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(3) Available projects for 2020-21

PROJECT 1

PROJECT SUMMARY

Introduction

Psychotic disorders such as schizophrenia (Sz) and bipolar disorder affect ~4% of the population[1] and comprise the 5th leading cause of disability in developed countries[2]. Thought Disorder (TD) is prevalent in psychotic disorders, and is related to marked impairment in social and role function[3], which is not surprising, as an individual needs to think and speak clearly in order to have friends and hold a job. TD appears early in the course of psychotic disorder, and is evident in patients with recent-onset psychosis across diagnoses, in whom it can persist stably for years[4]. Subtle TD also exists in clinical high-risk (CHR) cohorts, in whom it predicts psychosis onset[5-11]. In familial high-risk studies, both positive TD (semantic incoherence) and negative TD (speech paucity) are evident as early as age 9 in children who develop Sz a decade later, with 94% accuracy in prediction[12]. As yet, there is no evidence-based treatment for TD beyond antipsychotics, and their efficacy is limited. A deep understanding of the dimensions of language disturbance in psychosis and its risk states, and among putatively normal individuals across development, is needed to develop novel remediation strategies for TD. 12% of the population worldwide endorses at least one psychotic symptom[13], including delusions, hallucinations and TD.

Objectives and Hypotheses

This multi-site R01 aims to elicit open-ended 30-45 minute narrative, using optimal interviewing techniques[14], from a large (N = 450) English-speaking cohort, with a range of language production disturbance from none/subtle to severe (CHR, FEP, HV) assessed for linguistic features, symptoms, diagnosis, cognition and function. Automated NLP (LSA and POS) analyses will be done in collaboration with IBM (Cecchi), and include metaphoricity/bizarreness and speech graphs[15] as complementary measures respectively of semantic coherence and syntactic complexity.

- **Hypothesis 1***: Semantic coherence will be correlated with positive TD and functional impairment.*
- **Hypothesis 2:** *Measures of syntactic complexity (from POS and speech graphs) will be correlated with negative TD and functional impairment.*

Methods

Four hundred and fifty participants will be included in the study (n=150 SCZ, N=150 CHR and n=150 HV) across the sites. All participants will have an open-ended audiotaped narrative interview of 30 to 45 minutes to elicit free natural speech[16,17]. Site interviewers will be trained to minimize interruption, and use clarifying questions to promote speech production. Interview audiofiles will be transcribed and manually de-identified at each site (substitution of proper names with pronoun or role). Interviewers will also ask participants at the beginning of each interview to not use full names. These de-identified transcripts will be used for both clinical (TLC) and automated linguistic corpus-based analyses. Speech transcripts will be rated for negative and positive TD using the TLC scale by research assistants trained to reliability[18]. Auxiliary ratings of TD include the PANSS[19] Disorganization factor[20,21] and SIPS Disorganized communication (P5)[22]. Brief measures of IQ (WASI), verbal fluency, processing speed and working memory (from the MATRICS[23]) will be administered, and analyzed as potential covariates. Global social and role function will be assessed using brief measures designed and validated for CHR patients[24], and also applied to healthy teens/young adults[24] and recent-onset psychosis

patients[25]. Demographic information will be obtained, including age, sex, ethnicity, and Hollingshead socioeconomic status, as well as use of medications, cannabis and tobacco.

Data Analysis Plan

The main goal of this proposal is to create a large archive of language data for automated linguistic corpus-based analyses of semantic coherence and syntactic complexity, to better understand thought disorder.
Specific Aim 1: We will apply latent semantic analysis (LSA)[26] to measure semantic coherence in language production, and examine its association with positive TD and functional impairment. We will use complementary semantic measures of metaphoricity/bizarreness to see if these strengthen these associations.
Specific Aim 2: We will apply part-of-speech (POS) tagging[27,28] to measure syntactic complexity in language production and examine its association with negative TD and functional impairment. We will use complementary speech graph methods to see if these strengthen these associations.
Specific Aim 3: This large rich archive of language data will be available for further circuit-based and physiological levels of analysis to determine the neural correlates of these linguistic correlates of TD, both semantic and syntactic. We will make language data available for analyses with PSYSCAN/HARMONY imaging, EEG/ERP and genetic data, and also archive the data at NDA for investigators to conduct other linguistic analyses, such as morphology and discourse.
In keeping with the NIMH strategic plan, we adopt an RDoC style framework. This study focuses on *Cognitive systems; language production.* Automated linguistic corpus-based analysis of semantics and syntax is a promising new paradigmatic approach to the characterization of TD and language disturbance, dimensionally and transdiagnostically, across development.

