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**Melanie Abas**

MH094156-01A

Treatment for depression and adherence in people living with HIV in Zimbabwe

### **Cultural adaptation of an evidenced based intervention to improve depression and adherence to antiretroviral therapy in people living with HIV in Zimbabwe**

As the HIV epidemic in Sub-Saharan Africa continues to evolve, many challenges remain. Foremost among these are ways to improve adherence to antiretroviral therapy (ART) for the approximately 25% of people on ART in Africa who fail to adhere (Mills et al. 2006). Adherence of at least 80% is needed to suppress the virus and prevent drug resistance and progression to AIDS (Bangsberg, 2002). This problem is critical in Sub-Saharan Africa given the prohibitive cost of second and third line medication.

Risk factors for poor adherence include individual barriers, such as forgetting and depression, complexity of regimens, and structural barriers such as poor supply of drugs (Mills, Nachega et al. 2006). Depression is common in people living with HIV (PLWH) on ART, with major depression affecting around 8% and mild forms of depression found in up to 50%. Depression may increase poor adherence via symptoms of depression such as suicidal ideation and negative thinking, due to greater forgetting and poor concentration, or due to deficits in problem solving that come about through depressed mood (Safren et al, 2002). In high-income settings, depression can be successfully treated among PLWH using cognitive-behavioral therapy and antidepressants, with improvements also in HIV-related health outcomes (Olatunji et al. 2006). Targeting depression could thus be a key to improving adherence to ART.

Selecting interventions for depression and for ART adherence in an African setting is challenging. There is a need to ensure that interventions are culturally appropriate and can be ultimately delivered by non-specialists given the paucity of mental health professionals. In Zimbabwe we have conducted a non-randomised trial of a local low-cost culturally-adapted stepped care treatment for depression (Chibanda et al. 2011). This approach is feasible to be delivered in a general health care setting, and will form the basis for depression treatment for our planned intervention. Studies from the US suggest that adherence gains are more rapid using interventions that utilize motivation and problem-solving techniques compared with those that use just self-monitoring (Safren et al. 2001). Safren and colleagues have shown that the Life Steps collaborative structured adherence intervention integrated with psychological therapy for depression improves ART adherence in depressed PLWH in the US (Safren et al. 2004; Safren et al. 2009).

In Zimbabwe we are following CDC guidance in order to adapt Safren et al's evidenced based integrated 'CBT-Adherence' intervention, known as Life Steps, to improve depression and adherence to antiretroviral therapy. Components to consider during the adaptation process include theory, core components analysis, fidelity, expert consultation, and agency and community input. We will outline two steps we have followed so far, which are Assessment of the target population in Zimbabwe, of the evidenced-based intervention and of local capacity to implement the intervention; and Preparation of the intervention materials which has included

pre-testing the adapted materials with the target population, increasing agency capacity and developing collaborative partnerships to implement the intervention. Next steps for 2014 will be a pilot randomized controlled trial of the adapted intervention.

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Presenter: **Cristian L. Achim, MD, PhD**  
5R01MH094159

### Long Term Effects of Chronic HIV Infection on the Developing Brain

We are currently conducting a prospective case-control study, using a neuropsychological test battery validated in other international HIV cohorts, in order to evaluate the rate and severity of neurocognitive impairment in a homogenous group of young Romanian adults. The Romanian cohort can provide valuable information about the effect of chronic HIV-infection and exposure to combined antiretroviral therapy (cART) on the developing brain, based on its unique characteristics: young adults infected parenterally with HIV clade F in the early 90's, exposed to cART for over a decade.

In a preliminary study 49 HIV infected (HIV+) participants and 20 HIV negative (HIV-) controls were matched with respect to age, gender, although the HIV- group tended to be more educated. We found higher cognitive impairment rates in our HIV+ group (59.1%) vs. the HIV- group (10%), and the impairment rate remained significant higher even when the groups were matched based on the educational level (38.7% for the HIV+ group, vs. 10.0% for the HIV- controls ( $p = 0.025$ )). The nadir CD4 count was  $< 200$  in 71.4% of patients, but at the time of neurocognitive assessment 89.5% of patients had normal immunological status and 81.8% undetectable HIV load. Among the HIV-impaired group 26% of the participants had syndromic impairment while the other 74% had Asymptomatic Neurocognitive Impairment.

We found high rates of neurocognitive dysfunction in the Romanian young adults growing-up with HIV. The greatest HIV-related decline in cognitive functioning were in the domains of executive and motor functioning, consistent with a fronto-subcortical pattern. The results of this feasibility study suggest that the translated neuropsychological measures are valid and sensitive to the effects of HIV-associated brain injury in this Romanian cohort. The HIV+ participants had worse neurocognitive functioning than the HIV- group, despite being matched in terms of socioeconomic background. Thus, even though the participants in this study long-term survivors of infection that occurred during early childhood, and have had up to a decade of effective antiviral treatments that currently render them immunocompetent with good viral suppression, a significant proportion still have evidence of HAND. Importantly, our findings are not only of interest in the Romanian context, as worldwide it is estimated that 2.3 million children under the age of 15 are living with HIV.

In the last years we have seen an alarming increase in the number of intravenous drug users (IVDU), especially of the so-called "ethno-botanical" variety and consequently higher risk of acquiring multiple parenterally transmitted viral infections. Ethno-botanical drugs are obtained from cathinones (alkaloid extracted from the leaves of *Catha edulis*) and have psychoactive effects similar to those produced by amphetamines. Starting In 2009 ethno-botanical drugs are increasingly being used as they are cheaper and because they are considered "legal." In a recent retrospective study on 113 IVDU admitted at Victor Babes Clinical Hospital of Infectious

and Tropical diseases between January 2010 – October 2011 our Romanian collaborators have analyzed: 1) epidemiological risk factors; 2) serological markers and viral loads for hepatic viruses; 3) immunological status and HIV-RNA for HIV co-infected patients. The majority of IVDU were diagnosed in early HIV stages, especially those admitted with acute hepatic symptomatology. The preliminary results of this study show that long term prognosis in IVDU is poor due to: 1) more rapid evolution to the chronic state, 2) lack of adherence to cART; 3) lack of knowledge regarding drug interactions between cART and ethno-botanical drugs; 4) high risk of acquiring other severe bacterial infections.

Grant number: DA024626

Grant title: The Khat Research Program: Neurobehavioral Impact of Long-Term Use

PI: **Mustafa al'Absi**, Professor and Max & Mary LaDue Pickworth Chair, University of Minnesota Medical School (U.S.A.)

Foreign collaborators:

Molham Al Habori, Professor and Dean, College of Medicine, Sana'a University, Yemen

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This program addresses the growing use of khat and its harmful effects on health in many countries in Africa and the Middle East and among immigrant communities in Western Europe and North America. Khat (*Catha edulis*) is a flowering plant native to tropical East Africa and the Arabian Peninsula. It contains cathinone, an amphetamine-like stimulant. It is a controlled substance in many countries, but is legally available in many others. Little is known about its addictive liability and its effects on brain functions.

A partnership between the University of Minnesota and two universities in Yemen established the first ever multidisciplinary research and training program focusing on this substance. We have used this exploratory/developmental grant to achieve two primary goals. The first is to develop collaborative relationships and provide needed capacity-building resources that have includes a series of research training workshops, establishing an Institutional Review Board, conducting relevant training on ethical standards of research, and organizing semi-annual meetings to develop future programmatic research. The second goal was to complete preliminary research to determine cognitive, affective, and biobehavioral consequences of long-term khat use. The research agenda was geared towards maximizing the potential for advancing khat-related research in this and surrounding countries and facilitating later development of research that will guide efforts to develop methods to reduce the harm caused by khat and the concurrent use of tobacco. A multidisciplinary, international team with distinguished records and experience in all relevant topics was assembled. Both the training and research arms of the program have emphasized this breadth of expertise.

This program has been highly successful. It has built capacity and stimulated research not only in Yemen, but also in East African countries (Kenya and Ethiopia). We have so far published 14 scientific papers in highly-respected journals, have organized multiple national and international conferences, and have been successful in leveraging this program to secure additional funding to support our colleagues in East Africa and Yemen. This program has also permitted us to establish a worldwide research network on the topic that is likely to facilitate future research initiatives to develop means for effective intervention strategies. Combating this problem will have significant benefits on health conditions in many countries around the world.

PI name/ Country: Tatiana Balachova, PhD/USA

Major foreign collaborator name/ Country: Larissa Tsvetkova, PhD/Russia

**Tatiana Balachova, PhD**

Grant number: R01AA016234 (NIAAA/Fogarty International Center), R21TW006745 (PI Barbara Bonner, PhD) and a supplement award, NIH/ Russian Basic Science Foundation Collaborative Initiative (US-Russia Collaboration on HIV/AIDS Prevention; PIs: Tatiana Balachova, PhD (University of Oklahoma Health Sciences Center) and Alla Shabolta (St. Petersburg State University)

Preventing FAS/ARND in Russian Children

**Preventing FAS/ARND in Russian Children**

**Balachova T., Bonner B., Chaffin M., Isurina G., Tsvetkova L., and Volkova E.**

Introduction: Prenatal alcohol consumption can result in a range of adverse pregnancy outcomes including Fetal Alcohol Spectrum Disorders (FASD). Russia is a country with high rates of alcohol use, increasingly hazardous drinking in young women, and a lack of FASD prevention. FASD are completely preventable by avoiding maternal alcohol use during pregnancy; therefore, prevention of alcohol-exposed pregnancies (AEP) is extremely important.

Methods: A line of research projects aimed at developing FASD prevention in Russia that has been designed by researchers from the University of Oklahoma Health Sciences Center in collaboration with St. Petersburg State University and Nizhny Novgorod State Pedagogical University in Russia. The projects have been supported by NIH (Fogarty, NIAAA) and CDC<sup>1</sup>. An assessment driven translational research strategy was utilized to develop culturally appropriate FASD prevention that addresses women's specific needs and the health care system in Russia. This program of research began with a primarily descriptive and exploratory mixed-methods (qualitative/quantitative) study of alcohol and fetal alcohol exposure knowledge, attitudes and beliefs among young women and physicians in OB/GYN clinics. Information from the first project was used in a second project to design competing sets of informational materials which were tested. Subsequent studies designed a brief OB/GYN clinic-delivered dual-focus (i.e. contraception and alcohol use) primary FASD prevention intervention. The most recent study is testing this intervention in a two-arm cluster-randomized controlled clinical trial in 20 OB/GYN clinics in two regions in Russia with one-year follow-up. As part of this study, women completed structured interviews focused on HIV testing and status, knowledge, attitudes, and HIV risk behaviors. The study provided information about the role of alcohol and gender-related factors in HIV transmission risks. A total of 766 women at risk for an alcohol-exposed pregnancy (AEP) were enrolled in the clinical trial at 20 women's clinics in two regions in Russia.

Results: The initial study found that although many Russian women reduced alcohol consumption after pregnancy identification, few recognized the risks involved in combining alcohol use with the potential to become pregnant. Among non-pregnant women, 43% were not using contraception consistently along with at-risk drinking, posing risk for an alcohol-exposed pregnancy (AEP). The most influential contributor to women's decision regarding alcohol consumption during pregnancy was her own knowledge followed by physicians. The most believable message about drinking during pregnancy was an OBGYN's recommendation

followed by research data. Based on these findings, a preconceptional dual-focused (alcohol use/pregnancy planning) brief physician intervention (DFBPI) targeting women at AEP risk was designed based. Physicians trained in DFBPI demonstrated significantly improved skills in an educational trial. Results of the clinical trial support the feasibility of the DFBPI at OB/GYN clinics. OB/GYN physicians trained and monitored during the trial demonstrated close to ideal intervention completion.

Conclusions: Increasingly hazardous drinking in women indicates that prevention of alcohol-exposed pregnancies in Russia is an important public health issue. Formative assessment was crucial. The study data are promising for reducing AEP risk in Russian women. Developed FASD prevention intervention can be delivered to large numbers of women at OB/GYN clinics routinely.

PI name/ Country: Tatiana Balachova, PhD/USA

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**Larissa Tsvetkova, PhD**

Grant number: R01AA016234 (NIAAA/Fogarty International Center), R21TW006745 (PI Barbara Bonner, PhD), Supplement award, NIH/ Russian Basic Science Foundation Collaborative Initiative (US-Russia Collaboration on HIV/AIDS Prevention; PIs: Tatiana Balachova, PhD (University of Oklahoma Health Sciences Center) and Alla Shaboltas (St. Petersburg State University)  
Preventing FAS/ARND in Russian Children

**Preventing FAS/ARND in Russian Children: An international collaboration**

**Tsvetkova L.A., Balachova T., Bonner B., Chaffin M., Isurina G., and Volkova E.**

In 2003, when we began our R21 study, very little was known about FASD and clinical trials in behavioral and prevention research in Russia. The interdisciplinary collaborative research FASD prevention studies have changed this situation. The line of collaborative FASD prevention studies<sup>2</sup> has served as a model for international and interdisciplinary collaborations, prevention research studies, and clinical trial research. At the first step a consortium between the University of Oklahoma Health Sciences Center (OUHSC), St. Petersburg State University, and Nizhniy Novgorod State Pedagogical University (NNSPU) in Russia was established to conduct the studies. The projects included capacity building and the *Prevent FAS in Russia research group* was formed (PFAS). PFAS includes researchers from psychology, medicine, and public health who have been active in presenting, consulting and disseminating knowledge to faculty and researchers, mentoring students in research, and training physicians. Capacities developed over this program include: (1) NIH compliant IRB harmonization across the main research institutions; (2) Primary care clinic leadership has been engaged; (3) Research procedures, protocols, and measures are developed and staff is trained; and (4) Cross-site data quality control and sharing protocols are developed. Since 2003, PFAS faculty gave 106 presentations at national and international meetings and a number of materials have been produced by PFAS including 17 manuscripts in peer-reviewed journals, three books for health professionals, four education brochures and manuals for the general public, 19 abstracts in peer reviewed journals and papers in conferences proceedings, two educational websites for the general public and health professionals, publications in newsletters by the project faculty, 20 papers in scientific journals by the project faculty supported by other sources, and several publications about the studies. In addition, ten Master and Doctoral theses focused on FASD have been completed and supervised by the project faculty in the U.S. and Russia. Direct and indirect outcomes of the studies are far beyond the universities including establishment of the Coordination Council for the prevention of harm from alcohol and FAS at the Russian Federal Central Research Institute of Health Organization and Information (CNIIOIZ). International collaboration in research is challenging but productive and lessons learned from the studies will be discussed.

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Grant number: R01AA016234 (NIAAA/Fogarty International Center), R21TW006745 (PI Barbara Bonner, PhD) and a supplement award, NIH/ Russian Basic Science Foundation Collaborative Initiative (US-Russia Collaboration on HIV/AIDS Prevention; PIs: Tatiana Balachova, PhD (University of Oklahoma Health Sciences Center) and Alla Shabolta (St. Petersburg State University)

Preventing FAS/ARND in Russian Children

Alcohol-exposed pregnancy risk and tobacco use among childbearing age women in two locations in Russia

Balachova T., Zander R., Bonner B., Isurina G., Tsvetkova L., and Volkova E.

