University of Pittsburgh

Annual Progress Report: 2010 Nonformula Grant

Reporting Period

July 1, 2010 – June 30, 2011

Nonformula Grant Overview

The University of Pittsburgh received $4,999,916 in nonformula funds for the grant award period June 1, 2011 through May 31, 2015. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Reducing the Cognitive Consequences of Cannabis Use by Adolescents - Use of marijuana and other forms of cannabis is increasing in young adolescents. Convergent lines of evidence suggest that cannabis use impairs cognitive abilities, but proof of cause-and-effect and the brain mechanisms that explain this association are lacking. In this project we propose a set of integrated aims, employing innovative and complementary research strategies, to test a single hypothesis that onset of cannabis use before age 16 alters the developmental trajectory of neural circuits that are critical for the normal maturation of core cognitive abilities. We will also examine the feasibility of preventive interventions to reduce cannabis in a high-risk population of 12-year-olds and conduct a research training program to engage underrepresented minorities and other undergraduates in basic, clinical, and health services research on substance abuse.

Anticipated Duration of Project

6/1/2011 - 5/31/2015

Project Overview

Cannabis is the most widely used illicit drug in the United States. In 2009, the number of 12–17-year-olds who reported using marijuana *increased* by ~10 percent, and the proportion of this age group who thought smoking marijuana carried a great risk of harm *declined*. Prolonged cannabis use has been associated with cognitive impairments. However, whether cognitive impairments persist after cessation of cannabis use and whether these impairments are more pronounced and persistent in individuals who start using cannabis during adolescence, when cognitive abilities are still maturing, remain unknown. To address these questions, it is critical to understand the impact of cannabis use on working memory (WM), a core cognitive process that matures during adolescence and is dependent on the development of the dorsolateral prefrontal cortex (DLPFC).

Based on existing literature, we propose in this project that an early age (before age 16) of onset of cannabis use (EAOC) disrupts the normal developmental trajectories of DLPFC circuits

mediating WM, resulting in persistent WM impairments. However, the existing data that support this idea have several limitations. First, evidence of the long-term cognitive consequences of cannabis use in humans is limited by insufficient information about cognitive capacity prior to the onset of cannabis use. Second, no prospective studies have used assessments of WM and brain function with the sensitivity required to clearly demonstrate adverse effects of EAOC. Third, demonstrating causality requires experimental evidence of a biological mechanism that links age-related cannabis exposure with WM dysfunction.

We propose a set of integrated aims to test the central hypothesis that EAOC alters the developmental trajectory of neural circuits in the DLPFC, resulting in persistent impairments in WM function. Aim 1 examines the direction of the association between EOAC and cognitive function in epidemiological samples. Aim 2 assesses the neural substrates for the short- and long-term effects of EAOC on WM in a subset of subjects studied by Aim 1. Aim 3 directly tests tetrahydrocannabinol (THC) as a causal agent of WM impairment and DLPFC circuitry dysfunction in a non-human primate model system using the same measures employed in Aim 2. Aim 4 uses health services research methods in a cohort of 12-year-olds recruited by Aim 1 to explore novel strategies for preventing EAOC. Aim 5 seeks to train the next generation of substance abuse researchers, focusing on underrepresented minorities, by engaging talented undergraduates in the research conducted in Aims 1-4.

Principal Investigator

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Carl R. Olson, PhD - employed by Carnegie Mellon University
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Expected Research Outcomes and Benefits

The proposed studies will provide answers to the following questions that are essential for protecting the health and long-term well being of young Pennsylvanians and for guiding legislation and public policy in substance abuse. Aim 1 will determine the risk and protective factors for EAOC. In addition, by controlling for cognitive capacity and psychiatric symptoms prior to the initiation of cannabis use, this aim will robustly reveal the strength and directionality

of the association between EAOC, cognitive functioning, and symptoms of psychosis. Aim 2 will reveal the short- and long-term effects of EAOC on WM, a core cognitive process, and document the neural mechanisms that mediate these effects. By using both a cross-sectional design in young adults and a longitudinal design in 12-year-olds, the results will reveal the magnitude, dose-response relationship, and persistence of the effects of EAOC on WM and brain function. Aim 3 will provide a critical test of the cause-effect relationship between cannabis use during adolescence and WM dysfunction and reveal how cannabis alters brain development to impair WM. Aim 4 will demonstrate the feasibility of a method for implementing a computer-assisted decision support system that provides pediatricians with the resources to conduct assessments of risk for EAOC with adolescents and their parents, provide families with brief interventions to facilitate adherence to recommendations, and identify local treatment referral options tailored to individual family members. Aim 5 will deliver an effective program for engaging talented underrepresented minority and other undergraduate students in research activities designed to recruit and prepare them for a career in substance abuse research. In concert, the findings from these studies will provide critical and robust knowledge about the risk and cognitive consequences of EAOC that is currently lacking and, if our hypotheses are supported by the new data, will provide a compelling rationale for a new strategy to prevent or delay the onset of, and thus reduce the cognitive consequences of, cannabis use by adolescents.

Summary of Research Completed

Due to unforeseen delays, we received funding from the Pennsylvania Department of Health on June 17, 2011, approximately two weeks before the end of the reporting period. From June 17-June 30, we initiated participant recruitment for specific aims 1, 2, and 4 and the purchase of animals for Aim 3.