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SchizConnect: Mediating Neuroimaging Databases on Schizophrenia and Related Disorders for Large-Scale Integration

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Abstract

SchizConnect (www.schizconnect.org) is built to address the issues of multiple data repositories in schizophrenia neuroimaging studies. It includes a level of mediation—translating across data

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sources—so that the user can place one query, e.g. for diffusion images from male individuals with schizophrenia, and find out from across participating data sources how many datasets there are, as well as downloading the imaging and related data. The current version handles the Data Usage Agreements across different studies, as well as interpreting database-specific terminologies into a common framework. New data repositories can also be mediated to bring immediate access to existing datasets. Compared with centralized, upload data sharing models, SchizConnect is a unique, virtual database with a focus on schizophrenia and related disorders that can mediate live data as information are being updated at each data source. It is our hope that SchizConnect can facilitate testing new hypotheses through aggregated datasets, promoting discovery related to the mechanisms underlying schizophrenic dysfunction.

Keywords

Data mediation and integration; neuroinformatics; mega analysis; schizophrenia databases

1. Introduction

Schizophrenia is a complex psychiatric disease with heterogeneous clinical, behavioral, cognitive and genetic manifestations, and the literature, especially on neuroimaging studies, has yet to achieve a state of consistency and reproducibility. As a result, multi-site consortia have been created to coordinate the collection of large datasets in order to address these issues (Turner, 2014). Consortia such as the Functional Biomedical Informatics Research Network (FBIRN) (Friedman et al., 2008; Helmer et al., 2011a; Keator et al., 2008), the Mind Clinical Imaging Consortium (MCIC) (Gollub et al., 2013), North American Prodrome Longitudinal Study Consortium (NAPLS) (Addington et al., 2012) and Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) (Keshavan et al., 2011; Thaker, 2008) have led to the improvement of our understanding of brain circuitry, brain function and genetic variability in schizophrenia (Allen et al., 2011; Arnold et al., 2015; Cannon et al., 2015; Castro et al., 2014; Chen et al., 2012; Chen et al., 2013; Ehrlich et al., 2014; Hass et al., 2014; Hass et al., 2015; Kim et al., 2009; Kim et al., 2010; Mathew et al., 2014; Potkin et al., 2009). These efforts were successful in part because they were created with data sharing in mind, and they anticipated many of the difficulties in combining data from multiple sites in their design and schema. Yet, in building data repositories, many decisions were made that were specific to that particular repository or study, about what they would call different datatypes. In one study's data a structural MRI scan may be listed informatively as "T1-weighted scan", or something as complex as "5MPRAGE-AVG" or just "scan1". Combining data from datasets that do not share the same protocols and data structures is challenging and it remains a barrier to aggregating mega-datasets. When combining data across different sources, individual investigators face the difficult and costly process of understanding the different imaging, subject, assessment, meta-data content (definitions, formats, organizations) and converting the data into standardized terms. A critical and unmet need exists to automate and virtualize this process so that appropriate data can be retrieved and combined from different databases regardless of differences in the their structure and terminology.

In this paper, we describe the initial deployment of "SchizConnect" (publicly available at http://www.schizconnect.org/), a new resource aimed at establishing mega-datasets (Wang et al., 2014). Building on the success of previous consortia efforts, SchizConnect creates a resource that supports structured querying and retrieval of neuroimaging and related data across these consortia repositories.

2. Methods

2.1. SchizConnect Architecture

SchizConnect follows the classical virtual data integration framework (Florescu et al., 1998; Halevy, 2001; Lenzerini, 2002; Ullman, 1997; Wiederhold, 1992), which saw its initial theoretical application on schizophrenia neuroimaging data within the FBIRN consortium (Ashish et al., 2010). A distinct feature of this framework is that the data can reside at and be maintained at the original data sources in their original formats and schemas (i.e., their own ways to define the structure, content, and semantics of data). SchizConnect consists the following three fundamental components (Figure 1): 1) **the data sources** provide the data, structured according to native schemas; 2) **the mediation software (i.e., mediator)** reconciles the semantic differences in the data across the different sources through domain modeling and inter-schema mapping; and 3) **the web portal** provides a user-friendly interface for querying and downloading data.

The typical data flow begins with a user query constructed by dragging and dropping terms in a graphical user interface (GUI) at the SchizConnect web portal. The graphical query is translated to SQL and passed to the SchizConnect mediator. The mediator then relies on the SchizConnect domain model and inter-schema mappings to translate the user query into source-specific terms, and then queries each data source directly and concurrently, using the available source-specific query mechanisms, languages and variables. The results from the sources are collated and joined together by the mediator and provided to the SchizConnect web portal as a unified results table containing the mediated (harmonized) variables. The SchizConnect web portal then interacts with the user for further processing, including signing of data use agreements and data download. Below we describe each of the components in detail.

2.2. The data sources

SchizConnect accesses the data available at each of the sources in real time. It maintains a library of connectors (wrappers) to common source types, including relational databases, XML (Extensible Markup Language) or JSON (JavaScript Object Notation) databases, SOAP (Simple Object Access Protocol) or REST (Representation State Transfer) web services, or flat files. For previously unseen source types, the architecture is extensible to program new connectors. Each source runs their own server platforms with their own database schemas, formats and application programming interfaces (APIs). SchizConnect imposes no requirements on data sources with regard to databasing or access methods, but is flexible to special needs (see results below for specials case example).

2.3. SchizConnect Mediator

The SchizConnect mediator is built on the BIRN mediator (Ashish et al., 2010; Helmer et al., 2011b). The core idea is to define a common domain model/schema and inter-schema mapping rules that map between the domain schema and the different source schemas. The domain model defines an integrated view of the shared data in the application domain (i.e., SchizConnect). This concept is closely related to that of an ontology, but it is more limited in scope, in the sense that it only models the part of the application domain that is relevant to integrating a set of sources (Ashish et al., 2010). It can be viewed as an incremental, data-driven, pragmatic approach to domain ontology development. Inter-schema mappings are logical formulas, or rules, that relate the data models at each of the sources with the domain model, reconciling their semantic differences in the description of the data. The SchizConnect domain model consists of terms that are pertinent to schizophrenia neuroimaging research (such as those related to imaging protocol, disease severity or cognitive functioning). Definitions of these terms are provided via downloadable documents available on the SchizConnect web portal. During development, we have aligned the SchizConnect domain model terms with the standards provided by the ontology community: XCEDE (XML-Based Clinical Experiment Data Exchange Schema, http://www.xcede.org/XCEDE.html) (Gadde et al., 2012), NeuroLEX (the Neuroscience Lexicon, http://neurolex.org/) (Larson and Martone, 2013), NIF (the Neuroscience Information Framework, http://neuinfo.org/) (Gardner et al., 2008) and INCF (the International Neuroinformatics Coordinating Facility, http://incf.org/) (Bjaalie and Grillner, 2007; De Schutter, 2009), wherever appropriate. The domain terms with links to existing ontology can be found on the SchizConnect website documentations page. For example, the Positive and Negative Symptom Scale (PANSS) has an entry on NeuroLex (birnlex_3032, http://neurolex.org/wiki/Category:Positive_and_Negative_Symptom_Scale). In cases where no accepted ontology has been defined, such as the UPSA (University of California Performance-based Skills Assessment), we work with the neuroimaging and neuroinformatics community to define them. Although such effort is ongoing, since there doesn't yet exist a standard process for ontological term contribution, we will work with data contributors and the neuroinformatics community on a case-by-case basis.

