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TITLE: Genetic and Environmental Influences on the Pathogenesis of Parkinson's Disease: Young Adult Brain and Behavioral Risk Indicators

PRINCIPAL INVESTIGATOR: Virginia Rauh, ScD

CONTRACTING ORGANIZATION: TRUSTEES OF COLUMBIA UNIVERSITY

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6. AUTHOR(S)
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study addresses questions about the causes and progression of Parkinson's disease (PD) over the life course, specifically with respect to the role of a toxic chemical exposure, chlorpyrifos (CPF), an organophosphate pesticide. To understand how early exposure to CPF affects the nervous system, genetic susceptibility to CPF, and the long-term consequences of exposure, we are studying 200 young adults in an urban community cohort, now reaching 19-20 years of age, many of whom were routinely exposed to residential pesticides, as measured by a biomarker of CPF in cord blood. We are conducting neurological assessments of stiffness and gait, cardiac measures, sleep questions, measures of tremor, olfactory status, and other neuropsychological measures. We have access to previously-collected genetic information. The assessment requires 45-50 minutes; participants are paid $100 and cost of transportation. The purpose is to identify the earliest signs of risk for later PD that may appear long before clinical and motor symptoms can be seen, and to determine who is at greatest risk. We hypothesize that the individuals who were most highly exposed to CPF during the prenatal period (based on cord blood sample) will be more likely to show pre-motor and pre-clinical symptoms on these tests, as compared to individuals with lower exposure, and that some individuals may be more susceptible to exposure based on their genetic characteristics.

15. SUBJECT TERMS
NONE LISTED

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TABLE OF CONTENTS

1. Introduction

This study addresses the role of toxic chemical exposures, organophosphate pesticides (OPs), that may contribute to our understanding of the causes and progression of Parkinson's disease over the life course. To date, there is little knowledge about how OPs inflict nerve damage potentially resulting in parkinsonian symptoms, and even less information about how early in life the non-motor and pre-clinical signs of damage can be seen. To learn more about how these chemicals attack the nervous system, genetic susceptibility to these chemicals, and the long-term consequences of exposure, we will study an urban minority birth cohort, now reaching 19-20 years of age, many of whom were routinely exposed to residential OP use, prior to the indoor residential ban in 2001. We invite 200 of these young adults to participate in an examination, including neurological measures of stiffness and gait, cardiac measures, sleep questions, measures of tremor, and other neuropsychological measures. We also have access to genetic information, previously collected on the individuals. The assessment requires 45-50 minutes, and the purpose is to identify the earliest signs of risk for later PD that may appear long before clinical and motor symptoms can be seen. We hypothesize that the individuals who were most highly exposed during the prenatal period (based on a cord blood sample) will be more likely to show pre-motor and pre-clinical symptoms, as compared to individuals with lower exposure, and that some individuals may be more susceptible to the exposure based on their genetic characteristics.

2. Keywords

Parkinson's disease
Parkinsonism
Neurodegenerative disease
Neurotoxicity
Environmental exposure
Pesticides

3. Accomplishments

3a. Major Goals

Goal 1: Identify signs of early PD risk in the form of neurological dysfunction, REM sleep behavior disorder, autonomic dysfunction, and olfactory deficits in a sample of 200 19-20 year old individuals selected from a prospective cohort with varying levels of prenatal CPF exposure, as previously measured

Milestones associated with Goal 1 (all on-going through the 30th month of the project):

- Number of assessments to be counted as completed to achieve an average rate of 1-2 assessments/week
- Neurological examinations completed in face-to-face assessment (60% completion)
- Behavioral, olfactory and survey measures completed (60% completion)
- The Actiheart reads, meetings, processing and supervision will follow the same schedule (60% completion)
- Data entry and programming will begin in the 3rd month, after a lag time for the setting up of data entry screens, and will continue through the 30th month (60% completion)
- The review of the clinical assessments will be conducted as the examinations are completed (60% completion)

Goal 2: Measure associations between prenatal CPF concentrations (previously collected data) and signs of early PD risk (as identified in Goal 1)

Milestones associated with Goal 2 (no statistical analyses have commenced, since data collection is in the preliminary stages, and will be on-going through the 30th month of the project):

- Statistical analysis of associations between prenatal CPF, neurological measures, REM sleep behavior disorder, autonomic dysfunction (Actiheart), cognition and olfactory deficits (0% completion)
- Preparation of papers and reports (0% completion)

