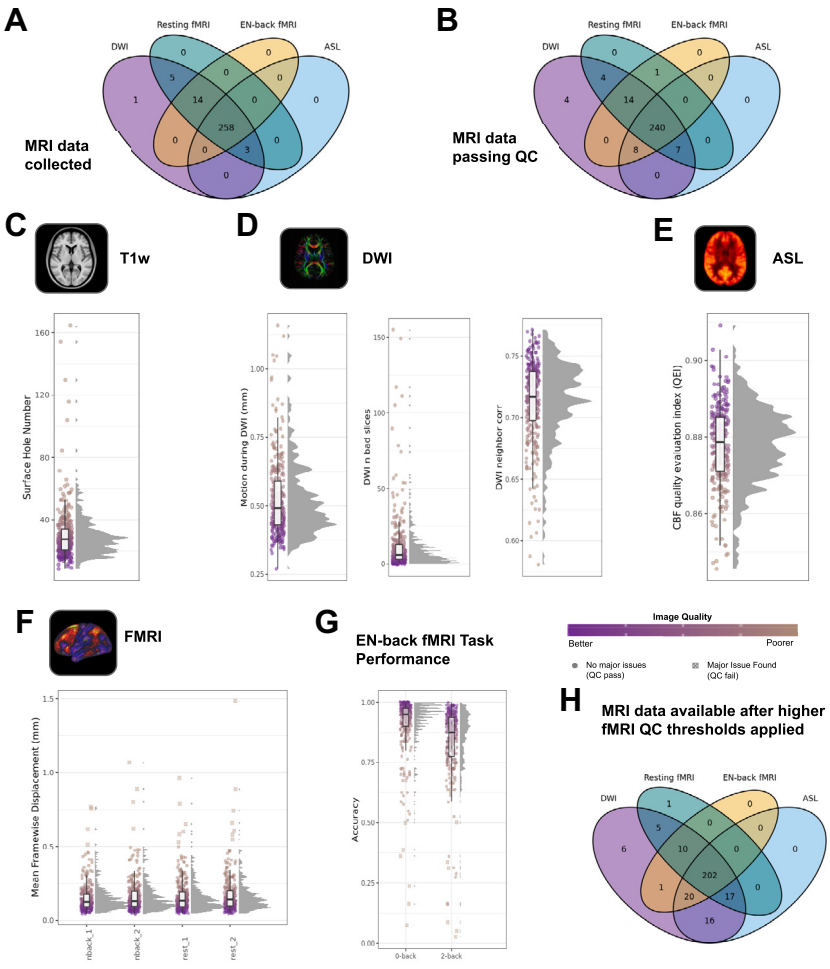

Figure 3. Magnetic resonance imaging (MRI) data quality results. **(A)** Venn diagram of MRI scans acquired (n = 281 participants total). **(B)** Venn diagram of MRI data available after quality control (QC) checks (see Figures S1–S4 for CONSORT [Consolidated Standards for Reporting Trials] flowchart of the QC process). **(C)** Number of surface holes calculated by FreeSurfer (version 6.0.1), a measure of T1-weighted (T1w) image quality (lower values are better) (n = 280, 1 scan excluded during visual QC and not shown with 373 surface holes). **(D)** Diffusion-weighted imaging (DWI) quality metrics calculated using QSIPREP, version 0.16.0RC3 (18) (n = 280, 1 excluded during visual QC not shown with >400 number of bad slices). DWI metrics: motion during DWI (mm, lower values better); DWI n bad slices (identifies slice-wise signal dropout within images, lower values are better); DWI neighbor correlation (corr) [higher values better; the mean Pearson correlation coefficient of the neighboring (in time) images (19)]. **(E)** Arterial spin labeling (ASL) quality evaluation index (QEI) calculated with ASLPREP, version 0.2.8 (20). **(F)** Functional MRI (fMRI) in-scanner motion (mean framewise displacement [FD]) across fMRI runs calculated using MRIQC, version 0.16.1 (21). Mean FD was 0.167 mm and 0.178 mm for resting state (runs 1 and 2, respectively) and 0.154 mm and 0.167 mm for emotional n-back (EN-back). Median FD was 0.13 mm and 0.14 mm for resting state (runs 1 and 2, respectively) and 0.125 mm and 0.13 mm for EN-back. **(G)** Task fMRI performance; accuracy (proportion correct) during the in-scanner EN-back task 0-back and 2-back conditions (n = 271; 1 participant excluded because responses were not measured due to technical issues). Mean EN-back task accuracy was 95% for the 0-back condition and 0.88 for the 2-back condition. **(H)** Venn diagram of available scans if a higher fMRI QC threshold (mean FD < 0.3) was applied. The points in plots **(C–G)** are colored according to their interpretation with regard to data quality, from purple (best) to orange (poorer). Scans that failed QC on the plotted measure are marked with an "x" shape. CBF, cerebral blood flow.

checks. A total of 271 participants completed the ABCD Study emotional n-back runs, and 255 participants (94% of participants, 90% of those with T1w) passed QC checks. Notably, scans that pass preliminary QC checks, as reported here, are free of major issues (e.g., very severe motion, missing sequences, and technical issues).