The mediator performs two core functions. First, it uses the inter-schema mappings to rewrite the user query, e.g., "T1 images from individuals with schizophrenia older than 30 years old," from the domain schema to the formats and languages specific to each source. It currently uses GAV (global-as-view) mappings (Ashish et al., 2010; Florescu et al., 1998; Halevy, 2001; Lenzerini, 2002; Ullman, 1997; Wiederhold, 1992), where each domain predicate is constructed as a query over the source predicates. Second, the mediator constructs, optimizes, and executes a distributed query evaluation plan, based on the rewritten source-level query, which provides the answers to the user query. The source queries are executed directly over the data sources in parallel through each source connector (which wraps the source APIs). Results from source queries are collated and joined together in the mediator, and served to the SchizConnect web portal as a unified table organized using the domain schema terms.

The query execution engine used by the mediator for source-level query evaluation is based on the Open Grid Services Architecture Data Access and Integration (OGSA-DAI) and Distributed Query Processing (OGSA-DQP) services (http://www.ogsadai.org.uk/) (Antonioletti et al., 2005; Grant et al., 2008; Lynden et al., 2009; Lynden et al., 2008). OGSA-DAI is a streaming workflow engine in which data resources and web services are wrapped through a library of connectors. OGSA-DQP is a query engine that optimizes and implements the query evaluation plan as an OGSA-DAI workflow, which accesses the multiple data sources.

The SchizConnect domain query language is SQL, expressed on the domain model terms. Each data source query is wrapped as an OGSA-DAI resource through its library of connectors to common data sources such as PostgreSQL, MySQL, or XML. For additional details on the mediator architecture, see our previous work on the BIRN mediator (Ashish et al., 2010).

2.4. SchizConnect Web Portal

SchizConnect has been conceptualized as a one-stop resource for querying and retrieving neuroimaging and related data from distributed, heterogeneous repositories. SchizConnect is therefore set up to facilitate user registration and compliance with data use agreement (DUA) with each data source. To maximize the usage and efficiency, while complying with NIH policies and best practices, the SchizConnect web portal is structured to have two query modes. The first is a preliminary search, for example, for the *number* of male subjects between the ages of 20 and 60 with diffusion MRI scans. This mode is completely open to the public, allowing for anyone to browse and immediately obtain useful, current information on a current summary count of available data without having the need to register. However, no subject-level data at this point are downloadable. In the second mode, the user registers and signs in, and with the same query is able to view subject-level data, sign DUAs and download the data. Only data for which DUA has been signed are downloadable. Signed DUAs are forwarded to each respective data source administrator for reviewing and filing. The administrators at SchizConnect as well as each data source will work with each user's institution for data use and institutional review board (IRB) terms upon request. Regarding to participant privacy, we require that it is the responsibility of the data source to ensure that data are shared in accordance to rules and regulations set forth by their IRB. The responsibility of SchizConnect is to confirm with each data source that they agree to this responsibility.

3. Results

The initial deployment of SchizConnect makes available data on 1,129 subjects from its contributing sources. Sample demographics can be found in Table 1 as well as on the SchizConnect web portal (http://schizconnect.org/#subject-stats). Of these subjects, 1,029 have scan data, which include structural MRI (sMRI), resting-state functional MRI (fMRI), task-paradigm fMRI, and diffusion MRI (dMRI) scans, totaling 21,309 volumes (Table 2 and Table 3). Demographic, neuropsychological measures, and clinical assessments are either available or in the process of becoming available. As the data sources take in new subjects/scans, they can automatically become available for querying through SchizConnect,

depending on the source data repository's policies. At the writing of this manuscript, SchizConnect has 49 users and 37 downloads, and that statistic is steadily growing (http://schizconnect.org/#user-stats).

3.1. SchizConnect Data Sources

Current data sources include the following schizophrenia-related datasets, which are all publicly available themselves and have been extensively curated, documented, and subjected to quality assurance. Detailed explanations of data can be found in the accompanying special papers describing the data source repositories, as well as the following papers: (Cetin et al., 2014; Glover et al., 2012; Gollub et al., 2013; Wang et al., 2013).

- *FBIRN Phase II dataset @ UCI* (http://fbirnbdr.nbirn.net:8080/BDR/)[1] (Glover et al., 2012; Potkin and Ford, 2009), containing cross-sectional multisite data from 251 subjects, each with two visits. (See paper on FBIRN data in this special issue.) Data include sMRI and fMRI scans collected on a variety of 1.5T and 3T scanners, including Sternberg Item Recognition Paradigm (SIRP) and Auditory Oddball paradigms, breath-hold and sensorimotor tasks. The underlying database is HID (Keator et al., 2009; Ozyurt et al., 2010) in PostgreSQL using the relational data model. Access is provided via Java database connectivity technology (JDBC), a database-access API for the Java programming language. Results from the query are returned to the Mediator as an SQL ResultSet.
- *NUSDAST @ XNAT Central* (https://central.xnat.org/REST/projects/NUDataSharing) (Wang et al., 2013), containing data from 368 subjects, the majority with longitudinal data (~2 years apart). (See paper on NU data in this special issue.) Data include sMRI scans collected on a single Siemens 1.5T Vision scanner. The underlying database is XNAT (Marcus et al., 2007), using the XML data model. Access is provided via XNAT REST API. The mediator constructs a query XML document conforming to the XNAT search web service specification. Results from the query are returned to the Mediator as an XML document.
- *COBRE & MCICShare @ COINS Data Exchange* (http://coins.mrn.org/) (Bockholt et al., 2010; Scott et al., 2011; Wood et al., 2014), containing data from 198 and 212 subjects from COBRE (Cetin et al., 2014) and MCICShare (Gollub et al., 2013) projects, respectively. (See paper on COINS data in this special issue.) Data for COBRE include sMRI and rest-state fMRI scans collected on a single 3T scanner. Data for the multisite MCICShare include sMRI, rest-state fMRI and dMRI scans, collected on 1.5T and 3T scanners. COINS data required special handling in order to satisfy SchizConnect's needs because the native COINS architecture involves dynamic data packaging following the query, which does not allow for data to be immediately returned to the query engine[2]. With permission from the COINS executive committee, an API was built to enable SchizConnect to extract domain-model defined variables (see below) from the COINS databases and

[1]This link will be replaced by the SchizConnect web portal in the near future.
[2]On the COINS website, after user builds a query, data are packaged offline and a link is provided for downloading. Therefore the user never sees the actual data until the data are downloaded via the link.

to duplicate them at the Mediator site. The database underlying the duplicated MCICShare/COBRE data is MySQL using the relational data model. Access is provided via JDBC to the MySQL server. Results from the query are returned to the Mediator as an SQL ResultSet.