Goal 3: Stratify the sample and measure associations between selected *PON1* gene variants and signs of early PD risk, regardless of exposure

Milestones associated with Goal 3 (no statistical analyses have commenced, since data collection is in the preliminary stages, and will be on-going through the 30th month of the project):

- Characterization of *PON1* genotype distribution (50% completion)
- Statistical analysis of main associations between *PON1* gene variants and all indicators of early PD risk (neurological measures, REM sleep behavior disorder, autonomic dysfunction--Actiheart, cognition and olfactory deficits) (0% completion)
- Preparation of papers and reports (0% completion)

Goal 4: Test for effect modification of the primary CPF exposure-PD risk outcome by subject genotype; conduct exploratory analyses of this effect modification using various combinations of maternal and child *PON1* gene variants to potentially identify those subjects who would be expected to be most susceptible to the adverse impact of CPF exposure on PD risk symptoms

Milestones associated with Goal 4 (no statistical analyses have commenced, since data collection is in the preliminary stages, and will be on-going through the 30th month of the project):

- Exploratory statistical analysis of the interaction effect of CPF and genotype (*PON 108* and *PON 192*) on neurological symptoms, physiological measures, and behaviors (0% completion)
- Preparation of papers and reports (0% completion)

3b. Activities, Objectives and Results to Date

Goal 1: Identify signs of early PD risk in the form of neurological dysfunction, behavioral and cognitive anomalies, REM sleep behavior disorder, autonomic dysfunction, and olfactory deficits in a sample of 200 19-20 year old individuals selected from a prospective cohort with varying levels of prenatal CPF exposure, as previously measured

Specific Objectives:

- Conduct a 45-60 minute assessment on each recruited and consented individual
- Neurological/clinical components of the assessment to include evaluations of extrapyramidal motor dysfunction, dystonia, bradykinesia and tremor
- Behavioral and physiological components to include evaluations of non-motor symptoms, REM sleep behavior disorder, cognitive components, and autonomic dysfunction (heart rate variability), and olfactory deficits

Major Activities:

A. *Implementation of the Protocol*

The following tools/methods, comprising the neurological, behavioral and physiological protocol were implemented during this 12 month project period:

- D-KEFS (Delis-Kaplan Executive Function System) Trail Making Test: 5 conditions
- D-KEFS Color-Word Interference Test (Stroop Test)
- CANTAB (Cambridge Neuropsychological Test Automated Battery [CANTAB] includes highly sensitive, precise and objective measures of cognitive function, correlated to neural networks. We measure: Episodic memory, Working memory, Executive function, Planning, Information processing. The specific tests include: Motor Screening Task (MOT), Paired Associates Learning (PAL), Reaction Time (RTI), Pattern Recognition Memory (PRM), One Touch Stockings of Cambridge (OTS), and Spatial Working Memory (SWM)
- Timeline Followback (TLFB) (Sobell and Sobell, 1992; Del Boca and Darkes, 2003) is one of several self-report tasks used to measure alcohol consumption, and is characterized by a retrospective daily self-report of alcohol use quantity for a period of time (often 30 days) preceding the assessment day. Also included is a 30 day recall use for Nicotine, Cannabis and other drugs
- BAI: Beck Anxiety Inventory® (BAI®) is a brief, criteria-referenced assessment for measuring anxiety severity and level
- BDI: Beck Depression Inventory®-II (BDI®-II) is a brief, criteria-referenced assessment for measuring depression severity
- COMPASS 31: This brief interview asks questions about movement, constipation, eye and mouth symptoms, and other autonomic functions.
- RBDSQ: REM sleep Behavior Disorder Screening Questionnaire to facilitate the identification of subjects with REM Sleep Behavior Disorder.
- UPDRS: Unified Parkinson's Disease Rating Scale
- Fahn-Marsden Scale (F-M) measures dystonia
- Spiral: ten Archimedean spirals with each hand inside a 10x10 cm square on 8.5x11 inch letter-size paper, using a wireless, inked writing pen on a 9x12 inch digitizing graphics tablet (Intuos 4,Wacom technology, Vancouver, WA) connected via standard USB to a computer using proprietary software.
- UPSIT: The University of Pennsylvania Smell Identification Test
- Actiheart (Heart Rate Variability device and software)

B. *Quality Control and Safety Read*

Dr. Sloan regularly reviews all HRV data. Any child scoring in the abnormal range on any measure has been contacted directly, and permission obtained to contact his/her physician for potential referral to the New York Presbyterian Hospital for clinical evaluation to confirm diagnosis of any serious disorder and to offer treatment if needed.