EEG Completion and Data Quality. Of the 53 participants who completed EEG, 92% had usable resting-state and auditory MMN task data, and 83% passed rigorous task QC. See the Supplement for reasons for exclusion. Resting-state EEG data from 4 participants did not pass QC (n = 1 with >5 bad channels, n = 3 with <70% good trials) (see Figure S6). Data from 9 participants were excluded due to poor MMN task behavioral performance (Figure S6B).

PET Completion. Of the 88 eligible participants, 93.2% expressed interest in participating (n = 82), and 6.8% declined participation (n = 6). Twenty-six participants have consented to PET scanning, and to date, 15 have completed their first PET scan with an arterial line.

Biosamples

Blood/Saliva/Urine Completion and Sample Quality. Of the 411 participants who agreed to provide a biosample, 341 were successfully able to do so. For those who participated in other RSA or MRI/EEG assessments, reasons for not participating in biosample collection (n = 15) included not consenting to biosample collection (n = 5), an unsuccessful blood draw (n = 4), the participant refusing to begin/finish (n = 4), and logistics/scheduling/staffing issues (n = 2). Of those who participated, 191 (56%) provided a blood sample, and 146 (43%) provided saliva. Given the high percentage of participants who provided saliva, additional strategies are being considered to optimize the available sample for planned biomarker analyses (see the Supplement for details). Of the total blood samples provided, 253 (96.48%) samples were of sufficient quantity to allow for storage of 1 mL of buffy coat, 2 mL of plasma-EDTA, and 4.0 mL of serum aliquots necessary for planned biomarker analysis. A total of 300 participants provided urine samples. Standard operating procedures have been adjusted with youth input to facilitate urine collection (e.g., encouraging intake of fluids prior to visit).

RSA Completion and Data Quality. In total, 338 participants completed RSA. Those who participated in other biosample or MRI/EEG assessments but not RSA (n = 13) included 3 participants who declined to begin/finish, 3 participants who did not consent to the RSA study component, 5 with technical issues, 1 with scheduling or staffing issue, and 1 who did not complete due to a medical incident. After QC procedures (see the Supplement for details), 337 (99%) had usable data.

DISCUSSION

The current report details the TAY Cohort imaging and biosample protocol and demonstrates the feasibility of collecting state-of-the-art multimodal imaging sequences and biosamples in participants of ages 11 to 24 years, seeking mental health care, using an approach that is harmonized with current large-scale, open-access, population-based research initiatives. High completion rates are likely influenced by the extensive engagement with youth and caregivers to enhance the experience of participation. This preliminary data collected thus far enhances our confidence that we will be able to collect high-quality TAY Cohort Study imaging and biosample data in a large cohort to test our main aims. Preliminary data collected across TAY Cohort Study protocols (i.e., clinical, cognitive, and biological markers) suggests that the TAY Cohort Study will also be in a position to integrate multilevel data to identify data-driven subtypes and generate individually predictive models of outcomes with utility for prognostic and treatment innovation in at-risk youth.

The current report provides summary QC metrics for the preliminary baseline imaging and biosample data collected between May 4, 2021, and February 2, 2023. Based on prior associations of imaging data quality with illness severity (17,48,49), we anticipated that initial data quality would be poorer. In comparing similar preliminary publications and reports of quantitative QC in clinically enriched and normative cohorts (17,18,48), the first quantitative approximation of data quality based on the preliminary TAY Cohort sample is promising. Here, we provide a preliminary estimate of inclusion/exclusion based on summary QC metrics for each sequence. Inclusion/exclusion decisions in the final TAY Cohort sample will vary based on the QC approach applied, the characteristics of the pediatric sample (48), and the potential need to recalibrate prior thresholds. Participants who completed neuroimaging and biosample assessments are also representative of the overall sample, which contrasts with recent studies showing that children and youth who were excluded following QC tended to be younger and more impaired (48). One explanation for our early findings may be the extensive preparation done by research staff with participants prior to the procedures and the input of youth with lived experiences on approaches to enhance comfort and engagement.