3.2. SchizConnect Mediator

The SchizConnect Mediator domain schema defines the following concepts: project, subject, imaging, cognitive, and clinical, described in detail below.

- **Project** contains the name and description of the 4 projects from 3 data sources for which data are collected (Figure 2A).
- **Subject** contains demographic and diagnostic information for individual participants, including “subject id”, “age”, “sex” and “diagnosis” (Figure 2B). Current diagnosis categories are: “no known disorder” (for healthy controls), “bipolar disorder,” “schizophrenia broad,” which includes “schizophrenia strict” and “schizoaffective.” We note that the precise definition of “control” may depend on specific studies and study populations, we did not use the term “control” to label the healthy comparison subjects provided by each data source. Instead, the term “no known disorders” is used.
- **Imaging_Protocol (MRI)** contains information on MRI scanner platforms and imaging protocols. “Imaging protocol” consists of “structural,” “functional,” “perfusion,” and “field mapping” categories. Both “structural” and “functional” protocols are subdivided for further distinctions, e.g., “T1,” “T2,” “resting state,” and “task paradigm” (Figure 2C).
- **Cognitive** domain contains neuropsychological assessments. The domain model uses the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008) terms whenever appropriate, which are “attention,” “executive function,” “learning,” “working memory,” “episodic memory,” “intelligence,” “language,” “motor,” “premorbid functioning,” “processing speed,” “social cognition,” and “visuospatial” (Figure 2D).
- **Clinical** domain contains full demographics, assessments of symptoms and functional capacity, and medical information. Demographics information includes “Race,” “Ethnicity,” “Education,” “SES (socioeconomic status),” and “Handedness.” Symptom measures include “PANSS (Positive And Negative Symptoms Scales),” “SAPS (Scale for the Assessment of Positive Symptoms),” “SANS (Scale for the Assessment of Negative Symptoms),” using the Unified Medical Language System (UMLS) terms whenever appropriate. Symptom measures also include “Depression,” “Mood,” “Suicide Ideation,”, and “Extrapyramidal Symptoms.” Medical information includes “Medical History/ Medication,” “SCID (Structured Clinical Interview for DSM Disorders),” and “Nicotine Addiction/Dependence” (Figure 2E).

The SchizConnect Mediator relates the above domain model concepts to the terms in the source schemas using inter-schema mappings (see Figure 2F for sample mappings). For

example, subject data for the NUSDAST source is obtained by calling the XNAT search web service and joining with a diagnostic code mapping table to harmonize the diagnoses; normalized diagnosis of Strict Schizophrenia for the subjects in the HID source is computed on the fly, by first joining three HID tables with subject and assessment data, then selecting the subjects according to a predefined algorithm on assessment values.

Currently, the SchizConnect model comprises 7 domain predicates, 17 source predicates (from the 4 sources HID, NUSDAST, COBRE and MCICShare, a local database that contains value mapping information, and utility functional sources), and 18 inter-schema mappings (10 for HID, 4 for NUSDAST, and 4 for COBRE/MCICShare). It is worth noting that since the inter-schema mappings are specified in a declarative rule language, the mediator is easily extensible to incorporate additional sources by writing the appropriate inter-schema mappings.

3.3. SchizConnect.org Web Portal and Example Queries

At the http://www.schizconnect.org/ web portal, the operating statuses of the data sources are displayed (Figure 3A). Queries are performed only on data sources that are operational. Data queries are constructed using a drag-and-drop GUI, in which a series of logical “AND” and “OR” operators can be concatenated filtering on domain model terms.

An example query is shown in Figure 3B, C, with summary return information presented in Figure 3D. Additional sample queries are listed in Table 3. Upon signing in, detailed subject-level information returned from the query is presented to the user as an on-screen table (Figure 3E). This table lists sortable domain model variables including provenance, age, sex, and scan parameters for each subject with downloadable images. The user can review and use this information to decide whether to further refine the query. The user also has the ability to modify, save and retrieve queries. A data download button is available that leads to the DUA page (Figure 3F). The user must sign the SchizConnect DUA, and has the option of choosing which participating source DUAs to agree with, and receives data only from data sources with which the DUAs have been agreed.

For downloading, the imaging data resulting from the queries are transferred out of the data sources and staged at the SchizConnect.org host, together with the returned meta-data table of the mediated variables. Transfer is performed via gridFTP, REST API, HTTP, or others, depending on the specific data transfer protocol at each source. Imaging data files are compressed and packaged into 10-GB easily reconstructable, individual 7-zip (http://www.7-zip.org/) segments, available for the user to download within a specified limited time period (currently 2 weeks). Depending on the size of the requested imaging data, it can take up to a few days for all data to be staged for download. These data files contain the original and/or preprocessed imaging data shared by each source, in DICOM, Analyze, or NIFTI formats. Links to these files along with unpacking instructions are sent to the user via email. The links are also available on the “My SchizConnect” page of the web portal (Figure 3G, H). Documentation for descriptions of image formats and directory structures can be found on the SchizConnect website (http://www.schizconnect.org/documentation). All cognitive and clinical data (see model description above) can be included in the download package along with the download imaging data. On the documentation page, the user can find useful

information including: Tutorials on how to use the website, DUAs of all data sources, data descriptions, data dictionaries, and peer-reviewed journal papers related to the data. Since not all neuroimaging data (such as scan sequence parameters) have been modeled into the SchizConnect domain hierarchy, it is important to provide technical information on our website to facilitate research. In the Data Description section, the NUSDAST description lists structural parameters (e.g., 3D MPRAGE: TR=9.7 ms, TE=4 ms, flip=10°, ACQ=1, 256×256 matrix, 1xl mm in-plane resolution, 128 slices, slice thickness=1.25 mm, 5:36 min scan time each) and the COBRE description lists resting-state parameters (resting state scans consisting of 149 volumes of T2*-weighted functional images, acquired using a gradient-echo EPI sequence: TR=2 s, TE=29 ms, flip=75°, slice thickness=3.5 mm, slice gap=1.05 mm, field of view=240 mm, matrix size=64 × 64, voxel size=3.75 mm × 3.75 mm × 4.55 mm). In the Publications section, we have provided a link to a peer-reviewed journal publication that provide detailed technical descriptions on each data source. For example, Gollub et al (2013) describes “the MCIC collection: a shared repository of multi-modal, multi-site brain image data from a clinical investigation of schizophrenia.” Similar papers describing all the other data sources currently participating in SchizConnect can be found here.