Transfer of Knowledge

Findings from this research will be presented in scientific conferences by the Principal Investigator and research staff periodically during the course of the study. After the completion of data collection, final analyses will be conducted and all study outcomes will be published in peer reviewed scientific journals and made accessible in public domain using PubMed central. As yet, psychiatrists rely primarily on clinical ratings derived from patient speech, expert assessments that have been informative in characterizing mental disorders. However, there are now objective and sensitive automated methods of "natural language processing" informed by developments in artificial intelligence, which can provide deep and comprehensive analysis of speech and language data. We have partnered with computer scientists at IBM to begin to apply these novel and powerful automated methods to speech analysis in psychiatric patients.

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PROJECT 2

PROJECT SUMMARY

Introduction

Schizophrenia (SCZ) is commonly identified with alterations in the dopaminergic system; however strong epidemiological evidence linking SCZ and cannabis suggests that the endocannabinoid (eCB) system plays a key role in disease pathophysiology. Early cannabis use increases the risk of developing SCZ by almost twofold in vulnerable individuals making cannabis a strong risk factor for SCZ acting through an unknown molecular mechanism [1,2]. An understanding of the neuropathology of the early course of SCZ such as First Episode Psychosis (FEP) and the state of clinical high risk (CHR) that precedes FEP is critically needed to identify new therapeutic targets for prevention and treatment.

Fatty acid amide hydrolase (FAAH) is the enzyme responsible for the metabolism of eCBs such as anandamide (AEA) setting the tone of the eCB, tightly regulating brain levels. In humans, dramatic elevations (up to eightfold) of AEA were detected in cerebrospinal fluid (CSF) of SCZ and FEP [3,4], and importantly in CHR [5], suggesting the presence of altered eCB metabolism (decreased FAAH) early in the course of SCZ, including its high risk states. However, no study has investigated FAAH, the eCB gatekeeping enzyme, in-vivo in brain in FEP or CHR, and its relationship with behavior and cognition is currently unknown.

Objectives and Hypotheses

To use a novel and validated radiotracer, [11C]CURB, to image the eCB enzyme FAAH using PET with a high-resolution research tomograph (HRRT) in antipsychotic-free patients with FEP and those at CHR of conversion to FEP as compared to healthy volunteers.

Hypothesis

- [11C]CURB binding (λk3) in the striatum and dorsolateral prefrontal cortex (DLPFC) will differ significantly across the three groups (FEP< CHR < HV).

Exploratory Aims and Hypotheses

(I)To examine the relation between [11C]CURB binding (λk3), and psychopathology and cognitive deficits in CHR and FEP participants. Hypotheses: [11C]CURB λk3 will correlate positively with (attenuated) psychotic symptoms (SOPS and PANSS) in the striatum, and DLPFC λk3 will be inversely correlated with cognitive deficits (RBANS score) in FEP and CHR. (ii) To examine the relation between [11C]CURB binding (λk3) and anxiety and stress. Hypotheses: DLPFC [11C]CURB λk3 will be positively related to anxiety (STAI) and chronic stress (TICS) and recent life events (RLE).

Methods

One hundred and fifty participants will be included in the study (n=50 SCZ, N=50 CHR and n=50 HV). The screening procedure includes a pre-screening phone interview and a baseline visit which includes a) psychiatric assessment including diagnosis, medication history and disease severity for SCZ and CHR; b) and collection of a urine sample (for toxicological screen and pregnancy test). All participants will undergo a [11C]CURB PET scan to quantify FAAH in brain, and an MRI scan for image analysis will be performed for each subject. Urine drug screen will be obtained for all subjects at screening and on the day of the PET scan visit if deemed necessary by QI. Clinical and neuropsychological/cognitive testing will also be performed.