Alcohol consumption during pregnancy can result in adverse pregnancy outcomes including pregnancy termination, still or premature birth, and a range of Fetal Alcohol Spectrum Disorders (FASD) in children. Maternal smoking during pregnancy is also known to increase risk of poor pregnancy outcomes, such as premature birth and spontaneous abortion. Concurrent alcohol and tobacco use during pregnancy is particularly concerning because of compound effects of prenatal alcohol and tobacco exposure. Recent research has found Russian women to be at high risk for alcohol-exposed-pregnancies (AEP). This current study aimed at determining risk for tobacco exposure during pregnancy and whether associations exist between cigarette smoking and alcohol consumption among childbearing women in Russia. In 2003-2005, through a consortium between the University of Oklahoma Health Sciences Center, and St. Petersburg State University and Nizhny Novgorod State Pedagogical University, a cross-sectional study “Preventing FAS/ARND in Russian Children” was conducted to obtain data necessary to design programs to prevent AEP\*. Childbearing-age women (N=648) were recruited as consecutively enrolled patients at public women’s clinics in St. Petersburg and the Nizhniy Novgorod Region. A total of 301 pregnant and 347 non-pregnant women completed a face-to-face interview focusing on alcohol consumption, contraception use, and risk factors associated with fetal alcohol exposure including smoking. A secondary data analysis revealed that among pregnant women, 25% consumed alcohol and 14% smoked cigarettes during their pregnancy. After stratifying non-pregnant women into AEP-at-risk and not-at-risk groups, it was determined that 45% of AEP-at-risk women were current smokers, whereas only 28% of women who were not-at-risk for an AEP smoked cigarettes (OR=2.15;  $p<0.01$ ). Multivariate logistic-modeling showed that smoking status and city of residence significantly predicted AEP-risk ( $p<0.0001$ ). These results display the high smoking prevalence among AEP-at-risk women, and emphasize the importance of developing public health intervention programs that target this dual-risk among childbearing-age women.

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**Eustache, Eddy/Haiti**  
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**R21-MH093298,**

**Title: Developing research capacity for mental health interventions for youth in Haiti**

**Background:** In 2010, after a major earthquake resulted in widespread destruction and a massive toll of casualties in Haiti, a cholera epidemic subsequently claimed thousands more lives. These two major acute stressors—superimposed on chronic social adversities—continue to impose an enormous burden of mental suffering in Haiti. Fortunately, mental health clinical services at Zanmi Lasante (ZL) have recently been expanded. However, there is not yet a robust culture of help-seeking for mental disorders in Haiti.

**Aims:** The present project has three aims: (1) Evaluation of the perceived burden of mental illness in school-going Haitian youth, associated unmet need, and relevant school and community-based priorities and capacities; (2) Delivery of didactic training specific to epidemiologic, social science, and implementation research on mental disorders in Haiti; and (3) Collaborative application of this didactic research training to the development, implementation, and evaluation of a novel school-based pilot mental health intervention in Haiti. Here, we present preliminary findings from Aim 3.

**Methods:** After conducting focus group discussions with Haitian educators, parents, and school-going youth to understand perceived burden of mental disorders and feasibility and accessibility of a school-based intervention to promote youth access to mental health services, we developed and implemented a pilot school-based program to provide secondary school teachers with basic skills to assist students with signs of mental illness. Teachers (n=22) recruited from four secondary schools in Haiti participated in a 2 ½ day training program and accepted assignment of up to 10 students to help them navigate to mental health care and/or promote resilience and well-being through meetings for 1 month. Subsequently, we enrolled student study participants (n=121) for school-based assessment of MDD, PTSD, and suicide risk by self-report, abridged SCID-based research interview, and clinical interview. Student participants received a clinical recommendation for mental health services at ZL if appropriate; all student participants were asked to arrange one or more meetings with an assigned teacher study participant.

**Results:** Two-tailed t-tests supported that both aggregate knowledge and attitudes improved significantly after teacher training ( $p < .0001$  and  $p = .014$ , respectively). Of the 121 student study participants, 120 completed the assessment and were asked to arrange to meet with their assigned teacher study participants (teacher-accompagnateurs) over the ensuing 3-4 weeks. Student and teacher study participant post-tests and program evaluation data will be completed in December 2013; analyses are thus pending.

**Conclusion:** Our preliminary findings suggest that Haitian teachers are receptive to developing knowledge and skills to recognize, respond to, and refer students with mental disorders to services. Moreover, our training was effective in increasing their basic knowledge about and improving attitudes toward mental disorders. Finally, preliminary data suggest that a school-based case finding and teacher-accompaniment program is feasible and culturally acceptable to implement in Haitian secondary schools.

**PI name/ PI Country: Dr. Walter Besio. USA**

**Major foreign collaborator name: Dr. Luisa Rocha. Mexico**

**Grant number: R21TW009384**

**Grant title: A US-MEXICO COLLABORATIVE EFFORT TO IMPROVE EPILEPSY CONTROL AND DIGNOSIS**

Gamma-Band High-Frequency Oscillations From Patients With Epilepsy Using Scalp Tripolar Concentric Ring Electrodes

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Epilepsy is the second most prevalent neurological disorder (~1% prevalence) affecting approximately 67 million people worldwide with up to 75% from developing countries. The conventional electroencephalogram (EEG) is plagued with artifacts from movements, muscles, and other sources. Tripolar concentric ring electrodes automatically attenuate muscle artifacts and provide improved signal quality. We performed basic experiments in healthy humans to show that tripolar concentric ring electrodes can indeed record the physiological alpha waves while eyes are closed. We then conducted concurrent recordings of EEG with conventional disc electrodes and tripolar concentric ring electrodes (tEEG) from patients with epilepsy. We found that we could detect high frequency oscillations on the scalp surface that appeared to become more narrow-band just prior to seizures. Overall, high-frequency oscillations (HFOs) were present in tEEG data from all five patients whose seizures were recorded. For these five patients, out of all the tEEG channels that contained HFOs an average of 71.4% were also in the seizure onset zone or irritative zone (patient minimum: 0%; maximum: 100%). The average percentage of the total number of tEEG channels recorded that contained HFOs is equal to 21.8% (patient minimum: 5.3%; maximum: 40%).

PI name/ PI Country: Dr. Walter Besio. USA

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Grant number: R21TW009384

Grant title: A US-MEXICO COLLABORATIVE EFFORT TO IMPROVE EPILEPSY CONTROL AND DIGNOSIS

**Effects of transcranial focal electrical stimulation alone and associated with a sub-effective dose of diazepam in pilocarpine-induced status epilepticus and neuronal damage in rats.**

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Experiments were carried out to determine the effects of transcranial focal electrical stimulation (TFS) applied via tripolar concentric ring electrodes, alone and associated with a sub-effective dose of diazepam on the expression of status epilepticus (SE) induced by lithium-pilocarpine (LP) and subsequent neuronal damage in the hippocampus. Immediately before pilocarpine administration, male Wistar rats received TFS (300 Hz, 200  $\mu$ s biphasic square chargebalanced 50 mA constant current pulses, for 2 min), alone or combined with a sub-effective dose of diazepam (0.41 mg/kg, i.p.). In contrast with animals pretreated with diazepam or TFS alone, animals receiving diazepam plus TFS demonstrated reduced incidence of, and enhanced the latency to, mild and severe generalized seizures and SE. The animals were sacrificed 24 h after the SE and the brain used to evaluate neuronal damage with Floro-Jade staining. In contrast with rats undergoing SE and pretreated with diazepam or TFS alone, animals that receive diazepam plus TFS demonstrated a significant reduction in the number of degenerated neurons in the hippocampus. The present study supports the notion that TFS combined with sub-effective doses of diazepam may represent a therapeutic strategy to induce anticonvulsant effects and reduce the SE-induced neuronal damage.

PI name/ PI Country: Dr. Walter Besio. USA

Major foreign collaborator name: Dr. Luisa Rocha. Mexico

Grant number: R21TW009384

Grant title: A US-MEXICO COLLABORATIVE EFFORT TO IMPROVE EPILEPSY CONTROL AND DIGNOSIS

**Transcranial Focal Electrical Stimulation Modifies the Glutamate Release in hippocampus during Pilocarpine-induced *Status Epilepticus* in Rats**  
**Luisa Rocha**

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**Background:** The increased release of glutamate in the hippocampus during Status Epilepticus (SE) induces a cascade of molecular and cellular changes that causes neuronal death and subsequent epileptogenesis. In previous studies we demonstrated that noninvasive transcranial focal electrical stimulation (TFS), in association with subeffective doses of diazepam, reduces SE-induced neuronal damage. However, it is unclear if this neuroprotective effect is a consequence of a decrease in the glutamate release or something else. The aim of the present study was to evaluate the effects of TFS on glutamate release in the hippocampus during SE. **Materials and Methods:** Male Wistar rats were implanted with a guide cannula, attached to a bipolar electrode, into the right ventral hippocampus. A tripolar concentric ring electrode was placed on the skull surface, approximately 5 mm behind the bregma. The animals were subjected to a microdialysis experiment during which SE was induced by administration of pilocarpine (300 mg/kg, i.p.). A group of animals was manipulated as described above, except that fifteen minutes after the establishment of the SE, TFS was continuously applied during 2 h (300 Hz, 200  $\mu$ s biphasic square pulses at 100  $\mu$ A, for 2 h). The dialysates were recovered throughout the microdialysis experiment and processed with high resolution liquid chromatography (HPLC) to determine glutamate concentrations. The animals were sacrificed at the end of the experiments and the brain was used to verify the implant site with Nissl staining. **Results:** Under basal conditions, the levels of glutamate were  $0.98 \pm 0.05 \mu\text{M}$ . After pilocarpine administration, the rats showed head myoclonus ( $15.2 \pm 3.9$  min), forelimb clonus ( $33.6 \pm 6.1$  min), rearing ( $33.7 \pm 5.5$  min) and wet dog shakes ( $37.9 \pm 2.49$  min). When the SE was established ( $43.09 \pm 2.49$  min), the release of glutamate demonstrated a significant increase (141%), and persisted to the end of the experiment (242%), 4 hours after pilocarpine administration. The TFS application during the SE reduced the behavioral and electrographic convulsive activity, a situation associated with glutamate levels similar to basal conditions. **Conclusions:** TFS reduced the behavioral and electrographic convulsive activity which may be due to a decrease in glutamate levels. It is possible that this effect plays a significant role in the neuroprotection induced by TFS.

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**Gretchen L. Birbeck**

R01NS061693

## **Title: Epilepsy-Associated Stigma in Zambia: Evidence-based Interventions and Outcomes**

### Background:

Epilepsy is the most common chronic neurologic disorder in many resource poor regions. In Africa, epilepsy-associated stigma and the resulting social sequelae and medical morbidity and mortality of the disorder contribute substantially to the burden of neurologic disease. Despite affordable medications, <10% of people with epilepsy (PWE) in sub-Saharan Africa are receiving treatment. Using insights and information gained from our previously conducted quantitative and qualitative work in Zambia (a BRAIN R21), we developed, implemented and evaluated a series of interventions aimed at decreasing epilepsy-associated stigma, improving the socioeconomic status of PWE and lowering the rates of seizure-related morbidity and mortality in Zambia. Research capacity building carried out in conjunction with the interventions included, (1) Research support skills for local staff; (2) Formal training in grants management for 2-3 Zambian administrators that was undertaken initially in the US but which later included sending US grants management specialists to Zambia to provide further on-site training; (3) PhD-level training in Community Health at the University of KwaZulu-Natal for Mr. Mbewe who completed his thesis developing and evaluating a screening tool for identifying comorbid depression or anxiety in Zambians with epilepsy; his dissertation has been accepted with minor changes and he will be granted his PhD in 2014 and (4) Graduate level training at the University of Zambia in Social Anthropology for Ms. Simusaku. She was awarded her Master's degree in 2012.

### Activities (some completed, some ongoing):

Several sub-studies were undertaken as part of this work

A study of the availability and costs of antiepileptic drugs (AEDs) in Zambia. As a result of this study and subsequent qualitative investigations, we identified structural barriers to AED availability that occurred as an inadvertent consequence of capacity building activities held by the World Health Organization (WHO) and aimed at the Pharmaceutical Regulatory Authorities in low and middle income countries globally. Though initially identified in Zambia, the barrier was found to be an issue for several low and middle income countries. The WHO's International League against Epilepsy developed a task force to further address this.

A Peer support group intervention was found to be effective for decreasing stigma and improving AED adherence for youth with epilepsy

Analysis is ongoing of a school-based interventions aimed at teachers. Preliminary analysis indicates the intervention improved teacher's attitudes and decreased stigmatizing attitudes and practices with a non-significant trend towards increases in the number of children with epilepsy who remain in school

Analysis is ongoing of a church-based intervention aimed at clerics

Quality indicators for epilepsy-care that can be assessed through review of the available medical record were developed and evaluated.

Analysis has recently been completed for a health sector-based intervention aimed at improving epilepsy care. Dissemination is anticipated in early 2014

A screening tool for identifying psychiatric comorbidities in people with epilepsy was developed, validated, evaluated and when implemented into use was found to be very successful in identifying for further care individuals with epilepsy and depression or anxiety requiring treatment

Further observational work was conducted to expand our understanding of the mother-child dyad in children with epilepsy, which is a complex relationship not amenable to simple interventions

A cost analysis was conducted to determine the overall costs to Zambia to tackle the epilepsy treatment gap.

(10) Evidence-based guidelines for the use of EEG in Zambia were developed and adopted by the Ministry of Health

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**Gretchen L. Birbeck**  
R21NS069228

**Title: The Malawi-MSU MRI Project: Acquiring normative data to elucidate the epidemiology of structural CNS abnormalities in the Malawian population**

Background:

In July 2008, magnetic resonance imaging (MRI) technology became available in Malawi for neurologic research aimed at elucidating pathophysiologic mechanisms of common, tropical CNS conditions. However, interpretation of findings was problematic. Acute clinical presentations were often associated with brain MRI findings more indicative of previous injury and structural lesions identified frequently seem unrelated to clinical symptomatology. Normative brain MRI data in the Malawian population was needed to facilitate clinical and research interpretation of images. To address this we conducted the BRINK (Brain Imaging in Normal Kids) study. Critical capacity building activities in BRINK included the development of NeuroInterp--an integrated program for systematic review and capture of data related to the radiologic interpretation of brain MRIs. The BRINK Study also support the sustainable development of human resource capacity for the continued successful and safe operation of the Malawi MRI through additional training opportunities for MRI technicians and professional development activities for Malawi's radiologists.

Activities:

We identified a representative, community-based sample of developmentally normal children 9-14 years old to undergo a brain MRI. No acute MRI abnormalities were seen. Radiographic evidence of sinusitis 29 (30%) was the most common MRI finding. Brain abnormalities were found in 16 (23%) including mild diffuse atrophy, periventricular white matter changes, multifocal punctuate subcortical white matter changes, vermian atrophy, empty sella, and multifocal granulomas. Having an abnormal MRI was not associated with age, sex, antenatal problems, early malnutrition, febrile seizures, an abnormal neurologic examination or housing quality (all p's > 0.05). No predictors of radiographic sinusitis were identified. Incidental brain MRI abnormalities are common in normal Malawian children. The incidental atrophy and white matter abnormalities seen in this African population have not been reported among incidental findings from US populations suggesting Malawi-specific exposures may be the cause. In addition to optimizing clinical interpretations, the normative data has proven critical to several ongoing neuroimaging research projects in Malawi.

NeuroInterp was fully developed and implemented as a web-based data entry form providing data validation upon entry. To date, NeuroInterp has facilitated the systematic study of the BRINK data, a study of the radiologic findings of acute cerebral malaria, and a study of the radiologic correlated of neurologic sequelae in cerebral malaria survivors. NeuroInterp offers a

feasible approach to the challenges of radiologic data acquisition and management especially for conditions with little prior descriptive data available. NeuroInterp is now being integrated into India-based research. Plans are also underway to transition from propriety software to open source software which should allow more broad use of this data management tool in cerebral malaria imaging research.

In 2010, a supplemental award was received for *Expanding neuroradiologic research expertise in Malawi: Optimizing the potential knowledge gained from MRI technology in sub-Saharan Africa*. NIHR21NS069228-01S1 (\$64,000) which allowed additional capacity building toward enhancing the human resources in Malawi for the optimal use of the Malawi MRI facility.