4. Discussions and Future Plans

These initial results demonstrate that SchizConnect allows combining of neuroimaging data from different databases via mediation to form compatible mega-datasets with accuracy and fidelity. In SchizConnect, data remains with the source rather than warehoused in a central repository. Providers maintain control of their data and do not need to modify them for sharing. The user query is done over a single, consistent, well-defined model that is translated to the schemas of the sources. This approach unburdens the user and each source from having to make contact and helping to interpret the data each time, especially when new data are being continuously added to the data source repository. The web portal is user-friendly and intuitive, appearing to the user as a single, virtual database with real-time query and download performance. As an on-going project, we are continuing to define additional domain model terms for neuropsychological and psychopathological variables, make available additional imaging modalities and subjects, and identify and evaluate potential new data sources. Work is also under way integrating with clinical research databases such as Research Electronic Data Capture (REDCap) (Harris et al., 2009) where clinical and cognitive assessment data are stored, further enhancing the functionality of SchizConnect by searching across imaging and non-imaging databases for the same subject.

SchizConnect shows considerable potential for overcoming current barriers for creating large-scale datasets to increase statistical power, accelerating the testing of new hypotheses and methods, and creating a resource for developing advanced techniques to better integrate disparate data at low cost. As a proof-of-concept for combining datasets, we compared SAPS/SANS and neurocognition across the current data sources. For SAPS/SANS, we found that while fewer schizophrenia subjects in the NU data scored 2 or higher, the distributions were not statistically different between sites. For neurocognitive measures, we computed z-scores on episodic memory, working memory, attention and executive function domains using each site’s own controls as reference sets. No statistical difference between

sites was observed (NU range: −1.23 to −0.71, FBIRN: −1.28 to −0.65), indicating that schizophrenia subjects across both consortia exhibit similar degrees of psychopathology and cognitive impairment. Nonetheless, subtle differences in cohort make-up may still exist upon closer inspection, but users will have the opportunity to explore the sources of potential heterogeneity and use such differences to benefit in developing new hypotheses.

SchizConnect was aimed at combining across different types of data repositories, and its current data sources are examples of classic types of data repository: The HID that houses the FBIRN data is a multisite study repository with prospectively collected data using predetermined protocols; The COINS Data Exchange that houses the MCICShare and COBRE data, and the XNAT Central that houses the NUSDAST data, are centralized data repositories where data from unrelated studies are uploaded and stored, and the database platforms provide the user with queryable data structures and interfaces. When owners of these datasets are willing to share subject-level data (i.e., scans, assessments), SchizConnect is designed to interact with such data repositories for mediation. When investigators are only willing to share measures, meta-analysis efforts such as the ENIGMA (Gupta et al., 2014; Thompson et al., 2014; Turner et al., 2015 (accepted); Wright et al., 2015 (accepted)) will be an excellent alternative for data sharing.

During the initial implementation of SchizConnect using the current data sources as test beds, we have established a series of domain models and their translations to the initial data source models. The SchizConnect mediation approach simply translates user queries into the query language of each data source (i.e., equivalent to the user performing the same query at the individual data source's own web portal). The SchizConnect data models can be extended easily to accommodate new data structures of a new data source while placing no restrictions on what the data source wants to share. Although the process of domain understanding and data modeling can be labor intensive, we have laid the foundation for extending SchizConnect to other schizophrenia neuroimaging data sources, which will build on the existing schemas. A limitation of the current domain model work is that the understanding and modeling of source data remains a manual step. In SchizConnect, this data mediation process starts with domain understanding by experts on the specific data that is being integrated so that we have a clear knowledge on the data terms and their definition. The data mediation experts can then integrate this new knowledge into existing SchizConnect models to enable the data to be accessed without requiring it to be modified. We have provided a questionnaire on the schizconnect.org web portal that can initiate the process, http://schizconnect.org/questionnaires/1/responses/new. It is important as a next step for us to develop approaches that learn from existing data to facilitate more automated procedures for inclusion of new data sources (e.g., following our previous work (Knoblock et al., 2012)). Another limitation is query evaluation in the virtual integration approach, is generally slower that query evaluation on a warehouse-model database.

Finally, SchizConnect is the only data finder (data broker) of its kind for researchers interested in combining neuroimaging data on schizophrenia and related disorders from disparate sources. Existing data portals such as the COINS, FBIRN, and XNAT Central, data sources used in this project, contain schizophrenia data but serve as repositories of these types of data. When users intent to combine data across these sources, harmonization of data

terms and mediation of these terms remain a critical challenge and barrier. SchizConnect is fulfilling this critical need, and the data mediation framework that SchizConnect created can be readily extended to other clinical domains including Bipolar Disorder. Recent developments on data harmonization have led to the creation of the Research Domain Criteria Database (RDoCdb) at the National Institute of Mental Health (NIMH) and its associated data repository, the National Database for Autism Research (NDAR) (Hall et al., 2012). It should be noted that SchizConnect is a virtual database that can mediate data sources that make ongoing updates to their repositories, and SchizConnect is focused on schizophrenia and related disorders. Administratively, the SchizConnect web portal is hosted at Northwestern University, the SchizConnect mediator is hosted at the Information Science Institute of the University of Southern California. For inclusion into SchizConnect, new data sources will be evaluated on completeness, quality, and enthusiasm to collaborate. The focus of the initial expansion will be the quickest return for the research community, so that larger, richer datasets that have been carefully collected and checked for completeness and quality (e.g., already analyzed and published) would be of the highest priority. Data repositories based on XNAT, or those are already in COINS can be more readily integrated, up to any new data models and new querying news. For valuable datasets without a database platform, we can help develop an XNAT, HID, or COINS.

It is our hope that SchizConnect can facilitate the testing of new hypotheses that are hitherto not possible, thus greatly promote discovery related to the mechanisms underlying schizophrenia. We aim to expand to repositories on psychosis and related disorders, thus facilitating large-scale dimensional research. We hope that SchizConnect will become the prototype for the study of psychiatric disorders, serving as a model for broader efforts for the integration and sharing of biomedical information across the greater scientific community.

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Highlights

- Query and combine imaging data from different databases within a single interface.
- A single, virtual database where live data remains at the sources.
- Web portal is user-friendly and intuitive, performing real-time query and download.
- It is the only data broker of its kind for schizophrenia and related disorders.
- SchizConnect currently contains data from 3 sources, and is extending to others.