The recent accumulation of large-scale imaging data and data sharing efforts have enabled unprecedentedly detailed insight into brain development (50). However, available data remain largely cross-sectional. Given that brain developmental trajectories may vary markedly between individuals, estimation using cross-sectional data may be challenging (51). With longitudinal studies in progress, such as the ABCD Study (17), more definitive knowledge regarding longitudinal trajectories, including intraindividual variation, in children and youth will be established. The TAY Cohort Study data will provide a unique opportunity to chart trajectories of brain development in children and youth who are already experiencing mental illness. Another unique opportunity relates to the relationship between brain development and dimensional assessment of behavior. Analyses connecting underlying circuitry with phenomenology, cognition, and even social determinants of health in youth have largely emerged from the PNC and ABCD Study datasets. However, in clinical samples, the focus is often diagnosis specific, and most large-scale studies have been conducted with adults. Recent analyses by the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) consortium that have addressed sample size challenges have confirmed the presence of widespread, nonspecific volumetric and cortical

thickness reductions among individuals with a specified psychiatric diagnosis compared to control participants [e.g., in schizophrenia (52,53), autism (54)]. However, cross-disorder analyses have also shown that related psychiatric disorders (e.g., obsessive-compulsive disorder, depression, attention-deficit/hyperactivity disorder, autism, schizophrenia, bipolar disorder) share morphometric findings (55–57). In clinical samples of children and youth, comorbidity is the norm, not the exception, and in the TAY Cohort Study, the median number of diagnoses per participant is 3.5 (19). Dimensional brain-behavior analyses are well positioned to determine the brain-based longitudinal trajectories that affect behavioral and functional outcomes in our large clinical sample of children and youth. Finally, important moderating variables such as, but not limited to, the social determinants of health, sex, and gender will enable further characterization of differential risk pathways for poor mental health outcomes during a developmental period when brain change is highly dynamic (58).

Some of the difficulty in predicting outcomes and designing optimal treatment programs, particularly for individuals with more complex presentations (59), may be enhanced via data integration approaches that can identify more similar subgroups of individuals with more similar trajectories. In combining imaging and cognitive modalities, early work applying data-driven tools to large transdiagnostic samples enriched for psychosis has shown promise [e.g., (60–62)]. While data-driven groupings found in these studies featured more distinct brain-behavior profiles than those found using traditional diagnostic groupings (i.e., using group-wise comparisons based on diagnostic labels), these groupings emerge from a cross-sectional time point. The translational impact and utility of such groupings must be tracked over time and tested for their ability to predict real-world outcomes in clinical populations where findings can inform clinical care (e.g., poor treatment response, emergency room visits, need for hospitalization, all collected in the current study).

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Establishing a TAY Cohort Study repository that will serve as a platform for data sharing (across the study team and with qualified researchers external to the study team and for comparison with findings from harmonized datasets) is critical to the success of this initiative. In support of open science, the TAY Cohort Study will use the data governance model established by the CAMH BrainHealth Databank, detailing policies, procedures, and processes for gaining and providing secure access to deidentified TAY Cohort Study data. In keeping with Canadian Ethical Standards, only data from participants who explicitly consent to sharing data for future secondary re-use will be included in data releases. Three data releases are planned: a baseline cross-sectional release, a release following completion of the year 3 longitudinal time point, and a final 5-year longitudinal release. Each release will be timed with the publication of primary research papers from the TAY Cohort Study Team. Released data will include summary scores, item-level data, and associated metadata and code. Before each data release, a risk of re-identification analysis will be conducted that includes an assessment for the uniqueness among indirect identifiers of the participants. The Brain Health Databank Data Steward may alter the initial dataset to mitigate the risk of reidentification.

The Brain Health Databank serves as the data repository for CAMH and is currently nearing approval by the CAMH Research Ethics Board. External researchers will use the web-based cohort finder to facilitate the completion of the data access request form. All researchers accessing the Brain Health Databank must agree to the Data Use Agreement terms, which detail how data would be cited and acknowledged. The Data Use Agreement also forbids re-identification; researchers cannot attempt to reveal the identity of any individual using the data provided. The data access requests reviewed and approved by a Data Use Committee will be available for download via the Brain Health Databank. Data will be available for download via the Brain Health Databank portal. Researchers will need to renew data access annually.

Limited data for a smaller sample size were presented in poster form at the 2023 Annual Congress of the Schizophrenia International Research Society, May 11–15, 2023, Toronto, Ontario, Canada (63).

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