Gretchen L. Birbeck/USA

Elwyn Chomba/Zambia

Edward Mbewe, Masharip Atadzhanov, Alan Haworth, Claire Simusaku, Philimon Ndubani,  
Henry Kansembe/Zambia

**Melissa A. Elafros/USA&Zambia**

R01NS061693

Epilepsy-Associated Stigma in Zambia: Evidence-based Interventions and Outcomes

## Peer Support Groups as an Intervention to Decrease Epilepsy-Associated Stigma

### Background:

Eighty percent of people with epilepsy (PWE) reside in low-income countries where stigma contributes substantially to social and medical morbidity. Although stigma has been well studied and specific stigma reduction interventions have been implemented, little can be found in the literature regarding the impact of these interventions. For stigma reduction interventions to be successful in low-income countries, they must be low-cost and require minimal expertise. Peer support groups (PSGs) are thought to be beneficial for people with stigmatized conditions and could be an inexpensive way to address stigma among PWE in low-income countries. Although PSGs are often formed for PWE, little data is available on their effectiveness.

### Activity:

We facilitated separate PSG meetings for men, women, and youth from three Zambian clinics for one year. Each PSG met once a month for two hours with content determined by meeting participants. Trained facilitators encouraged participants to share their experiences and, ultimately, exchange problem-solving advice and coping techniques related to epilepsy and epilepsy-associated problems. All participants were refunded 20,000 kwacha (~4 USD) to cover round trip transportation costs for each PSG meeting they attended. Pre- and post-intervention assessments measured internalized stigma, psychiatric morbidity, medication adherence, socioeconomic status, and community disclosure.

Of the 103 participants (39 men, 30 women, 34 youth), 80 PWE (78%) attended  $\geq 6$  meetings. There was no significant demographic differences between PWE who attended  $\geq 6$  meetings and those who attended  $< 6$  meetings. Among youth attending  $\geq 6$  meetings, internalized stigma decreased ( $p < 0.02$ ). Among adults, there was a non-significant stigma decrease. No differences were detected in medication use, medication adherence, or psychiatric morbidity.

Peer support groups effectively reduce stigma for youth and may offer a low-cost approach to addressing epilepsy-associated stigma in resource poor settings.

### Publication:

Elafros MA, Mulenga J, Mbewe E, Haworth A, Chomba E, Atadzhanov M, et al. Peer support groups as an intervention to decrease epilepsy-associated stigma. *Epilepsy & behavior* : E&B. 2013 Apr;27(1):188-92. PubMed PMID: 23454914. Pubmed Central PMCID: 3602129.

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R01NS061693

Epilepsy-Associated Stigma in Zambia: Evidence-based Interventions and Outcomes

Reexamining Instruments for Characterizing and Quantifying Epilepsy-Associated Stigma: The Stigma Scale of Epilepsy

Background:

Epilepsy-associated stigma is an often overlooked patient-centered outcome measure. Influenced by intrinsic patient factors as well as external, societal forces, stigma has long been recognized as a substantial, yet potentially modifiable, force in the lives of people with epilepsy (PWE). Although stigma reduction efforts are ongoing, there continues to be little consensus on how to best measure stigma. The instrument commonly used to assess felt stigma among individuals with stigmatized conditions, including epilepsy, is the 3-item stigma scale. The Stigma Scale of Epilepsy (SSE) is a 24-item Brazilian instrument that measures felt stigma among PWE and stigmatizing attitudes when administered to the general public. If cross-culturally valid, this tool may help elucidate determinants of stigma and provide an outcome measure for stigma reduction interventions.

Activity:

Using the 3-item stigma scale and the SSE, we measured felt stigma in 102 Zambian PWE. We examined the number of underlying latent traits assessed by the SSE using Item Response Theory. Confirmatory factor analysis compared the latent traits assessed by the SSE to the number of traits assessed by the 3-item stigma scale. Differential item functioning based on forced disclosure of epilepsy status was also examined.

The SSE loaded onto two latent traits – the first included questions regarding difficulties and prejudices faced by PWE, whereas the second loaded questions regarding emotions associated with epilepsy. Items from the 3-item scale loaded only onto the first factor, suggesting that it does not assess the second factor. Forced disclosure of epilepsy increased worry and pity - items associated with the second factor.

In Zambian PWE, the SSE captured two latent traits associated with felt stigma. One trait represents feelings associated with epilepsy, which has been theorized as a substantial, yet previously unmeasured, part of felt stigma. The SSE performs well across cultures, may be a more comprehensive measure for felt stigma, and may quantify stigmatizing attitudes among others. In addition, researchers employing the 3-item stigma scale among people with other stigmatized conditions may need to consider developing additional instruments that better capture both aspects of felt stigma.

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Izukanje Sikazwe/Zambia  
Omar Siddiqi/USA & Zambia  
Lisa Kalangwana/Zambia  
Melissa Elafros/USA & Zambia  
Igor Koralnik/USA  
Christopher Bositis/USA (ex. Zambia)  
William Theodore/USA

**Melissa Elafros**

R21NS073509

A Cohort Study of HIV-Associated Seizures and Epilepsy (CHASE)

Background:

Our present standards of care for treatment of the epilepsies, especially the important decision regarding whether/when to commence someone on long-term antiepileptic drug (AED) treatment, are based largely upon descriptive epidemiologic data. Natural history studies detailing the probability of further seizures and risk factors for seizure recurrence in people after their first epileptic event provide the evidence base for clinical decision-making. The risk for recurrent seizure(s) among people with HIV/AIDS who experience new onset seizure is not known and extrapolation of data from HIV negative populations is likely inappropriate. Given the potential for drug interactions between AEDs and antiretroviral therapies (ART), the decision to commence an HIV+ individual on AEDs is critical. No where is this clinical concern more problematic than in low income countries, such as Zambia, where older generation, enzyme-inducing AEDs are the only epilepsy treatment option and HIV/AIDS and epilepsy prevalence rates remain high.

Ongoing Activities:

The CHASE study is a prospective cohort study of HIV+ adult Zambians presenting with seizure(s) aimed at determining seizure etiology, the incidence of new onset epilepsy (i.e. recurrent seizure) and evaluating for risk factor for epilepsy development in people with HIV and new onset seizure. Investigations to assess etiology and risk factors for epilepsy include neuroimaging, CSF PCR studies evaluating for opportunistic infections, neuropsychiatric assessments to identify HIV associated neurocognitive disorder and psychiatric symptom burden. Capacity-building activities include enhancing the human resources necessary for the conduct of prospective cohort studies of persons with HIV and co-morbid neurologic disorders through expanding the research skills and qualifications of Zambian physicians in training as well as those with advanced clinical expertise in HIV care via provision of Master's Level training in research methodologies for Zambia's HIV specialists and enhancing clinical neurodiagnostic options at Zambia's main teaching and research institution by providing advanced training for the University Teaching Hospital's EEG technicians.

To date, 96 subjects have been enrolled and follow-up of this cohort is ongoing. With the support provided through CHASE as well as additional funding from the World Federation of Neurology, the University Teaching Hospital now has a fully functioning Neurodiagnostic Laboratory offering EEGs as well as EMG/NCV studies. Dr. Sikazwe, an HIV specialist and co-Director for the Center for Infectious Diseases Research in Zambia, will complete her Master's in Public Health degree from Michigan State University's distance-learning program in Spring 2014. Her capstone project involved additional work with the CHASE cohort. Final follow-ups and outcomes data for analysis will be available in February 2014 with dissemination of results to follow. An R01 application aimed at expanding this study to include rural regions and pediatric populations is anticipated in late 2014.

Melissa Elafros is an MD/PhD candidate at Michigan State University in the College of Human Medicine and the Department of Epidemiology. She has a Master's degree in bioethics and as part of the capacity building activities associated with this work, she has conducted extensive training in research involving human subjects with Zambian investigators and research staff. She resided in Zambia for over a year to assist in the logistical support of the CHASE study while also completing her dissertation research which addresses the burden of dual stigma in individuals with HIV and epilepsy and the drug side effects and interactions that also occur as part of this HIV and epilepsy double burden. She received funding from the American Medical Association for the support of her work in Zambia. She has served as AMSA's Global Pulse editor since 2011. Her advisor and colleagues hope she will seek a career in neurology after graduating from medical school in 2016.

**PIs: Michael J. Boivin (USA) & Noeline Nakasujja (Uganda)**

Presenter: **Michael J. Boivin, PhD, MPH**

Grant Number: R01HD064416

Grant Title: Computerized Cognitive Rehabilitation in Children after Severe Malaria.

**PRESENTATION TITLE:** Computerized cognitive rehabilitation training can improve neuropsychological outcomes in school-age Ugandan children surviving severe malaria.

**OBJECTIVES:** In Uganda 1 out of 4 school-age survivors of cerebral malaria (CM) has persisting attention, memory, or learning impairment two years after illness. No viable treatment presently exists to prevent these disabilities, and hundreds of thousands of children are affected each year in sub-Saharan Africa. **Principal Study Aim:** *To evaluate the effectiveness of CCRT in improving neuropsychological performance and psychiatric outcomes in Ugandan children who survive severe malaria, two years after illness.*

**METHODS:** Thus far 163 children 5 to 12 years of age have been enrolled (56 in cognitive rehab, 55 in active control, 52 passive control). These are comprised of 106 CNS malaria survivors and 57 non-malaria children recruited from their households (Kampala, Uganda), who do not have a history of severe malaria or other known brain injury. Both the CNS (two-years after illness) and non-malaria children were randomly distributed among the 3 treatment arms (Captain's Log CCRT, Captains Log locked at the simplest levels (active control), and no computer intervention (passive control). The Kaufman Assessment Battery for Children, 2<sup>nd</sup> ed. (KABC-2), visual and auditory Tests of Variables of Attention (TOVA), CogState computerized neuropsychological screening test, The Behavior Rating Inventory for Executive Function (BRIEF), and the Achenbach Child Behavior Checklist (CBCL). These tests have been administered before and after the 8-week training period. Captain's Log has an internal evaluator feature which will help us monitor the specific training tasks to which the children best respond.

**RESULTS:** An analysis of covariance comparison adjusted for age, gender, WAZ and socio-economic score. Neuropsychological (KABC, TOVA, CogState) and behavioral (BRIEF, CBCL) gains over the 8-week training period were compared for the three treatment arms (CCRT, active control, passive control) for the CNS and non-malaria children. CNS malaria survivors receiving CCRT showed significant improvements (compared to passive controls) on KABC-II Learning, KABC-II Conceptual Reasoning, CogState working memory, BRIEF Behavior Regulation Inventory, and Achenbach CBCL psychiatric symptoms. They also showed marginally significant improvements on the TOVA overall performance index (ADHD score). Non-malaria children receiving CCRT (compared to control groups) showed significantly greater improvement on KABC-II Story Completion, TOVA simple Response Time (an attentional measure), and CogState maze chase (visual-motor tracking/attention), and CogState maze learning. The non-malaria CCRT children also had marginally significant improvements on the BRIEF Behavior Regulation Index. Both CCRT and active controls had similar levels of improvement across the 24 training sessions using the Captain's Log internal evaluator outcomes, indicating comparable fidelity of training for the two computer intervention groups.

**CONCLUSIONS:** CCRT has proven effective and sustainable in rehabilitation for severe malaria. Comparable gains were observed for both the full Captain's Log CCRT and limited

Captain's Log (active control). CCRT and computerized cognitive tests is viable for treating brain-injured children in resource-poor settings.

PIS: Michael J. Boivin /USA & Nakasujja Noeline /Uganda

Presenter: **Itziar Familiar-Lopez**

Grants R01HD064416/R34MH084782

Grants' titles: *Computerized Cognitive Rehabilitation in Children after Severe Malaria/ Neuropsychological Benefits of Cognitive Training in Ugandan HIV Children*

**PRESENTATION TITLE:** The BRIEF and Achenbach CBCL provide distinct yet complementary evaluations of the emotional and behavioral adjustment of Ugandan children with HIV and those surviving severe malaria.

**Background.** The Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, Kenworthy, 2000) and the Achenbach Child Behavior Check List (CBCL) (Achenbach, 1991) are among the most widely used measures to assess behavioral, emotional, social, and functional problems in school age children. Although frequently used together in neurodevelopment assessments, the extent of overlap between the BRIEF and CBCL is unclear.

**Methods.** Parental ratings for the BRIEF and CBCL were obtained on 69 children (5.9-12.7 years old, 50% males) with a history of severe malaria and on 122 children (5-12 years old, 58% males) with HIV in Uganda. Exploratory factor analysis employing robust maximum likelihood estimation was used to evaluate the factor structure of the 8 scales comprising the two global domains for the BRIEF (Behavioral Regulation Index, Metacognition Index) and the 8 scales comprising the two principal problem (syndrome) domains of the CBCL (Internalizing Symptoms, Externalizing Symptoms). Extraction of factors was based on a series of decision rules including assessing the eigenvalues (selecting factors with a value close to 1), graphically representing the eigenvalues to visually analyze the relative importance of the factors, (scree plot), and a parallel analysis (comparing the number of real eigenvalues that are greater than the corresponding expected values from random data). We hypothesized that the scales comprising the two global domains for each of the two instruments would load into separate factors, in accordance with the general dimensions of emotional versus behavioral adjustment problems.

**Results.** Psychometric results showed that a 3-factor model representing 3 specific domains (i.e. metacognition, behavioral adjustment, and emotional adjustment) provided a reasonable fit to the data. The BRIEF Metacognition scales (i.e. initiate, working memory, plan/organize, organization of materials, and monitor) and the CBCL scales pertaining to Internalizing Symptoms (emotional adjustment) (i.e. anxious/depressed, withdrawn/depressed, somatic complaints, social problems) loaded as separate factors across both the HIV and severe malaria clinical samples. The BRIEF Behavior Regulation Index scales (i.e. inhibit, emotional control) loaded with the CBCL Internalizing (emotional) scales (i.e. anxious/depressed, withdrawn/depressed, somatic complaints, social problems). **Discussion.** The BRIEF was designed to screen for emotional and behavioral aspects of a child's executive functioning as assessed by the responses of the principal caregiver or parent. In contrast, the Achenbach CBCL was designed to screen for emotional and behavioral psychiatric symptoms. Both these instruments assess distinct dimensions of children's behavioral adaptation in the home and community in a consistent manner between two distinct clinical groups in the Sub-Saharan African context (HIV and severe malaria survivors). However, the BRIEF Behavior Regulation Index domain has scales that overlap with both the emotional and behavioral psychiatric symptom domains of the CBCL. We conclude that the BRIEF and CBCL assess distinct

dimensions of behavioral, emotional, and functional problems in school age children with infectious diseases that can have profound neurocognitive and psychiatric implications. Together, the BRIEF and the CBCL can provide for a distinct yet complementary emotional and behavioral profile of the adjustment of these at-risk children.