C. *Reimbursement for Travel and Volunteer Payment*

This was accomplished according to university policies involving a secure system to distribute and monitor cash payments at the time of the assessment.

D. *Institutional Review Board Approval*

Modifications were made to return to in-person assessments following the lifting of the COVID pause. IRB approval was obtained.

E. *Recruitment, Informed Consent, Scheduling and Testing*

Beginning with the oldest individuals in the eligible cohort, we have enrolled and tested 110 subjects. The full study team has met regularly to coordinate and monitor all start-up activities throughout the study period, initially in-person and using zoom calls during the pandemic pause. As described here (Results) and below in more detail (Changes/Problems), the protocol shifted to a remote format for a 5-month period, and resumed the in-person format on 09/01/2020.

Results:

- Data Collection:
  - N=110 subjects (56.0%) have been fully assessed between the start of the project (09/01/19) and the completion of this project period (08/31/21). Of these subjects, 83 have been assessed in person, and 27 by remote assessment only (during the COVID17 pause, see below). N=110 reflects the total study enrollment and assessment through the current project period.
  - Following the COVID in-person assessment pause in the previous project period, we have recontacted and brought into the study offices 33 of those subjects who had received remote testing during the pause (N=60), so that 27 reamin to be retested. This recontact has been time-consuming but very worthwhile in bringing us back up to our timeline.
  - This progress report covers work completed through 08/31/21. As noted in the previous annual report, in person assessment was resumed on 09/01/20 (following the COVID pause).
- Data entry: All data that have been collection (described above) have now been entered into the master data system. David Merle continues to oversee the data cleaning, entry and storage.
- Review of genetic data: Dr. Deliang Tang has retrieved the genetic data from the parent cohort and commenced review of the data for the 110 subjects who have been assessed either virtually or in person to date.

Goal 2: Measure associations between prenatal CPF concentrations (previously collected data) and signs of early PD risk, as identified in Goal 1

Major activities and objectives:
Statistical analyses that integrate clinical, behavioral and physiological data await the completion of data collection and data entry.

Results:
Nothing to report

Goal 3: Stratify the sample and measure associations between selected *PON1* gene variants and signs of early PD risk, regardless of exposure

Major activities and objectives:
Statistical analyses awaiting the completion of data collection are as follows: (a) analyze the distribution of polymorphisms and the associations between genetic factors and chlorpyrifos blood levels in mother and infan; (b) test the main associations between CPF exposure, genotype and known level of enzyme activity; and (c) explore the interaction effect of CPF and genotype (*PON108* and *PON192*) on neurological symptoms, physiological measures, and behaviors.

Results:
Nothing to report

Goal 4: Test for effect modification of the primary CPF exposure-PD risk outcome by subject genotype; conduct exploratory analyses of this effect modification using various combinations of maternal and child *PON1* gene variants to potentially identify those subjects who would be expected to be most susceptible to the adverse impact of CPF exposure on PD risk symptoms

Major activities and objectives:
Statistical analyses to accomplish this objective await the completion of data collection and data entry.

Results:
Nothing to report

3c. Opportunities for training and professional development

Nothing to report

3d. Dissemination of results to communities of interest

Nothing to report

3e. Plans for the next reporting period to accomplish goals

We plan to continue to work on Goal 1 during the next project period, and to commence work on Goals 2-4. We do not anticipate any changes in objectives and scope. We plan to recruit and assess 40-50 additional subjects from the parent cohort during the next semi-annual project period. With respect to Goal 1, we will continue to recruit subjects from the parent cohort, with varying levels of prenatal CPF exposure, for the purpose of assessing current neurological and neuropsychological function. The aim is to assess the prevalence of pre-clinical extrapyramidal motor dysfunction (dystonia, bradykinesia, arm tremor), prevalence of non-motor symptoms (REM sleep behavior disorder, autonomic dysfunction, cognitive anomalies, and olfactory deficits), which are known to precede motor symptoms in PD; and to subsequently link early CPF exposure to these outcomes. In addition, we will continue data cleaning and entry with the Data Coordinating Center (DCC) where all data will be deposited and integrated with previously-collected cohort data.