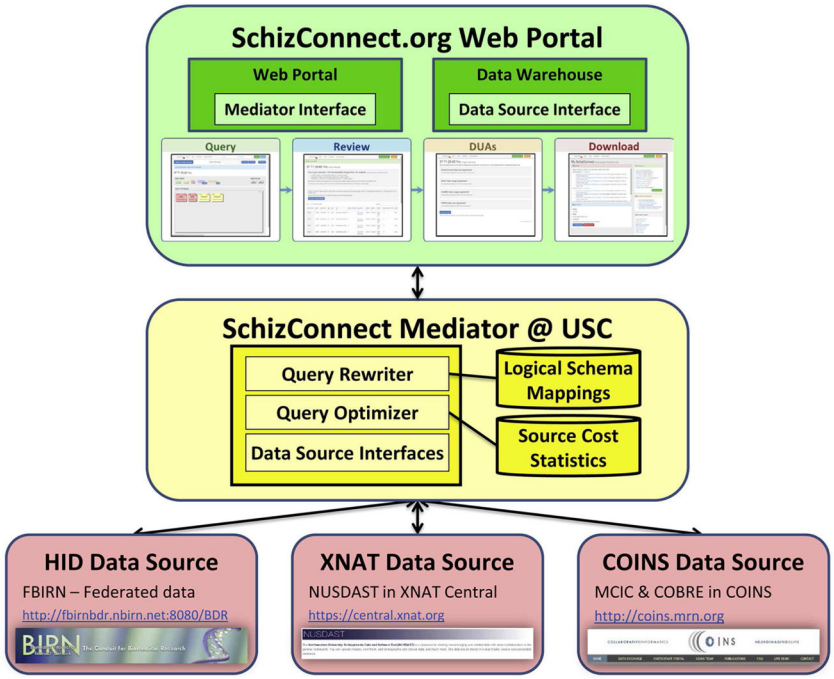


Figure 1. SchizConnect Architecture & Data Flow

The SchizConnect architecture has the following 3 components: the federated data sources, the SchizConnect Mediator, and the SchizConnect.org web portal. After the user builds the query at the SchizConnect web portal, the query command is passed to the SchizConnect Mediator engine. The Mediator engine then relies on the SchizConnect domain model to translate the incoming query into source-specific schemas, then queries each data source directly and in parallel, using source-specific query mechanisms, languages, and variables. The returns from the sources are handled by the Mediator engine, which provides the SchizConnect web portal with a unified results table. The SchizConnect web portal then interacts with the user for further processing, including signing of data use agreements and data download.

Figure 2a

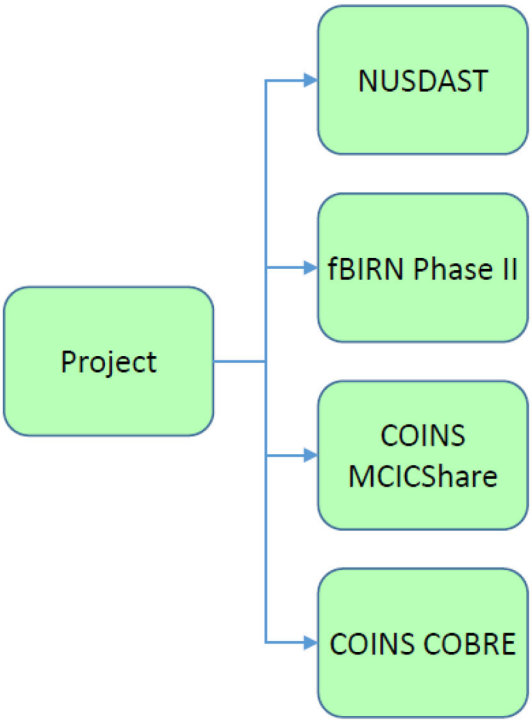
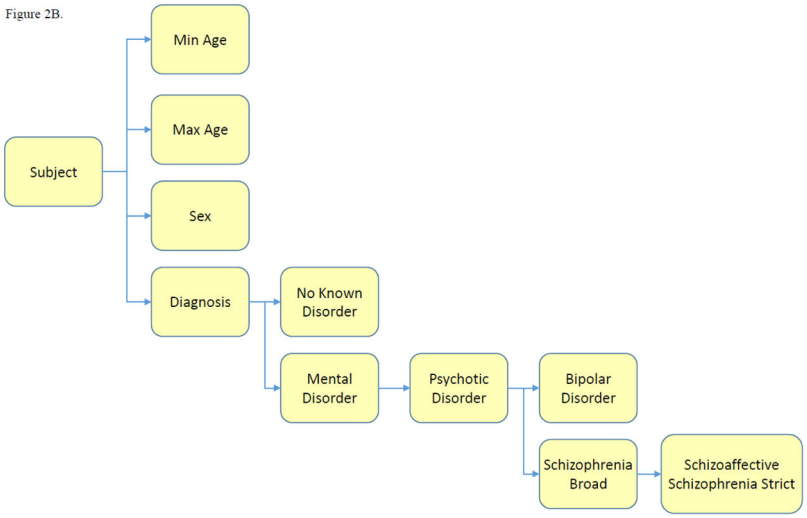


Figure 2B.