**PI:** Jonathan Burns  
**Title:** Psychotic disorders in an African setting: Incidence, early course, and treatment pathways (FEP-INCET)  
**Presenter:** Jonathan Burns

**ES Susser,<sup>1</sup> JK Burns,<sup>2</sup> S Mtshemla,<sup>2</sup> E Makhatini,<sup>2</sup> JN Baumgartner,<sup>1,3</sup> I Susser,<sup>4</sup> I McKeague,<sup>1</sup> G Davis,<sup>1</sup> L Labys,<sup>2</sup> MA Tomita,<sup>2</sup> L Myer,<sup>5</sup> W Veling,<sup>6</sup> WH Hoek,<sup>6</sup> G Thornicroft<sup>7</sup>**

<sup>1</sup>Columbia University, NY <sup>2</sup>University of KwaZulu-Natal, Durban <sup>3</sup>FHI 360 <sup>4</sup>SUNY, NY, <sup>5</sup>University of Cape Town, <sup>6</sup>Parnassia Institute, The Hague, <sup>7</sup>Institute of Psychiatry, London

**Aims:** This R21 project proposes *to pilot and build capacity* for a subsequent R01 study that will investigate the incidence rate, early course, and treatment pathways (**INCET**) of first episode psychotic disorders (**FEP**) among treatment seeking individuals in Vulindlela, KwaZulu-Natal, South Africa. The FEP-INCET study will be the first to derive incidence rates for FEP in an African setting. **Methods:** We consulted with community stakeholders including the tribal chief, traditional council, local traditional healers' organisation, health and education authorities, primary health care nursing staff, and local religious leaders. Ethnographic work focused on the behavior and perspectives of local people with respect to pathways to care for mental illness. This included residential participant observation with traditional healers (THs). Key informant interviews and focus groups were conducted with individuals from all stakeholder groups. We translated into isiZulu, adapted and piloted instruments for use in the INCET Study (CAPE, SCAN, PANSS, ASSIST, WHO-DAS, CAN, WHO Encounter; Lehman QOL). Finally, 50 THs from throughout Vulindlela were recruited and trained in the recognition of psychotic symptoms. They were requested to refer to us any clients who had sought their help complaining of a recent onset of psychotic-like symptoms. 200 help-seeking individuals were referred to the project by traditional healers and assessed with the CAPE, ASSIST and SCAN interviews. **Results:** A strong collaborative relationship has been established in the region, important insights have emerged from ethnographic and qualitative work, and THs have been successfully included in the pathway to care for individuals with incipient psychosis in the region. Several publications are in preparation and an application for an R01 for the FEP-INCET study will be submitted during 2014.

**PI name and Country:** Hélène Carabin, USA

**Major foreign collaborator name and country:** Humberto Foyaca-Sibat / South Africa

**Presenter name:** Hélène Carabin

**Grant number:** R21TW008434

**Grant title:** HIV-CNS Diseases and Parasitic Zoonoses in the Eastern Cape, South Africa

**Significance:** The Eastern Cape Province in South Africa is endemic for both HIV and *Taenia solium* cysticercosis. Cysticercosis results from the infection with the larval stages of *T. solium* migrating to various tissues. Neurocysticercosis (NCC) occurs when the larvae establish in the brain, causing neurological manifestations such as epilepsy. Epilepsy is believed to manifest following an inflammatory process in the brain. Since HIV infection is linked to reduced immunological processes, how it may affect how NCC manifests is of interest. This is particularly important in the context of increased access to antiretroviral therapy which could lead to a type of immune reconstitution syndrome among patients with NCC lesions in their brain.

**Capacity building activities:** During the course of this R21, we have strengthened the research capacity at the Walter Sisulu University and at the Mthatha Hospital Complex through the delivery of a workshop on grant writing and protection of human subjects in research as well as at the National Health Laboratory Services through a three-week training in the use of a Western-blot test to detect antibodies and an ELISA test to detect antigens to *T. solium*.

**Methods:** Four groups of patients seeking care at the Mthatha Hospital Complex were invited to participate in the study. The four groups were: Group 1: patients with HIV and neurological disorders not on ART and without a known diagnosis of AIDS; Group 2: patients without HIV with neurological disorders; Group 3: patients with HIV not on ART without a known diagnosis of AIDS and without neurological disorders and; Group 4: patients without HIV without neurological disorders. The four groups were frequency matched on age group and gender. Blood samples were collected to test for the presence of antigens and antibodies to cysticercosis and all patients in groups 1, 2 and 3 were invited to get a CT-scan of the brain.

**Results:** A total of 30, 37, 25 and 56 patients were recruited in groups 1, 2, 3 and 4, respectively. An important finding is that if the Garcia and Del Brutto (2005) criteria are applied to define NCC, there are no cases classified as definitive or probable NCC among the HIV positive group without neurological symptoms (group 3), although 43% of those patients had absolute or highly suggestive lesions of NCC at the CT-scan. This shows that this classification may not be appropriate in the context of HIV. Another striking finding was that the levels of CD4, which are indicators of immune-response, modified the association between neurological manifestations and all lesions of NCC (test of homogeneity with  $p=0.042$ ). Indeed, among patients with lower levels of CD4 counts (<250), the proportion of NCC among people with manifestations was lower than among those without manifestations. Among people with higher levels of CD4, there was a larger proportion of NCC lesions among people with neurological manifestations than among those without manifestations. This confirms our initial hypothesis that some level of CD4 counts may be required for patients to have sufficient inflammation in the brain to result in neurological manifestations such as seizures and epilepsy.

**Barriers:** Major delays in obtaining ethical approval in South Africa and in getting all the final data on the CT-scan reading and serological analysis. Data capture is almost finished and manuscripts will be submitted shortly.

**PI name and Country:** Hélène Carabin, USA

**Major foreign collaborator name and country:** Athanase Millogo / Burkina Faso

**Presenter name:** Amina Traoré and Dolly Tchio

**Grant number:** R01NS064901

**Grant title:** EFECAB: improving pig management to prevent epilepsy in Burkina Faso

**Abstract title:** Perceptions regarding epilepsy, sanitation and pig management practices in three villages of Burkina Faso.

*Taenia solium* is a cestode which establishes in humans' intestines following the consumption of undercooked contaminated pork. The environment is contaminated by eggs contained in human feces which, when ingested, can establish as larvae in pig and human tissues. Neurocysticercosis (NCC) occurs when the larvae establish in the brain, causing neurological manifestations including epilepsy and severe chronic headaches. NCC is believed to be the leading cause of late onset epilepsy in developing countries. Yet, there is no agreement as to which type of intervention is most cost-effective and sustainable to control the infection. Research in Tanzania has shown that improved pig management practices lead to a reduction in porcine infection while small pilot projects conducted in Latin America suggest that sanitation is a key element. The overall objective of EFECAB, a community-based randomized controlled trial, is to estimate the effectiveness of an educational program, developed using a PREDECE-PROCEED approach, to control human and porcine cysticercosis. The long term goal is to control NCC-associated neurological disorders. The aim of the qualitative component of the PRECEDE-PROCEED was to assess the general knowledge and perceptions of the population regarding epilepsy, the transmission of cysticercosis and to identify elements of the disease life cycle that could be interrupted through acceptable and sustainable behavioral change. The study was conducted in the villages of Batondo (province of Boulkiemdé), Sawa (Nayala) and Kikigogo (Sanguié). Six group discussions took place in each village according to age (less than 25, 25-45, and more than 45 years of age) and gender. The group discussions were led by a Bukinabè sociologist. The software QSR NVIVO 10 was used to classify all the answers by themes, sub-themes and characteristics. Themes and sub-themes were identified independently by two West African francophone students. The most recurrent themes included sanitation, pig management, attitudes towards people with epilepsy, cysticercosis and epilepsy. All age-gender-village groups had similar perceptions regarding cysticercosis and epilepsy. No group was able to provide a biologically plausible explanation of the mode of contamination and treatment of cysticercosis and its link with epilepsy. However, most groups acknowledged the risk of disease transmission associated with open-air defecation. Open-air defecation was not attributed to any cultural or traditional beliefs, but barriers to latrine use included the lack of money and knowledge for building them. Barriers to better pig management practices, such as keeping pigs in pens, included the difficulty of finding food to feed the pigs while confined and the financial challenge to build and maintain pens in suitable conditions for breeding. Overall, the populations were open to sensitization and reacted positively to education on cysticercosis, epilepsy, pig management, and sanitation. This qualitative analysis resulted in a shift of the initially planned intervention with a focus on pig management to a focus on sanitation. A 52 minutes comedy has been produced and presented to the villages randomized to the intervention group. The

intervention also included the PHAST method to raise awareness about the importance of stopping open air defecation, hand washing and food cleaning. The group discussion analysis is being conducted by two students at the University of Oklahoma originally from neighboring Mali and from Cameroon.

**PI name and Country:** H  l  ne Carabin, USA

**Major foreign collaborator name and country:** Athanase Millogo / Burkina Faso

**Presenter name:** H  l  ne Carabin

**Grant number:** R01NS064901

**Grant title:** EFECAB: improving pig management to prevent epilepsy in Burkina Faso

**Abstract title:** Spatial clustering of cysticercosis at village level of Nayala, Boulkiemdi  , and Sangui   provinces in Burkina Faso

**Abstract authors:** R Poudel, S Magzamen, A Millogo, R Ganaba, P Dorny, Z Tarnagda, H Carabin

**Background:** *Taenia solium* is a parasitic zoonosis transmitted between humans, the definitive and accidental hosts, and pigs, the intermediate hosts. Infected humans contaminate the environment with *T. solium* eggs in their feces. Yet, no field studies have assessed the survival of *T. solium* eggs in the environment. The few spatial studies of cysticercosis have not assessed the effects of land characteristics nor weather factors on human and porcine cysticercosis. The objective of EFECAB, a community-based randomized control trial, is to develop an educational program to reduce the risk of human and pig cysticercosis. However, to best interrupt the life cycle of *T. solium*, it is essential to identify where porcine and human clusters of infection occur, and how they are influenced by environmental factors. The aim of this component of EFECAB was to analyze clusters of porcine cysticercosis at the village level using GIS and spatial analysis. Results from the analysis of human cysticercosis clusters will be available in February 2014.

**Methods:** This study is secondary analysis of the baseline component of EFECAB. A total of 60 villages were randomly selected among 164 eligible pig-raising villages by blocks of 2 in each of 30 departments. After conducting a census of all concessions (a group of several households) in each village, a random sample of 10 sows and 30 piglets (< 12 months old) was selected from 10 and 30 concessions where sows and piglets were raised, respectively. Questionnaire answers as well as longitude and latitude coordinates of each concession were measured using PDAs. The presence of current cysticercosis infection was measured with an ELISA to detect antigens in pigs' sera. The prevalence of current cysticercosis infection was calculated as the ratio of the number of seropositive pigs to the total number of sampled pigs in each village. Clusters of village-level porcine infection were assessed using Gi\* in ArcGIS 10.1. Gi\* explains the spatial patterns of autocorrelation by detecting clusters of high prevalence areas (hot spots) and low prevalence areas (cold spots). We assessed the presence of clusters using threshold distances between neighboring villages of 7.5 km, 10 km, 11 km, and 15 km.

**Results:** The village-level prevalence of porcine infection ranged from 12.5% to 94.4% with an average of 44.3%. Among the 59 villages and 2238 concessions with available ELISA results, the largest number of clusters was identified using an 11 km threshold between villages. This resulted in the identification of five hot-spots and seven cold spots.

**Discussion:** As reported in Tanzania, India and Peru, porcine cysticercosis was found to cluster in Burkina Faso. By the time of the meeting in February, the impact of the location of rivers and of season on porcine infection will also have been determined. This approach will also be used to assess the presence of human cysticercosis clusters. Plans are now being made to assess the impact of other environmental factors such as temperature, vegetation cover and humidity on the infection levels. This data will be key to better understanding the transmission of *T. solium*, and to ultimately control it.

PI name/PI Country: Waldemar A. Carlo, United States of America

Major foreign collaborator name/Foreign Collaborating Country: Elwyn Chomba/India, Pakistan and Zambia

Presenter name: **Waldemar A. Carlo**

Grant number: TW-06703; HD053055; HD43464; HD42372; HD40607; HD40636

Grant title: Brain Research to Ameliorate Impaired Neurodevelopment: Home-based Intervention

**Randomized trial of early developmental intervention on outcomes in children after birth asphyxia in developing countries.**

Carlo WA, Goudar SS, Pasha O, Chomba E, Wallander JL, Biasini FJ, McClure EM, Thorsten V, Chakraborty H, Wallace D, Shearer DL, Wright LL; Brain Research to Ameliorate Impaired Neurodevelopment-Home-Based Intervention Trial Committee and the National Institute of Child Health and Human Development Global Network for Women's and Children's Health Research Investigators.

To determine if early developmental intervention (EDI) improves developmental abilities in resuscitated children.

This was a parallel group, randomized controlled trial of infants unresponsive to stimulation who received bag and mask ventilation as part of their resuscitation at birth and infants who did not require any resuscitation born in rural communities in India, Pakistan, and Zambia. Intervention infants received a parent-implemented EDI delivered with home visits by parent trainers every other week for 3 years starting the first month after birth. Parents in both intervention and control groups received health and safety counseling during home visits on the same schedule. The main outcome measure was the Mental Development Index (MDI) of the Bayley Scales of Infant

Development, 2nd edition, assessed at 36 months by evaluators unaware of treatment group and resuscitation history.

MDI was higher in the EDI ( $102.6 \pm 9.8$ ) compared with the control resuscitated children ( $98.0 \pm 14.6$ , 1-sided  $P = .0202$ ), but there was no difference between groups in the nonresuscitated children ( $100.1 \pm 10.7$  vs  $97.7 \pm 10.4$ ,  $P = .1392$ ). The Psychomotor Development Index was higher in the EDI group for both the resuscitated ( $P = .0430$ ) and nonresuscitated children ( $P = .0164$ ).

This trial of home-based, parent provided EDI in children resuscitated at birth provides evidence of treatment benefits on cognitive and psychomotor outcomes. MDI and Psychomotor Development Index scores of both nonresuscitated and resuscitated infants were within normal range, independent of early intervention.

**Investigators:** Nico Ballarini BSc, Nancy Carney PhD, Maria Camila Corzo Casadiego, MD, Silvia Lujan MD, Gustavo Petroni MD, MCR, Juan Carlos Puyana MD, Andres Rubiano MD

**Presenter:** Nancy Carney

R01-HD060570

**Title:** Missing Pieces in the Pipeline: The Orphan Project

This presentation is being submitted by a collaboration of researchers who have collectively received funding, through the BRAIN and D43 programs, for two R21s, two R01s, and two Trauma Research Training Grants. The U.S. grantee institutions are Oregon Health & Science University (OHSU – Carney PI) and University of Pittsburgh (U Pitt – Puyana PI). The Low- and Middle Income Country (LMIC) collaborating institutions are Centro de Informatica e Investigacion Clinica (CIIC – Lujan PI; Rosario, Argentina) and Fundacion Meditech (Meditech – Rubiano PI; Neiva, Colombia).

In Argentina, the OHSU/CIIC team conducted a pilot trial of an information technology intervention to enhance adoption of evidence-based guidelines for treatment of pediatric traumatic brain injury (TBI), and a 5-year program in which they provided students with 1- and 2-year certifications in TBI research, which now is a part of the curriculum of the University of Rosario. Subsequently they conducted two 5-year randomized trials – one of an acute medical intervention for adults, and a second of a post-discharge intervention for children. In Colombia, the U Pitt/Meditech team is conducting a pilot trial of decompressive craniectomy for severe TBI, and completed a 5-year training program in trauma research. Both collaborations have been successful in building free-standing research programs in their home countries which are financially independent of the originating FIC grants, and are serving local community needs. The four entities have come together to address an important gap in the NIH programs that provide research education and funding in LMICs.

There is a concern that, while international students are being provided exemplary education in research, when they return to their LMIC communities they do not have all the training necessary to build research programs and create opportunities for their work at the local level. When they return home many of them become, so to speak, “orphans.” Our group initiated a project to address the needs of international investigators returning to their homes, to build a collaboration among them, and to provide community leadership development as part of the research training program provided by FIC and NIH. The project will incorporate four components:

1) Survey. We have circulated a survey to 96 FIC programs to assess the needs of the international investigators. We are in the data collection phase, and will present the results at the symposium.

2) General Leadership Education. We have developed a curriculum designed to build Community Leadership capacity in our international students. We have submitted an application for funding to the Non-Communicable, Chronic Diseases (NCD) D43 program to develop and deliver research training about the NCD of TBI. Embedded in the curriculum is the Community Leadership program.