Data Analysis Plan

All analyses will be carried out using SAS. All statistical tests will be two-sided. Prior to testing, a series of univariate analyses including chi-square tests, correlations, t-tests and ANOVAs will be carried out to ensure that the assumptions underlying all subsequent testing are reasonably well met.

Primary Hypothesis: To address our primary study hypothesis, a multivariate analysis of variance (MANOVA) model will be used with [11C]CURB binding (λk3) in DLPFC and striatum as our outcome variables and study

groups (SCZ, CHR and HV) as predictor. Should the main effect of group achieve significance (at an alpha level of 0.05), we will follow up with three separate ANOVAs exploring the effects of group (HV vs CHR, HV vs SCZ, CHR vs SCZ) on each of the two regions. To control our Type I error rate, Bonferroni adjustment will be used in these follow up ANOVAs, which have been taking into consideration in our sample size calculations. The alpha level for these pre-planned follow up comparisons is thus adjusted for multiple testing.
Exploratory Analyses: We will use an additional series of general linear models to investigate the effect of sex, age and relationships between symptomatology, stress, and cognitive measures with [11C]CURB binding (λk3) to address our exploratory hypotheses. Inclusion of additional covariates, including FAAH1 rs324420 genotype and any past history of recreational cannabis use will also be explored.

Transfer of Knowledge

Findings from this research will be presented in scientific conferences by the Principal Investigator and research staff periodically during the course of the study. After the completion of data collection, final analyses will be conducted and all study outcomes will be published in peer reviewed scientific journals and made accessible in public domain using PubMed central. To our knowledge, this study will be the first to test FAAH in SCZ and CHR in-vivo, thereby providing a potential biomarker of disease, and a novel target for new therapeutic agents. We see this study as an important stepping stone in understanding the role of eCB in psychiatric disorders.

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PROJECT 3

PROJECT SUMMARY

Introduction

Schizophrenia (SCZ) is a chronic and debilitating mental disorder affecting about 1% of the world population characterized by positive (i.e. delusions and hallucinations) and negative (i.e. avolition, alogia, anergia, affective flattening and anhedonia) symptoms as well as cognitive deficits with a complex etiology [1, 2]. Consistent with reported reductions in grey matter volume, a decrease in synaptic density has been repeatedly demonstrated in post-mortem brains of patients with SCZ [3-5]. This decrease is proposed to be the result of an exaggerated synaptic pruning during puberty [6]. However, proof of this mechanism is lacking. The new radiotracer [18F]SDM-8 is a radioligand targeting the synaptic vesicle glycoprotein 2A (Sv2A), located in vesicular membranes [7], has been proposed as a novel, robust and reliable tool to quantify synaptic density in living humans [8, 9]. While a very recent study has reported reduced Sv2A in chronic schizophrenia [10], this study will be the first to measure synaptic density in FEP and CHR in vivo in brain testing for the first time the hypothesis of an exaggerated synaptic pruning as disease mechanism of SCZ.

Microglia have a critical role in regulating synaptic pruning and synaptic density in the brain11. Microglia abundantly express the ATP-gated P2X7 ion channel and drive neuroinflammation by release of pro-inflammatory cytokines and cell surface receptors [18-21]. While most previous studies have used translocator protein 18kDa (TSPO) as a proxy for microglial activation [24], using the novel P2X7 receptors provides an unprecedented opportunity to quantify microglial activation in brain. A recent study using schizophrenia patient-derived cells reported excessive synaptic elimination reflecting abnormalities in both microglia-like cells and isolated synaptosomes [14], providing evidence for a link between microglial activation and synaptic pruning in schizophrenia. This hypothesis is further supported by imaging and post-mortem studies reporting reductions in spine density and gray matter volume, cortical thinning and hippocampal atrophy in schizophrenia patients [15-19].

In summary, combining a novel neuroimmune PET marker of neuroinflammation with a measure of synaptic density is critical for understanding the brain alterations in the course of CHR to SCZ. The unique availability of both radiotracers [18F]SDM-8 and [18F]JNJ-64413739, provide an unprecedented opportunity to find early biomarkers for disease stratification and new candidates for therapeutic intervention early in the disease.