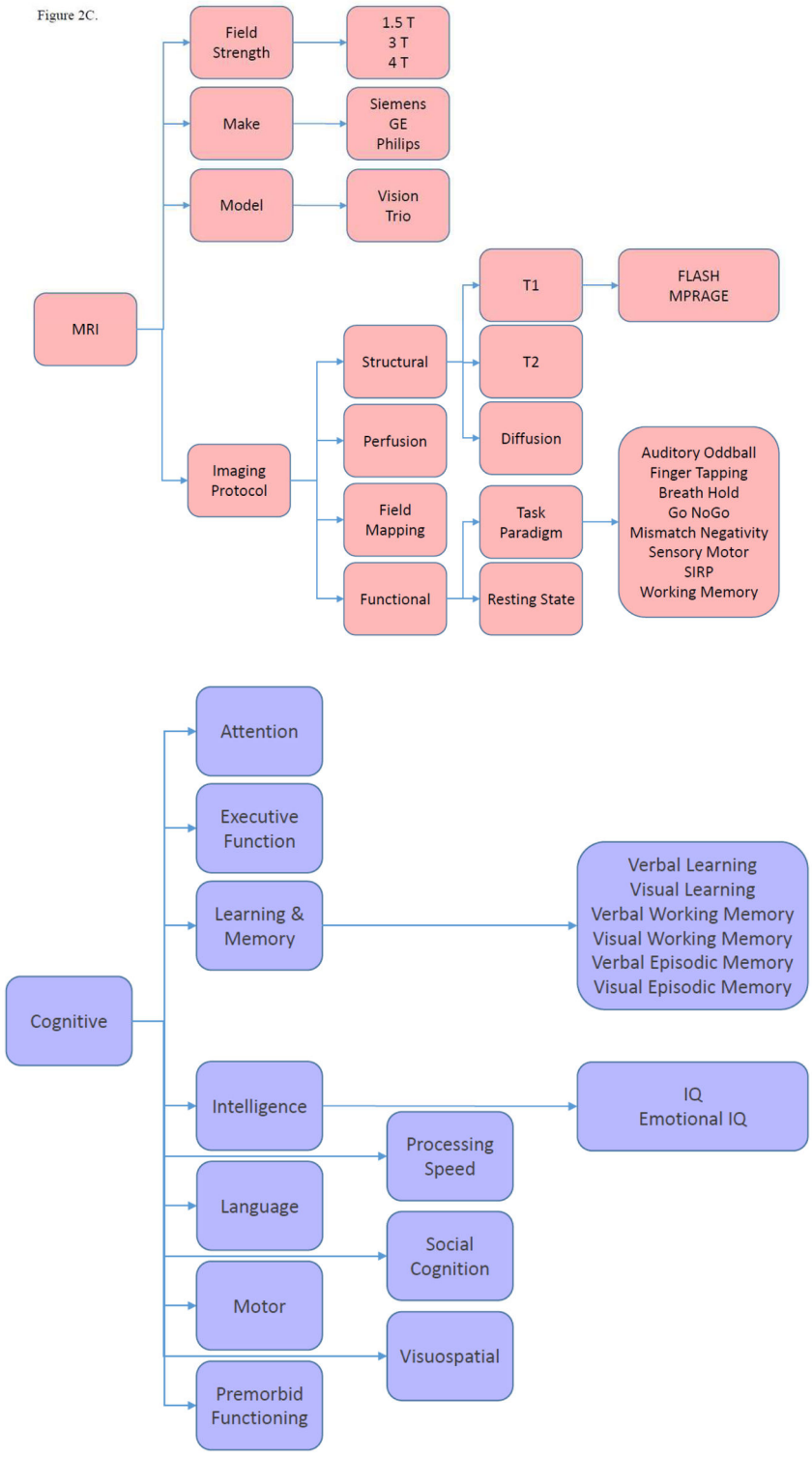


Figure 2d

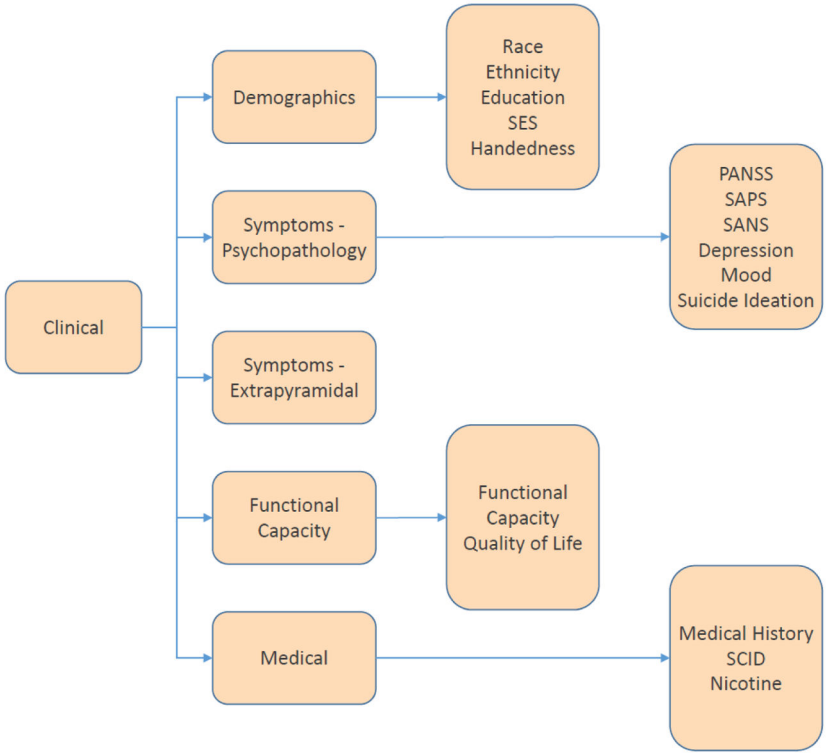


Figure 2e

```
subject("NUSDAST", SUBJECT_ID, AGE, SEX, DX) <-
   XnatSubjectResource_xnat__subjectData(project, SUBJECT_ID, AGE, SEX, SRC_DX, QS) ^
   MappingsMySQLResource_dx_mappings(DX, "NUSDAST", 777, SRC_DX, id)

subject("COINS", SUBJECT_ID, AGE, SEX, DX) <-
   COINSMySQLResource_subjects_v( SUBJECT_ID, SEX, yob, SRC_DX, STUDY_ID, AGE) ^
   MappingsMySQLResource_dx_mappings(DX, "COINS", STUDY_ID, SRC_DX, id)

subject("HID", SUBJECTID, AGE, SEX, DX) <- subject_age("HID", SUBJECTID, AGE) ^
                                 subject_sex("HID", SUBJECTID, SEX) ^ subject_dx("HID", SUBJECTID, DX)

subject_sex("HID", SUBJECTID, SEX) <-
   HIDPSQLResource_nc_assessmentvarchar( tableid2, nc_assessmentdata_uniqueid2, scoreorder2,
         owner2, modtime2, moduser2, textvalue2, textnormvalue2, comments2, SEX_SRC, datanormvalue2,
         storedassessmentid2, ASSESSMENTID2, SCORENAME2, scoretype2, ISVALIDATED2, isranked2,
         SUBJECTID, entryid2, keyerid2, raterid2, classification2, uniqueid2) ^
   (ASSESSMENTID2 = 28984) ^ (SCORENAME2 = "Gender") ^ (ISVALIDATED2 = "TRUE") ^
   MappingsMySQLResource_value_mappings(SEX, "HID", SEX_SRC, id)
...
subject_dx("HID",SUBJECTID, 'Mental_Disorder>Psychotic_Disorder>Schizophrenia_Broad>Schizophrenia_Strict')
<-  HIDPSQLResource_nc_subjexperiment( uniqueid, tableid, owner, modtime, moduser nc_experiment_uniqueid,
         SUBJECTID, nc_researchgroup_uniqueid) ^
    (nc_researchgroup_uniqueid = 9611 ) ^ (nc_experiment_uniqueid = 9610) ^
   HIDPSQLResource_nc_assessmentinteger( tableid1, nc_assessmentdata_uniqueid1, scoreorder1,
         owner1, modtime1, moduser1, textvalue1, textnormvalue1, comments1, DATAVALUE1, datanormvalue1,
         storedassessmentid1, ASSESSMENTID1, SCORENAME1, scoretype1, ISVALIDATED1, isranked1,
         SUBJECTID, entryid1, keyerid1, raterid1, classification1, uniqueid1) ^
   (ASSESSMENTID1 = 16415) ^ (SCORENAME1 = "SCID_P47") ^ (DATAVALUE1 = 3) ^
   HIDPSQLResource_nc_assessmentinteger( tableid2, nc_assessmentdata_uniqueid2, scoreorder2, owner2,
         modtime2, moduser2, textvalue2, textnormvalue2, comments2, DATAVALUE2, datanormvalue2,
         storedassessmentid2, ASSESSMENTID2, SCORENAME2, scoretype2, ISVALIDATED2, isranked2,
         SUBJECTID, entryid2, keyerid2, raterid2, classification2, uniqueid2) ^
   (ASSESSMENTID2 = 16415) ^ (SCORENAME2 = "SCID_P53") ^ (DATAVALUE2 = 1) ^
   (ISVALIDATED1 = "TRUE") ^ (ISVALIDATED2 = "TRUE")
```