3) Specific Leadership Education. Also embedded into the D43 curriculum will be specific training in community outreach; creating relationships with local political, business, and health care system leadership; building business models; and marketing. Instructors will be CIIC and Meditech investigators with demonstrated success in creating their own sustainable programs. The plan is to have the NCD D43 (if funded) be the platform for the delivery of the General and Specific Leadership Education.

4) Outcome Study – Results of the Orphan Project. In the context of the D43, we will conduct a pre/post study of the influence of the Orphan Project on establishing and sustaining independent research programs in LMICs. The results of this study will provide data relevant to the design of international research education programs.

We have succeeded in establishing research capacity in our communities in Argentina and Colombia. The purpose of this project is to identify and implement programs that will contribute to similar success across international research training programs.

**Contact PI, Professor Monique Chaaya, Faculty of Health Sciences, American University of Beirut (AUB), Beirut, Lebanon.**

**Co-PI, Professor Gunhild Waldemar, and Project Coordinator, Dr. Kieu Phung, Danish Dementia Research Center, Department of Neurology, Copenhagen University Hospital, Copenhagen, Denmark**

**Consultant: Professor Martin Prince, Department of Health Service and Population Research, Institute of Psychiatry, King's College London, London, UK.**

**Presenter: Dr. Kieu Phung**

**Grant number: 1R21AG039333-01**

**Grant title: Prevalence of Dementia in Lebanon: A Nationwide Community-Based Cohort Study**

### **Objectives**

Due to rapid aging in the Middle East and North Africa region (EMRO), dementia is becoming a major public health problem. The scarcity of studies allows no precise estimates of dementia prevalence and incidence. The high illiteracy rates among older people in the region present a great challenge for cognitive assessments. Validated diagnostic assessment for dementia is lacking.

The aims of this study were: 1) To validate the Arabic versions of the 10/66 Dementia Research Group (DRG) one-phase dementia diagnostic assessment and two brief screening instruments for dementia, the **Rowland Universal Dementia Assessment Scale (RUDAS)** and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) 2) To carry out a pilot study in two governorates in Lebanon, using the validated 10/66 DRG diagnostic assessment for case ascertainment, to generate preliminary data about dementia prevalence, and assess the feasibility of a large nationwide longitudinal community-based cohort study about dementia prevalence and incidence, risk and protective factors in Lebanon.

### **Methods**

For the validation study, 244 participants older than 65 years, 100 with normal cognition and 144 with mild to moderate dementia, were included. Dementia was diagnosed by clinicians according to DSM-IV criteria. Trained interviewers blind to the cognitive status of the participants administered the 10/66 DRG diagnostic assessment, RUDAS, and IQCODE, to the participants and the caregivers. The discriminatory ability of the assessments was evaluated against the clinical diagnoses.

For the pilot study, 521 community-dwelling participants 65 years and above and their caregivers from Beirut and Mount Lebanon governorates are being recruited through door-to-door knocking. Data collection is taking place in random clusters of Beirut and random villages in Mount Lebanon. Trained interviewers administer the 10/66 DRG diagnostic assessment, background and risk factor questionnaires.

### **Results**

The 10/66 DRG diagnostic assessment showed excellent sensitivity (92.0%), specificity (95.1%), and positive predictive value (PPV, 92.9%), and low false positive rate (FPR) among controls with no formal education (5.6%). At the cutoff of 22, the RUDAS demonstrated good sensitivity (80.0%), specificity (88.0%), and PPV (82.5%) but a relatively high FPR among those with no

formal education (14.5%). At the cutoff of 3.35, the IQCODE exhibited excellent sensitivity and specificity (both 93.0%), and PPV (90.3%), and low FPR among those with no formal education (6.5%).

Data collection for the pilot study is half way through, 230 participants and their caregivers have been interviewed. Data collection is expected to conclude in December 2013 and the preliminary prevalence data will be ready to be presented at the symposium in February 2014.

### **Significance**

The study provided the first validated cognitive assessments for Arabic speaking populations with high rate of illiteracy in EMRO. The 10/66 DRG assessment proved to be an excellent instrument to diagnose dementia and is particularly useful in epidemiological studies. The RUDAS and IQCODE demonstrated good discriminatory ability and can be used as brief screening instruments in clinical practice or in research.

The pilot study will hopefully lead to a nationwide longitudinal community-based cohort study about dementia prevalence, incidence, risk and protective factors in Lebanon, filling in the gap of knowledge about dementia occurrence in EMRO and providing the much needed knowledge about dementia determinants specific to the region for the development of health promotion and disease prevention strategies.

### **Challenges**

The unstable political situation in Lebanon makes it difficult to recruit participants by door knocking. Due to the lack of census and civil registration, it is impossible to estimate the numbers of household needed to knock in each chosen area to reach the number of participants required. Therefore, interviewers who are known to the local communities were used to recruit participants and they knock on every door in the area. This strategy has worked well in the low socioeconomic areas but failed in the high socioeconomic areas.

Training the field workers takes one week. Each returned questionnaire has to be checked right away to ensure the quality of data and the field workers immediately get their feedback. Half of the interviewers have resigned, perhaps because it is time consuming and challenging to recruit participants by door knocking and to do the interviews.

### **Building research capacity**

Lebanese researchers and clinicians have been trained in conducting the 10/66 DRG diagnostic assessment and 10/66 DRG study protocol for the nationwide longitudinal population-based study. The Lebanese trainees included an epidemiologist, a neurologist, an old-age psychiatrist, a geriatrician, a statistician, five medical residents in neurology, geriatrics, and family medicine, and eight non-medical university graduates in public health and sciences. Professor Monique Chaaya, the contact PI from AUB, and her local research team is fully capable of continuing the study beyond this grant.

PI: Hongtu Chen / USA

Foreign Collaborator: Somsak Chundras / Thailand

**Presenter: Hongtu Chen**

Grant number: R21 AG033530-01

Grant title: Dementia Care in Thailand: Infrastructure and Research Development

Funded period: 9/1/2011 – 8/31/2013

This R21 project was designed to obtain an in-depth understanding of the needs and strategies for improving dementia care in Thailand by conducting a qualitative ethnographic research. It is the first of its kind in the country.

Inspired by the project, an agency of Thai Ministry of Public Health (i.e., the Bureau of Health Policy and Services) provided supplemental funding to expand the original scope of the study within one province to 9 provinces, covering the major five regions of the entire country.

The project is a joint effort of U.S. investigators with two key Thai organizations: the Thai Gerontological Research Institute that, with its strength in national aging policy development, has successfully involved the experts from Thai Alzheimer's Association and the Thai Geriatric Society into this study; and the Society and Health Institute that has successfully mobilized the community health researchers from nine participating provinces to conduct the qualitative research on the situation of home care for elders with dementia in rural and urban Thailand.

Over forty community health research personnel from nine provinces of Thailand participated in five consecutive training workshops on topics of dementia, caregiver burden, ethnographic research methods, data collection procedure and tools, as well as qualitative data analysis.

Qualitative data including interview transcripts, direct observation notes, and photos have been collected from 201 Thai homes that provide care to frail elders, including 101 homes with cognitive impairment as assessed by using the Thai MMSE and physician diagnosis. Findings revealed, in both rural and urban areas, profound needs of dementia care families for knowledge, training, and support. The results including illustrative summaries of case reports have been compiled into an over 400-page report to be submitted to the Thai health care agencies.

After reviewing the data of needs and service gaps as well as short- and long-term situations of current aging initiatives in the country, the research team has determined that a local hospital based home care support program that aims to build a collaborative care between health personnel and family caregivers is the best intervention model from perspectives of care support delivery, sustainability, and quality management. We are poised to submit an R01 application to test the effectiveness of this intervention scheme, in order to obtain policy support to institutionalize training and management structure that are necessary for national dissemination of the solution to dementia care in Thailand.

The project also has supported the establishment of the Global Initiative on Caregiving for the Elderly at the Harvard University Asia Center, of which the PI of this project has served as the director.

**Joan Y. Chiao / USA**

Jack van Honk / SOUTH AFRICA

1R21MH098789-01

**Title: Cross-cultural neuroimaging of emotion in South Africa, Japan and United States**

The goal of our research is to examine the influence of culture on neurobiological mechanisms of emotion. Prior research has shown that culture affects mental health outcomes, such as prevalence of anxiety and mood disorders, across nations as well as neural responses during processing of social and emotional information. However, little is known about how culture affects neural responses of emotion in genetically diverse populations. Given that most neuroimaging research to date has been conducted in Western industrialized nations, our goal is to build research capacity for cross-cultural neuroimaging research of emotion in South Africa in order to conduct a cross-cultural comparison of neural response to emotion in Xhosa living in South Africa, Japanese living in Japan and Caucasian-Americans living in the United States. In order to build research capacity, we are building a novel experimental stimuli database that consists of emotional expressions created by Xhosa South Africans (AFEE) to complement existing standardized stimuli databases of emotional expressions consisting of Japanese and Caucasian-Americans (JACFEE). Additionally, we are implementing a cross-site scanning comparison of neural response from three functional neuroimaging sites in order to assess cross-scanner signal-to-noise ratio. Our current research will provide a foundation for future research in cultural neuroscience examining cultural influences on neurobiological mechanisms of emotion and related psychological processes that affect population mental health.

**Chilton, FH/ USA**

**Kumari, S/ India**

**Chilton, Floyd H.**

**Grant title: 5R21TW008916-02**

**Grant title: Effect of FADS gene variants on fatty acid synthesis & brain development in India**

FH Chilton<sup>1</sup>, AK Shetty<sup>1</sup>, RA Mathias<sup>2</sup>, S Kumari N.<sup>3</sup>, S Sergeant<sup>1</sup>, M Bekal<sup>3</sup>

<sup>1</sup>Wake Forest University Health Sciences, <sup>2</sup>Johns Hopkins School of Medicine and <sup>3</sup>NITTE University

Long-chain polyunsaturated fatty acid (LC-PUFA), such as docosahexaenoic acid (DHA) and arachidonic acid (AA) are vital for brain and eye development during embryonic and fetal progression as well as in early childhood. Without adequate concentrations of LC-PUFA, visual and cognitive development is markedly impaired in infants and children. A lack of LC-PUFAs or an imbalance between  $\omega$ -3 and  $\omega$ -6 LC-PUFAs, has been associated with a number of behavioral abnormalities, as well as neurological and psychiatric disorders in both children and adults, particularly attention-deficit hyperactivity (ADHD) and autism spectrum disorders, and uni- and bi-polar depressive disorders. LC-PUFAs such as DHA and AA can be obtained preformed in the diet. In certain human populations, these LC-PUFAs can also be synthesized from dietary plant-based 18-carbon (C18) essential PUFAs. The developing fetus (especially in 3<sup>rd</sup> trimester) and young children (<18 months) in developing countries are particularly vulnerable to inadequate DHA and resulting brain development deficits as their diets are often composed of foods that contain little or no  $\omega$ -3 C18 precursors or LC-PUFAs. Recent studies in our laboratories suggest that different human population vary markedly with regard to their capacity to convert (C18-PUFAs) to LC-PUFAs, especially DHA. Specifically, we have examined the variants in the genes of the rate-limiting steps involved in LC-PUFA biosynthesis in 52 populations described in the Human Diversity Panel and have shown there are dramatic frequency differences in high and low conversion efficiency variants in the fatty acid desaturase (*FADS*) cluster on human chromosome 11 (12.2q). Specifically, our new data indicates that one or more mutations occurred in early human development (~85,000 years ago) that allowed for more efficient conversion of plant-based C18-PUFAs to LC-PUFAs. Selective signatures indicate a pattern of selective pressure within Africa that has led to a fixation of the alleles that favor this enhanced efficiency of conversion within the African continent. In contrast, our data reveals that endogenous populations in Southeast Asia, Central and South America have far lower frequencies of the more efficient variants, which likely limit their capacity to synthesize LC-PUFAs from plant-derived precursors. Taken together, these data suggest that there is a critical need to understand gene-nutrient and particular gene-PUFA interactions to better determine the populations that are most vulnerable to DHA and AA deficiencies, which could manifest themselves in the form of a variety functional brain deficits. Additionally, it is imperative to recognize these gene-PUFA relationships to be able to provide adequate diets and

optimize supplementation approaches that maximize early brain development in the developing world.

A large proportion of the children who suffer from malnutrition reside within India. However, there are no studies that have examined the genetics of PUFA metabolism in an Indian population. The objective of this proposal was to initially establish a collaborative research program between Wake Forest University Health Sciences /Johns Hopkins School of Medicine and NITTE University/AB Shetty Memorial Institute of Dental Sciences (ABSMIDS)/K.S. Hegde Medical Academy (KSHEMA), Mangalore, India to put in place the infrastructure to analyze fatty acid nutritional status, circulating fatty acid levels and allele frequencies in the *FADS* gene cluster in populations in the coastal city of Mangalore in the State of Karnataka in Southern India. We have provided training mechanisms for the investigators and PhD candidates from the Department of Biochemistry at NITTE University, KSHEMS and ABSMIDS, Mangalore, India in the areas of public health aspects of human genomics, nutrition and the consequences of impaired brain development, in the molecular and statistical techniques necessary to examine SNPs, genotypic/phenotypic associations and in methods involved in the analysis of food and blood lipids focusing on fatty acids. This project has created a fertile local academic environment and a developing infrastructure needed to initially examine this critical gene-diet interaction necessary for brain and eye development in a single Indian population and to prepare for a much larger examination in diverse populations throughout India. In the initial funding period, obstacles encountered have included perceptions of human research and cultural as well as other barriers (intra- and inter-institutional possessiveness among groups) that prevent effective collaboration. Continued involvement in the greater project will be important for ultimately achieve sustainability.

Alexander Cohen / United Kingdom

Oye Gureje / Nigeria

**Alexander Cohen**

5R21MH093304-02

Scaling up services for people with psychosis in Nigeria: a pilot study

## **BACKGROUND**

Psychoses impose a comparatively large burden of disease and are also associated with excess mortality, suicide in particular, as well as stigma, discrimination, and violations of human rights. In low-income, the burden of these disorders is amplified by a lack of treatment, rehabilitation, and support services that can reduce symptomatology, increase functionality, and decrease family burden. In Nigeria, the situation is especially dire because research has demonstrated that the prevalence of psychoses is relatively common (1.1%) but that biomedical treatment and support services are relatively rare.

## **AIMS**

- 1) Within two local government areas of Ibadan, Nigeria (Ibadan South East and Ona Ara) document and map all sources of treatment and care, both biomedical and alternative methods, for persons with psychosis;
- 2) Explore the range of needs of persons with psychosis and their caregivers;
- 3) Identify the barriers to and facilitators of scaling up of services for persons with psychosis.

## **METHOD**

- 1) Located and visited sites where people with psychosis might seek care;
- 2) Interviewed inpatients and outpatients (under the care of biomedical facilities and alternative healers), caregivers, primary care workers, private practitioners, and alternative healers;
- 3) Conducted focus groups with caregivers of persons with psychosis;
- 4) Administered the Camberwell Assessment of Needs Survey to 20 informants.

## **RESULTS**

The care and treatment of persons with psychosis who reside in the catchment areas is dominated, to a very large extent, by spiritual and traditional healers. The healers – who reported that they never referred patients to biomedical care and charged large fees for their services – often confined and chained their patients for long periods of time. Primary care staff, as well as private physicians, demonstrated little capacity for providing psychiatric care for persons with psychosis. Caregivers generally reported high levels of distress associated with looking after persons with psychosis. Caregivers also frequently mentioned their need for financial support, and rehabilitation programs for persons with psychosis. Pathways to care were complex and it appears that help-seeking is as much determined by the effectiveness of treatment and financial matters as by explanatory models of psychosis.

## **CONCLUSIONS**

Scaling up services for persons with psychosis who reside in Ibadan Southeast and Ona Ara will require extensive planning, training of primary care staff, and investment of resources so that it will be possible to monitor services and provide specialist supervision of non-specialist health workers. Ideally, resources should also be invested in the establishment of rehabilitation services and support services for caregivers.