4. Impact

4a. Impact on the development of the principal discipline(s)

Nothing to report

4b. Impact on other disciplines

Nothing to report

4c. Impact on technology transfer

Nothing to report

4d. Impact on society beyond science and technology

Nothing to report

5. Changes/Problems

5a. Changes in approach and reasons for change

As noted above, and reported in the previous annual report, in-person data collection was paused on 03/31/20 as a result of the COVID-19 pandemic. During the pause period, covered in our previous progress report(04/01/20 – 08/31/20), we were fortunate to be able to continue to recruit, consent and assess new subjects using all data collection methods that could be conducted using a zoom platform, without a major change to the scope of the work. These assessments included an online version of the CANTAB, all survey instruments and the UPSIT mailed to the subjects and administered in real time by zoom. The Actiheart test

and clinical neurological exam were paused during the remote testing phase. Because of the commitment and diligence of the project coordinator and RA, who quickly pivoted to remote data collection, we were able to recruit and partially assess 60 new subjects, at a rate that exceeded our target rate of 1-2 subjects per week. Incentives were payed to the subjects at a reduced rate because of the partial assessment, and we were able to save the cost of transportation. These activities were reported in the previous annual progress report. This current annual progress report includes the re-contact and in-person assessment for 33 subjects, who were missing the clinical and physiological assessments because of the COVID pause. This effort has brought us in line with our original timeline.

5b. Actual or anticipated problems or delays and actions or plans to resolve them

We have brought back 33 of those subjects who were remotely assessed on the survey, UPSIT and cognitive measures in order to complete in-person testing (neurological exam and heart rate variability test). This assessment has been considerably shorter and we are almost completely caught up to the planned data collection schedule. The Columbia University medical campus has put in place excellent safety procedures, and although COVID has made research activities more challenging, we are glad to report that we are successfully meeting our milestones.

As noted in our previous progress report, the unanticipated COVID-19 pandemic, requiring a shift in the venue and the timing of test administration, has resulted in an interesting opportunity to collect some test-retest reliability data, comparing remote versus in-person assessments. To the extent possible, we plan to re-administer the UPSIT and several other survey and cognitive measures (which were conducted remotely) to 10-20 subjects following the resumption of in-person testing, and to compare test results. In the event that there is a future spike in COVID-19 cases, and a forced lock-down in the future, requiring us to reactivate the remote protocol, we will have some useful information about the reliability of assessments.

5c. Changes that had a significant impact on expenditures

Subject compensation for travel and volunteer payments were reduced during the COVID pause (when a partial assessment was completed requiring less subject time). The cost savings has permitted us to bring those subjects into the office to complete the remainder of the testing in person (neurological exam and heart rate variability) for which they have been compensated.

5d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

- Significant changes in use or care of human subjects None noted
- Significant changes in use or care of vertebrate animals NA
- Significant changes in use of biohazards and/or select agents NA

6. Products

- **Publications, conference papers, and presentations**
  Nothing to report

- **Website(s) or other Internet site(s)**
  Nothing to report

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Nothing to report

- **Other Products**
  Nothing to report

7. Participants & Other Collaborating Organizations

Name:	*Virginia A. Rauh, ScD*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-3164-9892*
Nearest person month worked:	*2.0*
Contribution to Project:	*Dr. Rauh has overseen all aspects of the project, including hiring training, protocol development, Human Subjects approvals, and met regularly with the research team.*
Funding Support:	*NA*

Name:	*Roy N. Alcalay, MD*
Project Role:	*Co-I*

Researcher Identifier (e.g. ORCID ID):	*0000-0002-5717-4875*
Nearest person month worked:	*1.0*
Contribution to Project:	*Dr. Alcalay has supervised the collection of clinical data on the study participants including the motor and non-motor examinations. He has reviewed and scored the videos of movements.*
Funding Support:	*NA*

Name:	*Hiral Shah, MD*
Project Role:	*Movement disorders neurologist (junior faculty)*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-6854-0263*
Nearest person month worked:	*.80 cal months** [note this effort was reduced for Y2 due to Dr. Shah's resignation from Columbia and Dr. Kwei coming on board to take her place.*
Contribution to Project:	*Dr. Shah has clinically examined study participants, including administration of the MDS-UPDRS.*
Funding Support:	*NA*