Figure 2f

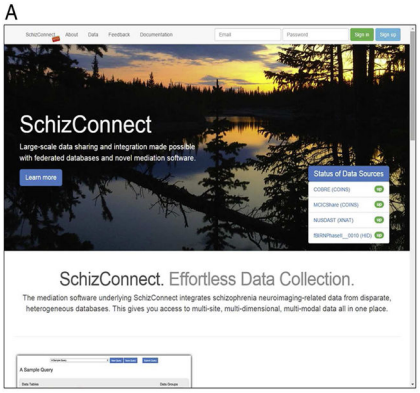
Figure 2. SchizConnect Mediator (Virtual) Domain Schema and Inter-schema Mappings

(A) Project, containing description of the research project for which data are collected. Currently 4 projects from 3 data sources are included in the domain model. **(B) Subject**, containing demographic and diagnostic information for individual participants of the project. “Subject” is subsequently defined by “minimum age,” “maximum age,” “sex,” and “diagnosis.” Current diagnosis categories are: “no known disorder” (for healthy controls), “bipolar disorder,” “schizophrenia broad,” which includes “schizophrenia strict” and “schizoaffective.” We note that the precise definition of “control” may depend on specific studies and study populations, we did not use the term “control” to label the healthy comparison subjects provided by each data source. Instead, the term “no known disorders” is used. **(C) Imaging_Protocol (MRI)**, containing information on MRI scanner platforms and imaging protocols under which subject imaging data were collected. “Imaging protocol” is subsequently defined by “structural,” “functional,” “perfusion,” and “field mapping.” Both “structural” and “functional” protocols are subdivided for further distinctions including “T1,” “T2,” “resting state,” and “task paradigm.” **(D) Cognitive** domain contains neuropsychological assessments. The domain model uses the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008) terms whenever appropriate, which are “attention,” “executive function,” “learning,” “working memory,” “episodic memory,” “intelligence,” “language,” “motor,” “premorbid functioning,” “processing speed,” “social cognition,” and “visuospatial.” **(E) Clinical** domain contains full demographics, assessments of symptoms and functional capacity, and medical information. Demographics information includes “Race,” “Ethnicity,” “Education,” “SES (socioeconomic status),” and “Handedness.” Symptom measures include “PANSS (Positive And Negative Symptoms

Scales),” “SAPS (Scale for the Assessment of Positive Symptoms),” “SANS (Scale for the Assessment of Negative Symptoms),” using the Unified Medical Language System (UMLS) terms whenever appropriate. Symptom measures also include “Depression,” “Mood,” “Suicide Ideation,”, and “Extrapyramidal Symptoms.” Medical information includes “Medical History/Medication,” “SCID (Structured Clinical Interview for DSM Disorders),” and “Nicotine Addiction/Dependence.”

(G) Examples of inter-schema mappings. For example, subject data for the NUSDAST source is obtained by calling the XNAT search web service and joining with a diagnostic code mapping table to harmonize the diagnoses; normalized diagnosis of Strict Schizophrenia for the subjects in the HID source is computed on the fly, by first joining three HID tables with subject and assessment data, then selecting the subjects according to a predefined algorithm on assessment values.

A



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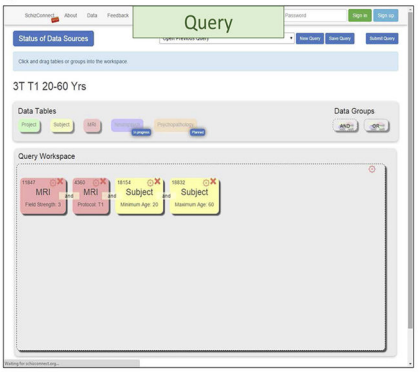

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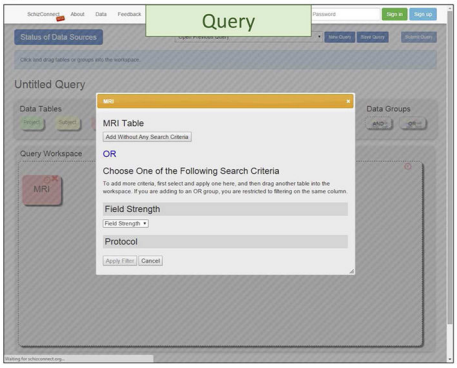

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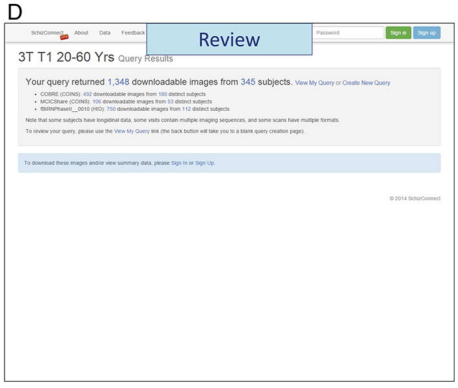

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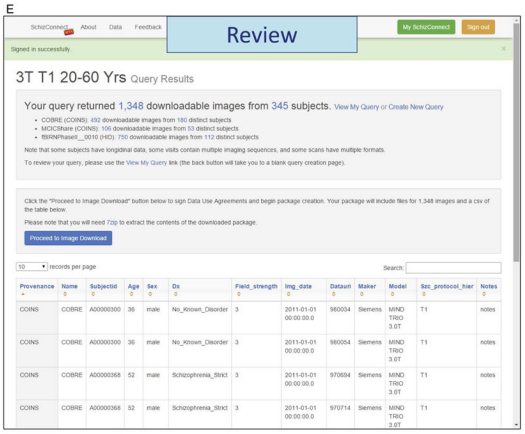

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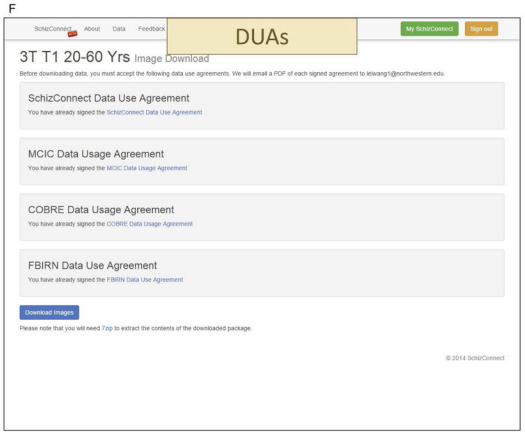