**PI:** Adriana B. Conforto/Brazil

**Major foreign collaborator name:** Leonardo G. Cohen/USA

**Presenter name:** Adriana B. Conforto

**Grant number:** D71TW009132-01

**Grant title:** Novel strategies for stroke rehabilitation (planning grant)

### **Abstract**

**Title:** Translational neurorehabilitation research in the third world: what barriers to trial participation can teach us

Authors: Sarah M. Anjos, Leonardo G. Cohen, Annette Sterr, Karina N. F. de Andrade, Adriana B. Conforto

### **Abstract**

**Background and Purpose:** Most stroke rehabilitation studies have been performed in high-income countries. The aim of this study was to identify the main barriers for patient inclusion in a research protocol performed in Brazil.

**Methods:** We evaluated reasons for exclusion of patients in a pilot, randomized, double-blinded clinical trial of stroke rehabilitation. Descriptive statistical analysis was performed.

**Results:** Only 5.6% of 571 screened patients were included. Recurrent stroke was responsible for exclusion of 45.4% of potentially eligible patients.

**Conclusions:** Almost half of the patients who fulfilled inclusion criteria for the study had history of previous stroke. In Brazil, rates of recurrent stroke are higher than those reported in high-income countries. External validity of rehabilitation trials will benefit from definition of study criteria according to regional characteristics of patients, including rates of recurrent stroke.

**PI name/ PI country: Leslie L. Davidson-USA,  
South African collaborator and PI: Shuaib Kauchali, UKZN, South Africa  
South African co-investigators – Meera Chhagan, Jane Kvalsvig, Myra Taylor  
US co-investigators – Stephen Arpadi, Claude Mellins, Zena Stein, Ida Susser  
Dr. Leslie L. Davidson  
Title: Health & Psychosocial Need: Children with Neurodevelopmental Disorders in a  
Time of HIV(DA0236967)**

With the long term goal of intervening to promote better developmental and psychosocial functioning of children in South Africa, this study is investigating how the ability of children with neurodevelopmental disorders to function cognitively and socially is influenced by both health-related (HIV, anemia, other infection), contextual (socio-economic and environmental, access to care and therapeutic intervention) and psychosocial factors (caregiver characteristics including mental health and substance use, family functioning). 1581 preschool isiZulu children in five tribal areas of KwaZulu-Natal in South Africa were enrolled in the study with 80% of their caregivers. Nearly 90% were seen again about two years later for a second assessment. About 29% of these children live with caregivers who are HIV positive and 13% have a parent who has died. AIDS. Over half the children of known HIV+ mothers had never been tested for HIV. Almost 5% of the surviving children are themselves HIV positive. Over 50% were anemic and 17% were stunted. Just under 4% had moderate or serious neurodevelopmental disabilities. However, given the commitment of the South African Government to providing care and support to children infected by and affected by HIV, only one child in 1581 died between the enrollment of children in Phase 1 and the followup in Phase 2. Analysis of children experiencing unprovoked seizures demonstrated associations with the following: prenatal - bleeding in 2nd 3rd

trimesters, labor > 24 Hours, breech or footling delivery; neonatal – having been taken away from mother at birth, difficulty difficulty feeding; later child health and development, difficulty feeding and behavior problems. Analyses found that children who were HIV positive had a greater prevalence of both conductive and sensory hearing losses. Additional challenges such as poverty, inadequate access to health care and to education are common; many other risks to child health and well-being, including inadequate nutrition, infection and partner violence, as well as caregiver depression or PTSD (27%) and binge drinking (6%) affect many children. As a result, we are finding that many children do not function at optimal levels, and are at risk for developmental disabilities. The children were assessed for physical, neuro-developmental and mental health problems and offered HIV testing and relevant referrals. Caregivers were assessed for overall physical health and mental health and offered HIV testing.

The study design allowed us to investigate first cross sectionally and then longitudinally the relationships among neurodevelopmental disorders, the above mentioned social, caregiver risk factors and the study's key outcome factors, child cognitive and psychosocial functioning. Longitudinal analyses assessed school functioning as well as cognitive assessment. Community ethnographic studies linked to the findings of the epidemiologic study will facilitate the understanding of the quantitative findings and will identify culturally appropriate interventions. The Study team will identify factors open to intervention known to affect child risk and resilience and have worked with community leaders in a participatory approach to develop an effective community based intervention. The need to train the South African non professional team from scratch meant that the time frame was inadequate to complete and publish all planned analyses. Training was offered for many South African staff, professional and non professional, throughout the study, leading to an experienced team ready to join other research initiatives. An important benefit to the study was the training of non professionals in research skills. The study has been engaged in translating and validating a number of research measures such as the SDQ and the CDQ. Challenges included the findings that simply translating and back translating measures validated in the North, is not good enough in developing research measures suitable for use in subSaharan Africa. We found that interweaving epidemiology and ethnography approaches allowed us to strengthen inference from the study findings.

*PI:* Michael R. DeBaun, MD, MPH; Muktar Aliyu, MBBS, MPH, DrPH; Lori Jordan, MD, PhD

*PI Country:* USA

*Major Foreign Collaborator Name/Country:* Aminu Kano Teaching Hospital, Nigeria

**Presenter: Najibah Galadanci, MBBS, FMCPATH**

*Grant Number:* 1R21NS080639-01

*Grant Name:* Primary Prevention of Strokes in Nigerian Children with Sickle Cell Disease

## **ABSTRACT**

**Title:** Screening for Strokes in Children with Sickle Cell Disease a Low Income African Country using Transcranial Doppler Ultrasound is an Acceptable and Feasible Strategy.

**Background:** Sickle cell disease (SCD) is the most common genetic disease in the world. African children are disproportionately affected with the disease. **Approximately 150,000 children are born each year with SCD in Nigeria, making it the country with the largest burden of SCD in the world.** In the US, elevated transcranial Doppler ultrasound (TCD) velocity in the middle cerebral artery or internal carotid ( $\geq 200$  cm/sec) is associated with an approximately 11% risk of stroke in 12 months. The STOP phase III trial demonstrated that monthly blood transfusion therapy is an effective strategy to decrease the rate of strokes in participants with an elevated TCD measurement when compared to observation, with a relative risk reduction of 90%. However, this preventive therapy is not feasible in Nigeria due to inadequate supply of blood, a high rate of infection with blood borne pathogens and the reluctance of Nigerian parents to accept blood transfusion therapy for primary stroke prevention

in their children with SCD. Given that blood transfusion therapy is not an option for children with elevated TCD measurements living in sub-Saharan Africa, the only alternative is hydroxyurea therapy. **The primary hypothesis for the definitive phase III trial is that low dose hydroxyurea (20 mg/kg) is non-inferior and associated with less adverse effects when compared to maximum tolerated dose of hydroxyurea for preventing strokes (typically greater than 30 mg/kg).** The international research (Nigeria, UK, and the US) team has met face-to-face three times in the last 15 months to ensure appropriate standardization of TCD, neurological, and cognitive assessments. Our aims are: 1. Determine the adherence rate to daily hydroxyurea therapy in children with SCD and elevated TCD measurements; and 2. Assess the safety of hydroxyurea, as it relates to infection associated with hospitalization and mortality.

**Methods:** This is a single arm feasibility trial of hydroxyurea therapy in children with elevated TCD measurement, with one year follow up at Aminu Kano Teaching Hospital in Kano, Nigeria. Children between 5 and 12 years of age with Hb SS or SB<sup>0</sup> without evidence of strokes are asked to participate in the trial. Of those children that meet eligibility criteria, two TCD measurements are performed by two radiologists. If cerebral blood flow velocity is  $\geq 200$ cm/sec, then children are eligible to receive hydroxyurea therapy. Adherence will be measured during monthly research visits, based on the Morisky Scale, using the sum of all the correct answers: high adherence (8 points), average adherence (6 to 7 points) and poor adherence (0 – 5 points) and morbidity will be defined as an illness requiring hospitalization. We will include a comparison group of 210 children with SCD and normal TCD measurements followed for 1 year.

**Results:** To date, a total of 134 children with SCD have enrolled of which, 11% (15 of 134) had elevated TCD velocities and were eligible for HU therapy. Among this high risk group, 73% (11 of 15) agreed to participate in the trial and are currently receiving low dose hydroxyurea for a mean follow up period of approximately 4 months. Parents of children with normal TCD measurements have consented and assented, 43% (52 of 119), to be followed for one year to determine the background rate of strokes and morbidity.

**Conclusion:** Our preliminary results indicate that screening for elevated TCD measurements for primary stroke prevention in SCD is feasible in a low income country. If the phase III trial is successful hydroxyurea could be an effective strategy to prevent strokes in children with elevated TCD measurements in sub-Saharan Africa, and potentially in the US.

**Funding:** NIH/NINDS 1R21NS080639-01 (MRD, MA, LJ), Doris Duke Charitable Foundation (MRD and MA) and Aaron Ardoin Foundation for Sickle Cell Anemia (MRD).

PI Name/Country: Gabriel de Erausquin, Argentina

Major foreign collaborator/Country: Maria Calvo, Argentina; Carla Gallo, Peru; Guillermo Rivera, Bolivia

Presenter: **Gabriel de Erausquin**

Grant: NIH/FIC R21-TW007882-04

Grant Title: Investigation on the Movement Abnormalities and Genetics of Schizophrenia (IMAGES)

Publication List: None

### **ABSTRACT:**

In the context of the study IMAGES (NIMH 7K08MH077220-05, NIH/FIC 7R21TW007882-04) we identified and evaluated Kolla subjects with chronic schizophrenia never exposed to medication, their first degree relatives and aged, sex and educational level-matched controls. The results show a clear predictive model of schizophrenia risk that may be the basis for a primary prevention program. As a consequence of IMAGES, duration of untreated psychosis in the province declined from an average of several years to a few months, and the provincial government instituted an early detection/early intervention program funded locally and staffed with researchers trained by IMAGES. We created capacity building tools including a translation and cultural validation of our assessment instruments in the Kechwa language (spoken by more than 10 million indigenous people in South America), an *on line* training webpage for the use of the Schedules for Clinical Assessment in Neuropsychiatry (World Health Organization) (<http://images.health.usf.edu>), the creation of a mobile platform (Android based) for data acquisition, transmission and sharing, and the creation of an USF supported Multidisciplinary

Training Program on Neuropsychiatry and Behavioral Disorders in First Nations (NEUFIN) that is under review as a D43 application. Hand in hand with capacity building tools, we created an interactive website and data repository for the study (<https://utiquay.health.usf.edu>), and published a public website for analysis of complex genotype/phenotype relations (<http://131.247.59.63/fenogeno/>). Data analysis of the phenotypes and partial analysis of the genetic information has been completed and submitted for publication. The next stages include an R01 application to PsychENCODE to analyze the epigenetic contributions to risk of schizophrenia in our sample, and R21 submission to develop induced pluripotent stem cells from skin samples donated by subjects in the study, and an additional R01 application for the GWAS analysis of the extended sample (including subjects recruited in Bolivia and Perú) that will be submitted in the next cycle.

PI: Nancy Fiedler, USA  
Co-I: Wattasit Siriwong, Thailand

Presenter: **Nancy Fiedler**  
Grant Number: R21ESO18722  
Grant Title: Neurobehavioral Effects of Pesticide Exposure Among Children in Rural Thailand (Fogarty)

#### Abstract

Authors: Fiedler, Nancy<sup>1</sup>; Siriwong, Wattasit<sup>2</sup>; Rohitrattana, Justhiri<sup>2</sup>; Barr, Dana<sup>3</sup>, Panuwet, Parinya<sup>3</sup>, Ryan, Barry<sup>3</sup>, Robson, Mark<sup>1</sup>  
Schools: Rutgers University<sup>1</sup>; Chulalongkorn University, Bangkok, Thailand<sup>2</sup>; Emory University<sup>3</sup>

Title: Neurobehavioral effects of pesticide exposure among children in rural Thailand  
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Exposure to pesticides is a growing problem in Thailand due to the exponential increase in pesticide importation for agricultural purposes. Despite the increased vulnerability of the developing organism, few studies have evaluated the neurobehavioral effects of pesticide exposure in children. Fifty-three 6 to 8 year old children from rice farming (n=24 exposed) and shrimp farming (n=29 control) districts outside of Bangkok, Thailand completed a repeated measures study to evaluate exposure to organophosphate (OP) and pyrethroid (PYR) pesticides and neurobehavioral performance. Tests of attention, memory, motor speed, and visual motor coordination from the Behavioral Assessment and Research System were adapted for use in Thailand. Overnight urine samples were collected for each subject on the morning of each

testing session. Metabolites of OPs indicate that children living on rice farms had significantly higher concentrations of organophosphate dialkylphosphate metabolites (DAP) than children living near shrimp farms regardless of season ( $p=0.0003$ ). PYR metabolites did not differ significantly between rice and shrimp farm subjects. Comparisons of the groups based on farming location and practices revealed no significant reduction in performance for subjects living on rice vs. shrimp farms during either the high or low exposure testing sessions. After controlling for age and home environment, none of the OP or PYR metabolites were significant predictors of reduced neurobehavioral performance during either the low or high exposure seasons. Thus, the current study did not find significant adverse effects of exposure to OP or PYR pesticides among 6 to 8 year old Thai children. Capacity building activities include an experiential workshop on questionnaire development, statistical analysis, and cultural adaptation of questionnaires for 26 students from the Chulalongkorn School of Public Health. Psychology and public health students participated in two separate, one month intensive fellowships providing training in behavioral assessment (Rutgers) and laboratory methods for analysis of pesticides (Emory University). Ongoing pilot studies using the HOME and neurobehavioral measures for younger Thai children are being conducted in preparation for further studies in Thailand.

**Annette L. Fitzpatrick / United States**

**Quang van Ngo / Viet Nam**

**Annette L. Fitzpatrick, 1 R21 TW008431, Neurological Manifestations of Cerebrovascular Disease in Da Nang, Vietnam.**

Increasing economic and demographic development in countries such as Viet Nam has resulted in a shift from acute communicable diseases caused by poverty toward chronic, non-communicable disease related to lifestyle. In terms of both mortality and disability-adjusted life-years (DALYs), the burden caused by stroke overshadows all other non-communicable as well as communicable diseases in Viet Nam. The primary goals of the study were to develop collaborations, implement research, and integrate capacity building into a collaborate effort evaluating cerebrovascular disease in Da Nang, Viet Nam. The study was successful in fulfilling all of its objectives initiating the first NCD studies in the region and establishing long-term relationships between investigators, providing training, and increasing capacity for conducting further work in stroke research. Research and training activities are briefly described below.

**Development and Implementation of a Stroke Registry in Da Nang Hospital:** A stroke registry was developed and implemented at Da Nang Hospital utilizing the World Health Organization's Stroke STEPS instrument resulting in 754 strokes occurring over one year. Mean age was 65 years, 39% were female, and nearly 50% of strokes were hemorrhagic. Crude mortality rates were 51.0% and 20.3% for hemorrhagic and ischemic strokes, respectively. In addition to clinical training, this study identified underutilized approaches for early identification and treatment and inexpensive interventions to improve outcomes or reduce recurrent stroke.

**Development and Implementation of a Community-Based Survey of CVD Risk Factors:** The study resulted in evaluation of 1,621 adults, mean age 52.0 years ( $\pm 12.5$ ) and 56.1% women; and 27.3% were found to have hypertension. More than two-thirds of participants with measured hypertension were unaware of their condition and one-fourth of participants were identified as having previously experienced at least one stroke symptom in the past. These data highlighted the critical need for education on cardiovascular risk factors as well as information on stroke systems and need for responding to them.