Name:	*Kwei, Kimberly, MD*
Project Role:	*Movement disorders neurologist (junior faculty)*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-0907-2807*
Nearest person month worked:	*.60 cal months** [Dr. Kwei has taken the place of Dr. Shah*
Contribution to Project:	*Dr. Kwei has clinically examined study participants, including administration of the MDS-UPDRS.*
Funding Support:	*NA*

Name:	*Elinol Lopez*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-6744-9924*
Nearest person month worked:	*6.0*
Contribution to Project:	*Ms. Lopez has made recruitment calls, consented and administered all questionnaires and cognitive tests.*
Funding Support:	*NA*

Name:	*Wanda Garcia*

Project Role:	*Project Coordinator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-5559-2432*
Nearest person month worked:	*3.00*
Contribution to Project:	*Ms. Garcia has overseen all protocol activities, including the finalization of measures, IRB tasks, compensation of participants, scheduling, and data collection. She has organized regular staff meetings and ongoing internal reports.*
Funding Support:	*NA*

Name:	*David Merle*
Project Role:	*Database programmer*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.0*
Contribution to Project:	*Responsibilities include establishment of the database schema and electronic capture forms required to integrate data acquired from all sources in the proposed research into the central Columbia Center for Children's Environmental Health database. Mr. Merle oversees batch uploads of data, and works closely with the Wanda Garcia*

	(project coordinator) and Dr. Rauh. He programs the generation of self-documenting statistical files in including SAS, SPSS, R and any other format that may be required for data analysis.
Funding Support:	*NA*

Name:	*Grace Liu*
Project Role:	*RA for Heart Rate Variability Analysis-Data Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.0*
Contribution to Project:	*Responsibilities include collection and recording of data on each physiological signal. She is responsible for file storage on a shared, secured server; visual review of each type of data; and manually correcting invalid data points and/or annotating segments of unusable data via keyboard input.*
Funding Support:	*NA*

- **Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period**

For Dr. Rauh's other support document, the following grants are no longer active:

- 17-A1-00-006514-02 Prenatal WTC Chemical Exposures, Birth Outcomes and Cardio Metabolic Rates

For Dr. Alcalay's other support document, the following grants are no longer active:

- **What other organizations were involved as partners?**

Nothing to report

- **Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period**

For Dr. Rauh's other support document, the following grants are no longer active:

- 2P50ES009600-16 EPA 8361540, Columbia Center for Children's Environmental Health
- R01 ES021806 05 Pre- and Postnatal PBDE Exposure Thyroid Hormones and Neurodevelopment
- Grant #1189, Ecological Assessment of Health Interventions to Achieve Communities of Opportunity in Affordable Housing Settings

The following grants are newly active:

- NIH R01ES030950 (Margolis) Environmental bisphenol exposure, infant brain and behavior: Human and animal models.
- RFMH 137497 (R01ES027424-04) (Herbstman and Beebe), Prenatal endocrine- disrupting chemicals and social/cognitive risk in mothers. Role: Co-Investigator

For Dr. Alcalay's other support document, the following grants are no longer active:

- PF-SPE-1923 (Alcalay, Project PI) The Parkinson's Foundation, PDGENE Survey
- MJFOXFD 13841 (Alcalay PI) The Michael J Fox Foundation, Analysis of GBA-related Biomarkers in Parkinson s Disease
- Inflammatory markers in GBA/PD (Alcalay, Dzamko PI) The Michael J Fox Foundation, Analysis of inflammatory biomarkers in GBA carriers with and without PD from the Spot study
- T Cell-Mediated Autoimmune Responses in PD (Alcalay, Sulzer PI) The Michael J Fox Foundation
- Genetic modifiers of GBA-associated PD (Alcalay/Gan-or PI) The Michael J Fox Foundation
- Phosphatidylethanolamine metabolism alteration in Parkinson disease: a novel mitochondrial Biomarker (Guardia-Laguarta, PI) The Michael J Fox Foundation
- GBA-pathway lysosomal genes in PD (Alcalay/Gan-or PI),The Michael J Fox Foundation

The following pending award is now active:

- NIH P50 NS108675 UAB Udall (Yacoubian)(subcontract), Macrophage cells from LRRK2 carriers and controls

- **What other organizations were involved as partners?**

Nothing to report

8. Special Reporting Requirements

- **QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

Appendices

1. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report.* ***DO NOT RENUMBER PAGES IN THE APPENDICES.***