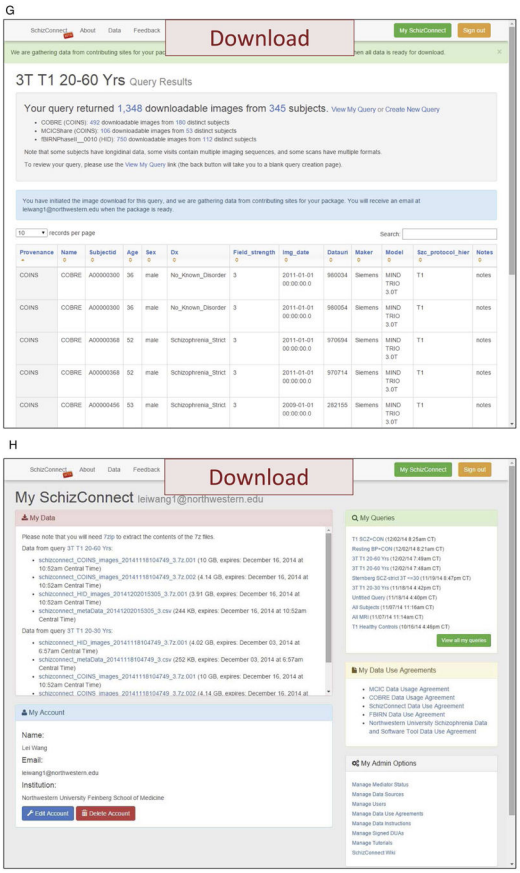

Figure 3. SchizConnect Web Portal, Query, and Return

(A) SchizConnet.org At the web portal, the status of the data sources are shown. If one or more of the data sources are unavailable due to source site maintenance or whatever reason, since each data source is queried independent of the others, data sources that are operational can still be queried. The end user is warned of the down sites and therefore their lack of return. **(B, C, D) Query and review without signing up.** Even without signing up, any end user has the ability to query SchizConnect. Here an example is shown for a query of "T1-weighted 3T scans of subjects between the ages 20 and 60." The query is built from a drag-and-drop user-friendly graphical user interface. This particular query would return 1,348 downloadable images from 345 distinct subjects from COBRE, MCICShare and fBIRNPhaseII datasets. **(E) Query and review after signing up.** After signing in, detailed subject-level information returned from the query are now provided as an on-screen table. This table lists sortable variables including provenance, age, sex, and scan parameters. The end user can review and use this information to decide whether to further refine the query. The user has the ability to modify, save and retrieve queries. A data download button is also active at this point, which will lead to the data use agreement page and then data downloading. In the case where multiple images are returned for the same subject, for example as the result of multiple acquisitions within the same MRI session, these images will be indicated with unique "Datauri"s (such as the first 4 entries seen here) fields. **(F, G, H) DUA and data download.** The user has the option of choosing which DUAs to agree with, and receive data only from data sources with which the DUAs have been agreed. The

imaging data resulting from the queries are first transferred out of the data sources and staged at SchizConnect.org host together with the mediated meta-data table for a specified limited time period for downloading. Imaging data files are compressed and packaged into 10 GB individual segments, easily reconstructable with the 7-zip utility (http://www.7-zip.org/). They contain the original and/or preprocessed imaging data shared by each source, in DICOM, Analyze, or NIFTI formats. Links to these files along with unpacking instructions are sent to the user via email and are available on the “MySchizConnect” page of the website.

Table 1

Sample Characteristics on Modeled Terms.

Dx	No Known Disorder	Schizophre nia Broad	Schizophre nia Strict	Schizoaffective	Bipolar Disorder	Sibling of Schizophrenia Strict	Sibling of No Known Disorder
Number of Current Subjects*	481	117	333	38	10	44	66
Gender (m/f)	295/186	87/30	242/91	22/16	5/5	21/23	16/50
Age (years) (mean±s.d.)	34.2±12.9	34.4±11.0	35.4±12.9	39.5±10.0	46.6±14.4	21.6±3.7	20.4±3.5
Age range (years) min – max	13 – 67	18 – 61	17 – 66	19 – 59	21 – 64	14 – 28	14 – 28

*40 subjects from the FBIRN database contains no diagnosis information and are not listed here.

Table 2

SchizConnect Data Sources, including Current and Planned Sample Sizes.

Data Source	FBIRN	NU	MRN
Project Name	FBIRN Phase II	NUSDAST	MCIC & COBRE
Database (Language)	HID (PostgreSQL)	XNAT (XML)	COINS Data Exchange (*)
URL	http://fbirnbdr.nbirn.net:8080/BDR/	https://central.xnat.org/REST/projects/NUDataSharing	http://coins.mrn.org/
Number of Current Subjects (with Imaging Data)	255 (251)	451 (368)	423 (410)
Image Type	Structural MRI Resting-state fMRI Task fMRI dMRI	Structural MRI	Structural MRI Resting-state fMRI Task fMRI dMRI
Number of Current Subjects with Multimodal Imaging$	208	-	404
Number of New Subjects (Timeline)	400 – fBIRN Phase 3 (2015)	130 (2015)	200 (2016)

*The native COINS architecture involves dynamic data packaging following the query, which does not allow for data to be immediately returned to the query engine. With permission from the COINS executive committee, an API was built to enable us to extract domain-model defined variables from the COINS databases and to duplicate them at the Mediator site. The database underlying the duplicated MCICShare/COBRE data is MySQL using the relational data model.

$Multimodal imaging is defined as having any of the combination of the following: T1, diffusion MRI, task-paradigm fMRI, and resting-state fMRI.

Table 3

Example Queries and Returns at SchizConnect.org.

Query Terms	Number of Images & Distinct Subjects Returned				
	Total	fBIRN @ HID	COBRE @ COINS	MCICShare @ COINS	NUSDAST @ XNAT
T1 SCZ+CON	3,178	1,048	484	264	1,382
	737	185	173	95	284
3T T1 20–60 Yr	1,348	750	492	106	-
	345	112	180	53	
T1 Healthy Controls	1,846	655	243	264	684
	439	113	94	95	137
Stemberg SCZ 3T<=30 Yr	210	210	-	-	-
	18	18			
Resting BP+CON	103	-	103	-	-
	101		101		
Sensory Motor + T1,SCZ+CON, 30–50 Yr (multimodal)	1,310	1,140	-	170	-
	119	83		36	
All MRI	21,309	13,552	1,596	4,347	1,814
	1,029	251	198	212	368