Objectives and Hypothesis

To quantify Sv2A and P2X7 in vivo using [18F]SDM-8 and [18F]JNJ-64413739 PET in patients with psychosis related disorders (FEP and CHR) as compared to healthy volunteers (HV).

Hypotheses:

- [18F]SDM-8 binding (VT) in the prefrontal cortex (PFC) and hippocampus will be significantly different between study groups (HV>CHR>FEP).
- [18F]JNJ-64413739 binding (VT) in the prefrontal cortex (PFC) and hippocampus will be significantly different between study groups (HV<CHR<FEP).

Exploratory Aims and Hypotheses: To examine the relationship between synaptic density (indexed as [18F]SDM-8 binding (VT)) and neuroinflammation (indexed as [18F]JNJ-64413739 binding (VT) with a) grey matter volume and microstructure, b) cognitive function, and d) overall psychopathology in CHR and FEP.

Hypotheses: Decreased [18F]SDM-8 binding (VT) and increased [18F]JNJ-64413739 binding (VT) in PFC and hippocampus will be associated with a) decreased grey matter volume and neuritic density, and increased qT1 and mean diffusivity, b) decreased verbal learning and declarative memory performance, and c) increased total psychopathology in CHR and FEP.

Methods

Up to 135 participants (completers) will be included in the study (n=45 FEP, N=45 CHR and n=45 HV. The screening procedure to determine eligibility includes a pre-screening phone interview and a baseline visit which includes a) informed consent (FEP and CHR participants must be capable to provide consent as determined by the MacArthur Competence Assessment Tool for Clinical Research (MacCAT); b) clinical assessments to determine diagnosis and symptom severity, review of medical history, current and past medications used, and weight and height, and c) collection of a urine sample (for toxicological screening and a pregnancy test for female participants). Urine drug screen will be conducted for all participants at the baseline visit, and an additional urine drug screen may be requested on the day of the PET scan if deemed necessary by the QI. Clinical and neuropsychological/cognitive testing will also be performed.

Data Analysis Plan

All analyses will be carried out using SPSS and R software. Statistical tests will be two-tailed. Prior to testing, a series of univariate analyses including chi-square tests, correlations, t-tests and analyses of variance (ANOVAs) will be carried out to ensure that assumptions underlying all subsequent testing are reasonably well met.
Primary hypotheses: The relationship between [18F]SDM-8 binding (VT) and schizophrenia diagnosis or groups (HV, CHR, FEP), psychotic symptoms and sex will be tested using a random-effect linear mixed model with group as fixed factor, region of interest ROIs (PFC and hippocampus) as a repeated within-subject fixed factor with a diagonal covariance structure, participant identification number or subjects as a random effect (including intercept), and regional [18F]SDM-8 (VT) as the dependent variable. To address our primary study hypothesis, we will test the difference between groups (HV, CHR, FEP) in [18F]SDM-8 binding (VT) as the outcome measure, using a mixed-effect model. Common sources of confounding factors such as age, sex, medications and tobacco may be included as covariates, if needed. Should the main effect of group achieve significance (at an α level of 0.05), we will follow up with separate ANOVAs exploring the effects between clinical groups.
Exploratory analyses: We will use an additional series of general linear models to investigate the effect of sex, age, antipsychotic medication exposure and relationships between MRI outcome measures (grey matter volume, neuritic density, mean diffusivity and qT1), psychopathology, and cognitive measures to address our exploratory hypotheses. Inclusion of additional covariates, including past/current use/history of recreational cannabis use will also be explored.

Transfer of Knowledge

Findings from this research will be presented in scientific conferences by the Principal Investigator and research staff periodically during the course of the study. After the completion of data collection, final analyses will be conducted and all study outcomes will be published in peer reviewed scientific journals and made accessible in public domain using PubMed central. To our knowledge, this study will be the first to test Sv2A and P2X7 in SCZ and CHR in-vivo, thereby providing a potential biomarker of disease, and a novel target for new therapeutic agents. We see this study as an important stepping stone in understanding the role of synaptic density and neuroinflammation in psychiatric disorders.

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