**Training and Capacity Building:** Six week-long seminars on Epidemiology, Biostatistics and Clinical content on stroke were provided: We found DOH staff to be very receptive to our providing clinical and epidemiologic training to staff throughout the study. They were very eager to learn more about stroke diagnosis and treatment in the US as well as to learn how to conduct their own research on topics of interest. Topics included 1) Stroke Diagnosis, Treatment and Prevention, 2) CT and MRI Imaging, 3) Evaluating CVD Risk Factors, 4) Basic Epidemiology and Biostatistics, 5) Data Management and Analysis, 6) Data Collection and Monitoring. Over the course of the study we also developed a centralized research laboratory to provide the necessary tools to encourage research in cerebrovascular disease in Da Nang:

This study was the first to measure prevalence and risk factors for stroke in Da Nang. Collaboration with the Ministry of health allowed resource development and training to introduce new investigators to the approach and design for conducting stroke research and to

initiate clinical interest in development of standards of care and interventions for early diagnosis and treatment. Barriers for sustainability include the lack of neurologists in the region, the continuing battle with infectious disease, maternal/child and nutritional problems that compete for resources, and the lack of continuity with US collaborators for guidance and mentorship in addressing NCD public health issues.

Brian W.C. Forsyth, MB ChB, FRCP(C)/U.S.A

Ilgi Ertem, MD/Turkey (Co-principal investigators)

Vibha Krishnamurthy / India; Mphelekedzeni Mulaudzi / South Africa; Yanina Sguassero / Argentina

**Brian W.C. Forsyth, MB ChB, FRCP(C)**

1R01HD057834-01A2

**Development of an International Guide to Monitor and Support Child Development (GMCD)**

**Introduction:** More than 200 million children age < 5 in developing countries fail to reach their developmental potential, a problem that is now increasingly recognized as an important contributor to morbidity in children and adults. Little attention is paid, however, to the early identification of developmental difficulties and there is no universally accepted, easily administered method for identifying and monitoring children’s development.

**Aims:** The overall goal of the study is to further develop the Guide for Monitoring Child Development (GMCD), which was originally developed in Turkey, so that it can be used internationally in countries with diverse cultures and different languages. The specific aims of the research are to:

1. Standardize the GMCD in four countries (Turkey, India, South Africa and Argentina) that have very different demographic, cultural and linguistic characteristics so as to make it appropriate for universal use.
2. Establish valid scoring criteria for the GMCD that enables accurate detection of developmental difficulties when used in different cultures and languages.
3. Conduct a pilot study in the four countries to identify approaches to implementing and sustaining ongoing developmental monitoring using the GMCD

**Methods:** The first phase of the study (aim 1) is now being completed. In each of the four participating countries approximately 100 children were recruited in each of 24 different age intervals between 1 and 42 months. Caretakers were asked about their children’s development in interviews taking approximately 10 minutes, using a structured, open-ended format. In addition, socio-demographic data were collected, children’s growth parameters were recorded and a finger stick hemoglobin was obtained. Standardization of the GMCD requires a “prescriptive” sample of healthy, normal children. Criteria for exclusion from the prescriptive sample included: Low birth weight (<2500 gms), presence of pre-defined illness, perinatal illness, anemia and any growth parameter < 3<sup>rd</sup> percentile.

<b>Table 1</b>	Turkey	India	South Africa	Argentina	Total	prevalent cause for exclusion, affecting one-third of subjects in
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# Enrolled	2759	2977	2601	2565	10902
# Prescriptive	2040	1709	1354	1720	6823
% Excluded	26	43	48	33	34

**Results:** Of the 10,902 children enrolled, 34% of the children were excluded from the prescriptive sample with rates of exclusion varying from 26% in Turkey to 48% in South Africa (Table 1). Anemia was the most depression, 8.6% of mothers were categorized as depressed with this being more prevalent in Turkey and South Africa (both 11%).

**Percent Excluded by Reason (each case could include >1 reason)**

**Conclusions:** These early results demonstrate very high rates of risk factors for poor child development. Further analyses will identify the developmental milestones to be used in the international GMCD through examining similarities among countries and accounting for differences in socio-demographic

<b>Table 2</b>	Turkey	India	South Africa	Argentina	Total
Anemia	17.0	20.3	33.7	22.5	23.2
Low birth weight	7.4	14.3	12.6	9.2	11.0
Predefined illness	2.6	7.4	5.0	6.4	5.4
Growth < 3 <sup>rd</sup> %	3.2	20.6	6.3	5.6	9.2
Perinatal illness	0.2	3.6	4.0	5.5	3.3

characteristics. In addition, we will explore the degree to which adverse risk factors used to exclude subjects from the prescriptive sample might contribute to developmental difficulties with populations.

PI: Mark Gluck/USA,  
Mohammad Herzallah/Palestine  
**Mohammad M. Herzallah**  
1R21MH095656,  
Collaborative Research on Cognitive Correlates of Clinical Depression

## **Cognitive Function in Major Depressive Disorder Depends on Medication Status and Task Demands**

Mohammad M. Herzallah, M.D.

### **ABSTRACT**

To better understand how medication status and task demands affect cognitive function in Major Depressive Disorder (MDD), we evaluated three groups of subjects: medication-naïve MDD patients, medicated MDD patients receiving Serotonin Selective Reuptake Inhibitors (SSRI) and healthy control subjects. All were given two cognitive tasks to assess their ability to learn novel associative relationships. The first task had two phases, an initial sequence learning phase followed by a generalization phase that involved a shift in context. Medication-naïve patients were slow to learn the initial sequence, but were normal on subsequent generalization of this learning. In contrast, medicated MDD patients learned the initial sequence normally, but were impaired at generalization. Based on previous studies with this and similar tasks, we argue that this pattern of data is consistent with (1) an MDD-impairment in striatal function, resulting in a deficit in sequence learning which is remediated by SSRIs and (2) an SSRI-induced impairment in medial temporal lobe function, resulting in a deficit in generalization of learning not otherwise seen in medication-naïve MDD patients. In summary, these findings suggest that SSRIs might have both a beneficial effect on striatal function, but a detrimental effect on the medial temporal lobe (MTL) structures critical for contextual processing and generalization. A second deterministic category-learning task allowed for a more refined dissociation between the acquisition of positive feedback (reward) and negative feedback (punishment) during learning. Although both medicated and medication-naïve MDD patients were impaired at reward learning as compared to health controls, medicated MDD patients were less sensitive to punishment during negative-feedback trials. This suggests that the improved learning found with SSRI medication in the sequence learning phase of the first task may be due, in part, to SSRIs bringing reward- and punishment-based learning into better balance by reducing sensitivity to punishment, so that it is more evenly matched to the MDD-related deficits in reward processing. This balance between reward and punishment-based learning is especially important in learning category associations, as seen in the second task, where appropriate sensitivity to the balance between positive and negative feedback is critical. These findings shed the light on the importance of dissociating the cognitive consequences of MDD from those of SSRI treatment. Although a reduced sensitivity to negative-feedback has a natural correlate to the mood-enhancing properties of SSRIs, the impairments to generalization raise clinical concerns with regard to SSRI-treatment used in combination with behavioral therapies that expect the patient to generalize newly learned cognitive skills from a therapeutic setting to the rest of their daily lives.

**PI: Mark Gluck/USA**

Mohammad Herzallah/Palestine

**Joman Y. Natsheh**

1R21MH095656,

Collaborative Research on Cognitive Correlates of Clinical Depression

## **Abstract**

### **Dopamine Transporter 3'-UTR VNTR Polymorphism Modulates Learning from Positive and Negative Feedback**

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Understanding the functional role of genetic variation in the dopaminergic system is key for clarifying how such variations contribute to individual differences in cognition, as well as to risk factors for mental disorders and differential responses to therapy. To examine the influence of the 3' variable number of tandem repeats (VNTR) polymorphism in the dopamine transporter gene (DAT1) on cognitive function, we used a probabilistic category-learning task that allowed for dissociation between the acquisition of positive feedback (reward) and negative feedback (punishment). Of note, the DAT1 polymorphism influences expression of the DAT protein and ultimately dopamine levels in the striatum, and previous research has shown that variations in dopamine levels can influence whether one learns more from positive or negative feedback. We tested 120 racially homogenous, healthy volunteers and grouped them according to DAT1 VNTR genotype into 9-repeat carriers and 10-repeat homozygotes. Carriers of the 9-repeat allele, who presumably express less DAT1 and thus exhibit higher levels of dopamine, were more efficient in learning from positive feedback. Conversely, individuals homozygous for the 10-repeat allele, who express more DAT1 and have less synaptic dopamine, learned more effectively from negative feedback. These results contribute to a growing body of data that implicate the dopaminergic system in striatal-dependent feedback-based learning, and add weight to the proposition that individual differences in cognition have a strong genetic basis. Future studies will examine the effects of the interaction between DAT1 VNTR and other functional polymorphisms in the dopaminergic system and their relation to cognitive function, as well as clinical risk factors for disorders of the dopaminergic systems.

PI name/ Country: **Rodolfo Goya**, Argentina  
Major collaborator name/ Country: Martha Bohn, USA  
Presenter name: **Rodolfo G. Goya**  
Grant number, RO1 AG029798  
Grant title: Neuroprotective Gene Therapy in the Brain of Senile Rats

**GENE THERAPY IN THE AGING BRAIN**  
Brain Disorders in the Developing World Meeting  
February 11-13, 2014 at the Natcher Auditorium, NIH, Bethesda, MD

Insulin-like growth factor I (IGF-I) is a powerful neurotrophic molecule which appears to be part of the physiologic self-repair mechanisms of the adult brain. Using the aging female rat as a model of age-related brain dysfunction, we have implemented short-term restorative IGF-I gene therapy in the hypothalamus and cerebral ventricles. Short-term (17 days) intrahypothalamic IGF-I gene therapy achieved a nearly full restoration of hypothalamic dopaminergic (DA) neuron function as determined by morphometric analysis and by correction of the chronic hyperprolactinemia that typically develops in senescent (28-30 mo.) female rats as a consequence of hypothalamic DA neuron dysfunction. Short-term intracerebro-ventricular (ICV) IGF-I gene therapy was able to ameliorate motor performance in senescent females which typically show a marked decline in motor function as compared to young (2 mo.) counterparts.

In the female rat, reproductive aging is characterized by a gradual disruption of regular estrous cyclicity at middle age (9 mo). There is evidence suggesting a regulatory role for IGF-I on reproductive function. We assessed the effectiveness of long-term IGF-I gene therapy in the hypothalamus of adult female rats to extend regular cyclicity and preserve ovarian structure when the animals reach middle age. Using a bicistronic adeno-associated vector (AAV) carrying the gene for IGF-I, we assessed the patterns of estrous cyclicity from 34.2 through 49.5 weeks of age. At the end of the study ovaries were removed and processed for histomorphometric analysis. We observed that while most of the rats injected with the IGF-I-vector had a normal estrous cyclicity until the end of the experiment, the control animals (receiving a placebo vector) showed a high percentage of acyclic rats at the end of the study. Most of the ovaries of rats submitted to IGF-I gene therapy showed fresh corpora lutea as well as growing follicles whereas control ovaries showed the expected high incidence of ovarian cysts and atretic follicles. These results suggest that overexpression of IGF-I in the hypothalamus started during the premenopausal stage extends normal ovarian function in middle-aged female rats and delays reproductive aging.

**Future directions**

Profiting from the biotechnology platform established in our laboratory during our R21 and R01 grants, we are constructing a regulatable adenoviral vector expressing four pluripotency genes namely, Sox2, c-Myc, Klf4 and Oct4 (the Yamanaka genes), in order to reprogram rodent fibroblasts into neurons and cardiomyocytes. Our long-term aim is to implement regenerative medicine in animal models of neurodegeneration and myocardial infarct.

**Biomedical significance of our research**

The increase in life expectancy achieved in developing and developed countries has led to a progressive rise in the incidence of age-related neurodegenerative diseases like Alzheimer's and Parkinson's, with their destructive consequences on cognition and other brain functions. In this

context, new biotechnological strategies like gene therapy and regenerative medicine, emerge as promising therapeutic tools for the prevention and treatment of these devastating pathologies.

**PI name/ Country: Rodolfo Goya, Argentina**

**Major collaborator name/ Country: Martha Bohn, USA**

**Authors: Micaela Lopez-Leon, Claudia B. Herenu, Paula C. Reggiani, Rodolfo G. Goya**

**Presenter name: Rodolfo G. Goya**

**Grant number, RO1 AG029798**

Grant title: Neuroprotective Gene Therapy in the Brain of Senile Rats

**POSTER ABSTRACT**  
**TRANSDIFFERENTIATION OF FIBROBLASTS INTO NEURONS BY CELL**  
**REPROGRAMMING**

Brain Disorders in the Developing World Meeting  
February 11-13, 2014 at the Natcher Auditorium, NIH, Bethesda, MD

In 2006, Takahashi and Yamanaka reported that the transfer of the four pluripotency genes Oct4, Sox2, cMyc and Klf4 (known as the Yamanaka genes), to somatic cells can reprogram them, taking the cells to a stage in which they behave as embryonic stem cells. The possibility of generating this type of cells, known as induced pluripotent stem cells (iPSC), has opened a horizon of hitherto unimagined possibilities for the development of personalized therapeutic strategies. Cell reprogramming is also a powerful methodology to transdifferentiate a somatic cell type into a different somatic cell lineage. In particular, there is a keen interest in transdifferentiating fibroblasts and other somatic cell types to either mature neurons or neural precursors (NP) which can later be used for implementing cell therapy for neurodegenerative pathologies like Alzheimer's (AD) and Parkinson's disease (PD).

It is known that neurons and NP can be produced by direct transdifferentiation of mature fibroblasts. In one study transdifferentiation was achieved by transferring the Yamanaka genes to tail-tip mouse fibroblasts. This study revealed that a brief (4 days) expression of these four genes takes the fibroblasts to a stage of "epigenetic instability" which under appropriate culture conditions revert towards NP and neurons. The first step for cell reprogramming involves the transfer of an appropriate set of pluripotency genes to the somatic cells to be reprogrammed.

Our research group has established an advanced technological platform for the construction of adenoviral vectors and regulatable gene expression systems as well as for the implementation of the magnetic field-assisted gene transfer technology called magnetofection. Since the main interest of our group is the development of interventive strategies aimed at the treatment of age-related neuropathologies, we have decided to incorporate cell reprogramming to our battery of technologies in order to perform experimental regenerative medicine in suitable animal models. Capitalizing on our expertise in the construction of regulatable adenoviral systems we have undertaken a collaborative effort with Dr. G. Mostoslavsky of the Boston University School of Medicine, with the goal of constructing a regulatable helper-dependent (HD)-adenoviral vector harboring an expression cassette, termed STEMCCA, constructed in 2009 by Mostoslavsky's team. This polycistronic cassette expresses the four Yamanaka genes and therefore allows transdifferentiating somatic fibroblasts into neuronal cells. We report here the construction of a regulatable helper-dependent-recombinant adenoviral vector (HD-RAV) for the simultaneous expression of the pluripotency genes Sox2, c-Myc, Klf4 y Oct4 and the reporter gene for humanized green fluorescent protein (hGFP). These genes are being cloned in a regulatable bidirectional system recently constructed in our laboratory. The system consists of a regulatable

bidirectional cassette which expresses hGFP and has an empty multiple cloning site (MCS) available for cloning genes of interest. In this case, the MCS is being used for cloning a tandem harboring the four pluripotency genes mentioned above. Both, the hGFP gene and the pluripotency gene tandem are under the control of a single regulatable (Tet-Off) bidirectional promoter which can be reversibly inhibited by the antibiotic doxycycline (DOX). We plan to use this new gene delivery tool for implementing regenerative medicine in the brain of aging rats.

**PI: Elena L. Grigorenko, PhD / USA**

**Major Foreign Collaborator: Phil Thuma, M. D. / Zambia**

**Presenter: Tan, M., Reich, J., Hein, S., Thuma, P. E., & Grigorenko, E. L.**

**Grant No: 1 R21 TW006764**

**Grant Title: Epidemiological Survey of Learning Disabilities in Zambia**

**Poster Title: Differences in mathematics performance between in-school and out-of-school children: Informal contributions to mathematical thinking**

**Background.** We know that there are differences in children's mathematical performance that are related to culture. For example, international research on the mathematical skills of children in various cultures has shown that children belonging to groups who regularly engage in commercial activities develop more sophisticated strategies to solve mental addition problems than those who live in more agriculturally-oriented communities. This is similar to the findings on Brazilian children who develop mathematical strategies in daily purchasing activities, which exemplifies how various daily tasks may contribute to children's mathematical thinking. While in-school or school-related sources of such effects may be easily apparent—e.g., quality of teaching, methods of delivery, curriculum—culturally-related mathematical abilities that children develop outside of school (informally) may be less apparent. These informal contributions to mathematical thinking are important to an overall understanding of how mathematics skills may be acquired, developed and expressed by children. That is, what types of mathematics skills may be acquired informally, and what are the various activities that may be related to the acquisition of these skills? Additionally, in what types of math problems might children best express these informally acquired skills?

**Method.** To investigate the contributions of out-of-school or informal learning to mathematical understanding and performance, we will look at the performance of approximately 1800 Zambian children (about 57% were enrolled in school at the time of the study; mean age = 11.68 years) on the Zambian Achievement Test-Math (ZAT-M; 60 items), which assesses math concepts and calculation, from number recognition and counting to division and calculating averages, using a multiple-choice format. The items of ZAT-M will be classified by four experts in three dimensions: content, presentation (abstract vs. contextualized-verbal vs. contextualized-verbal-visual), and the cognitive complexity demanded by the item. We will use these classifications to submit the 60 items to a series of confirmatory factor analyses with the goal of finding the best fitting structure of ZAT-M to the data. Then we will conduct ANCOVAs to compare the performance of in-school versus out-of-school children, controlling for gender and age. Finally, we will carry out multiple regression analyses to explore the possible contributing factors (SES, gender, and related out-of-school activities such as chores) to various math subskills (as identified by the CFA) of both groups of children. These analyses can contribute to the understanding of children's development of mathematical skills outside of the classroom in this rural African community.

**Hypothesis.** We hypothesize that on items requiring basic knowledge of numbers and quantitative concepts (e.g., more than, less than), as well as items that provide visually and verbally contextualized situations, both in-school and out-of-school children will perform similarly, with out-of-school children perhaps performing better at some tasks, depending upon

the types of chores they carry out at home. This is based on the premise that children's cognitive abilities in general and their informal mathematical knowledge in particular develop similarly cross-culturally and across schooling conditions. We also hypothesize that while out-of-school children may not do as well on more academically-oriented problems (those using specialized vocabulary or notations, or requiring familiarity with abstract concepts—e.g., logical series, prime numbers), they may still perform equally well on cognitively complex problems that are contextualized or are more practically-oriented. We expect that the variable that best explains the performance of children out-of-school is the variety of activities that they engage in, while for in-school children the relevant variable might be the amount of time that they have spent in school.

**PI: Elena L. Grigorenko, PhD / USA**

**Major Foreign Collaborator: Phil Thuma, M. D. / Zambia- POSTER ONLY**

**Presenter: Reich, J., Hein, S., Thuma, P. E., & Grigorenko, E. L.**

**Grant No: R01 TW008274**

**Grant Title: Reading Disabilities in Zambian Children**

**Background.** Some, but not all English verbs with two objects can have the objects in two orders (e.g., Mindy bought a book for Sharon; Mindy bought Sharon a book; Mindy filed a report for Sharon; \*Mindy filed Sharon a report). In English, children need to learn which verbs allow for two objects, and of them, which verbs allow for two orders. Hypotheses about verb structure acquisition have been restricted to the data available, which have not included all of the world's languages. Crucially, languages with less complicated learning requirements for double object constructions (e.g., Bantu) can provide a better context for observing the earliest stages of relevant verb structure acquisition, but have not been adequately explored. In Chitonga, all double object constructions follow the same rule for word order (i.e., only one order is possible) benefactive-first ordering while other Bantu languages follow an animacy hierarch instead (e.g., Sesotho).

**Method.** The design followed from the previous Sesotho study (Demuth, K., Machobane, M., Moloji, F., & Odat, C., 2005). Thirty-six children (ages 4-15) and fourteen adults, all native speakers of Chitonga, were asked to listen to puppets say pairs of sentences that varied only in the order of their objects and choose and repeat the better of each pair. This tested their use of ordering rules in double object constructions across five conditions (human-inanimate; animal-inanimate; human-animal; inanimate-inanimate; recipient-inanimate).

**Results.** The Sesotho results provided evidence that very young children are aware of word order rules and that the verb structure associated with double object constructions is acquired at a earlier age than previously believed; however, the results of the Chitonga study show variation among both children and adults in their selection and repetition of sentences. Further, in the Chitonga study the most adult-like child performance was observed in conditions in which the animacy and benefactive-first ordering rules match.

**Conclusions.** Collectively, research from Bantu languages highlights the informative potential of investigations of less commonly studied languages for the acquisition of grammatical structures. However, the differences in the results from the Sesotho and Chitonga studies provide evidence that verb structure acquisition is even more complex than previously thought. The additional word and pragmatic knowledge that must be acquired for English does make the acquisition of verb structure for double object constructions considerably harder; however, there is still variation in the difficulty of acquiring relatively easier systems. Moreover, the variation in the Chitonga data observed among adults could be indicative of a shift in grammatical acceptability or influence from multilingualism.

## References

Demuth, K., Machobane, M., Moloi, F., & Odat, C., 2005. Learning Animacy Hierarchy Effects in Sesotho Double Object Applicatives. *Language*, 81 (2), 421-447.



**PI: Elena L. Grigorenko, PhD / USA**

**Major Foreign Collaborator: Phil Thuma, M. D. / Zambia**

**Presenter: Hein, S., Reich, J., Tan, M., Thuma, P. E., & Grigorenko, E. L.**

**Grant No: 1 R21 TW006764**

**Grant Title: Epidemiological Survey of Learning Disabilities in Zambia**

**Background.** Research over the last decade has revealed complex interactions between genotype and environment that contribute to individual differences in cognitive skills and academic achievement. In developed countries, universal schooling is one of the major environmental contexts in children's socialization that exerts an important influence on children's cognitive development. However, in the developing world it is less clear (1) to what extent genetic variation influences academically-related cognitive skills in reading and mathematics; (2) in what ways differences in formal (i.e., access to Western-style schooling) and informal (i.e., family and community apprenticeship) education contribute to individual differences in these skills; and (3) in what ways environments modify the effects of a given genotype on the phenotype (i.e., gene by environment interaction). This study extends the scope beyond research in developed countries and examines whether the relationship between haplotypes of SNPs and reading and mathematics performance differs as a function of environmental inputs from the school and home contexts.

**Method.** The total sample comprised approximately 1800 children (about 57% were enrolled in school; mean age = 11.68 years) from Zambia. Children's performance in reading (i.e., letter and word recognition, pseudoword decoding, reading comprehension) and mathematics (i.e., knowledge of numeracy, calculation, problem-solving) was assessed along with indicators of children's school and home environment. Children were genotyped for five single-nucleotide polymorphisms (SNPs) in the catechol-*O*-methyltransferase (*COMT*) gene—a gene that plays a role in regulating synaptic dopamine within the prefrontal cortex, which in turn is associated with cognitive functioning.

**Results.** We analyzed sets of functional haplotypes to model interactions between variations in the *COMT* gene across multiple SNPs and environmental characteristics in the prediction of performance on complex multidimensional tasks involving multiple aspects of reading and mathematics skills. Results showed a number of small but significant interactions between *COMT* haplotypes (mostly for combinations of three SNPs) and schooling in the prediction of reading and mathematics performance. However, *p*-values for tests of overall model significance were sensitive to parameter specifications, mostly to the threshold of minimum haplotype frequency and the distributional features of the dependent variable.

**Conclusions.** Consistent support for the assumption that genetic influences on mathematics skills and reading skills are more pronounced in more favorable environments (i.e., through Western-style schooling and higher family SES) was not found. Moreover, the relative contribution of genotype-environment covariance may differ across different reading and mathematics sub-skills.

**Potential Role of ApoE4 in Protecting Cognitive Development of Favela Children with Heavy Diarrhea Burdens in Northeast Brazil and in Preventing Enteropathy**

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**PI name/ PI Country: Richard L. Guerrant, USA**

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**Presenter name: Reinaldo B. Oriá**

**Grant number: (1 R01 HD053131)**

**Grant title: APOE and the Effects of Malnutrition on Cognitive and Intestinal Development**

**SUMMARY**

Having found that the cognitive deficit seen with heavy diarrhea burdens in favela (shantytown) children is an “Alzheimer’s-like” effect on semantic fluency (Patrick, Oriá et al. Child Neuropsych 2005; 11: 1-12.), and then that ApoE4 is protective of cognitive development in favela children experiencing heavy diarrhea burdens (Oriá et al. Pediatr Res 57: 310, 2005), we pursued the potential that its association with upregulation of arginine transport (Colton et al. Ann NY Acad Sci 962: 212, 2002; J Neuroimmunol 134: 44, 2003) might have in protecting against cryptosporidial infection (a leading enteric pathogen in children worldwide) in our murine model. We found that arginine was indeed protective against both growth impact and parasite intensity of infection (Castro IC et al Nutr 28: 678, 2012). This occurred through both iNOS dependent and arginase dependent pathways. In our studies, we have addressed the effects of under nutrition alone or compounded with enteric pathogens to study the vicious cycle of enteric infections and under nutrition during early post-natal development using murine models. This unique approach of studying components of the intestinal and brain adaptations against early challenges of undernutrition has established a sustained model to evaluate key interventions to ameliorate the short and long-term deficits we have seen with environmental enteropathy (tropical enteropathy). Environmental enteropathy (with recurrent episodes of enteric infections/malnutrition) afflicts young children living in impoverished areas of the developing world and causing a syndrome of chronic intestinal malabsorption, that ultimately leads to growth stunting and cognitive deficits in times of important developmental milestones, therefore jeopardizing one’s full genetic potential. In this report, we have shown data from controlled-models of under nutrition (alone or combined with enteric infections) in the first post-natal (by litter size clustering or by maternal-offspring separation) and post-weaning (with a low protein diet or a Brazilian northeastern-regional diet) days of life. In addition, we have addressed nutritional interventions with glutamine (or alanyl-glutamine), zinc or arginine in these selected models to evaluate their role during intestinal and brain adaptations after the challenge. Finally, in collaboration with Dr. Michael Vitek and Patrick Sullivan (Duke University, Durham, NC), we have assessed different apoE genetic backgrounds, including apoE deficient and apoE targeted replacement mice carrying either E4 or E3 human genes, and found that cryptosporidial infections caused less growth decrement, less histologic damage and lower cryptosporidial infection burdens (by qPCR) and increased ileal CAT-1 expression in the ApoE4 targeted

transgenic mice, all suggesting potential mechanisms by which ApoE4 may be protective in young children exposed to heavy diarrhea burdens and enteric pathogens in formative early life and perhaps even provide a basis for this allele in human evolution, thereby potentially extending our findings from our cohort studies with Brazilian shantytown children.

Valerie Harder, MHS, PhD, UNITED STATES  
Africa Mental Health Foundation / KENYA  
**Presenter: VALERIE HARDER**, 1R21TW009786-01  
“Mobile Substance Use Intervention for HIV Prevention”

**Background:** Evidence-based brief interventions for alcohol use disorders, such as motivational interviewing (MI), are common practice in developed countries, yet very little is known about their acceptability and efficacy in developing countries, such as Kenya. Untreated alcohol use disorders in Kenya pose a substantial public health risk for the transmission and acquisition of HIV/AIDS, especially among those of lower socioeconomic status. We hypothesized that MI would be an acceptable intervention in the Kenyan context and would be efficacious in reducing heavy alcohol use among impoverished Kenyan adults being tested or receiving treatment for HIV/AIDS in a Nairobi slum.

**Methods:** Adults (ages 18 – 59 years; 53% female) were randomly selected from the Voluntary Counseling and Testing clinic (N=500) and from the Comprehensive Care Clinic (N=300 HIV+) and screened using the 10 question Alcohol Use Disorders Identification Test (AUDIT). Those with a score of eight or above were offered one session of MI lasting approximately 15 minutes provided the same day by a trained Kenyan clinical psychology masters students or a practicing clinical psychologist. A waitlist control group was used as the comparison not receiving MI and reassessed after one month before receiving MI. Approximately one month after MI, attempts were made to contact subjects for reassessment using three questions known as the AUDIT-C. Reassessment at one year was done using the AUDIT. Community health workers were sent to homes to find subjects that were hard to reach over the mobile phone. Independent t-tests were used to compare mean differences in AUDIT scores between those receiving MI and waitlist controls. Paired t-tests were used to test the within subject mean change in AUDIT-C scores from baseline to one month follow up for those receiving MI, waitlist controls, and the combined sample. Finally, a paired t-test was used on the combined sample to test the within subject mean change in AUDIT score from baseline to one year follow up.

**Results:** Descriptive: Out of 800 adults screened, 90 (11%) scored eight or above on the AUDIT, and were offered MI same day (N=36; 40%) or after one month on a waitlist (N=54). Out of 90 heavy alcohol users, 73% were male, 51% were less than 30 years old (mean 31.4 years), 43% were employed, 56% had less than a high school education, and 38% were married. Our response rate to receive MI was 70% (63 out of 90) and our response rate for reassessment one month after MI was 89% (56 out of 63) and one year after MI was 90% (57 out of 63). Statistical Tests: At baseline, there were no differences between the mean AUDIT scores between subjects offered MI immediately and the waitlist controls (mean difference=.23,  $t=.13$ ;  $p=.90$ ). There was also no difference in the mean AUDIT-C score for waitlist controls (N=37) from baseline to reassessment before MI (mean difference=.16,  $t=.28$ ,  $p=.78$ ). As hypothesized, there was a significant decrease in the AUDIT-C score among the whole sample (N=56) from baseline to

reassessment after MI (mean decrease=2.96,  $t=7.02$ ,  $p<.0005$ ). We note that 10 out of 56 subjects (18%) increased their alcohol use from baseline to reassessment. However, only one subject had a substantial increase of five points on the AUDIT-C, while the others were two or one point increases. Among all those receiving MI and reassessed after 1 year ( $N=57$ ), there was a significant decrease in AUDIT score (mean decrease=11.04,  $t=8.83$ ,  $p<.0005$ ) and AUDIT-C score (mean decrease=3.65,  $t=7.20$ ,  $p<.0005$ ).

Discussion: Our study suggests that MI is an acceptable brief intervention for heavy alcohol use among Impoverished Kenyan adults being tested for or living with HIV/AIDS. Over a relatively short follow up time, those receiving MI had significantly decreased alcohol use while no change was seen among otherwise comparable waitlist controls over the same time period. Despite the limitation of having no control group at one year, our study found significantly lower alcohol use out to one year, suggesting a potential lasting effect of brief MI in this population. These data are encouraging and form the basis of our continuing testing MI in Kenya. Our next project tests the acceptability and feasibility of mobile phone-based MI.

## **Psychomotor development up to 24 months: Measurement issues and sources of variability in an HIV-exposed population**

Penny A. Holding/Kenya,  
Chris L. King/USA

**Patricia Kitsao-Wekulo**

5R01MH080601-03

HIV, MALARIA AND NEUROBEHAVIORAL DEVELOPMENT IN EARLY CHILDHOOD

**Introduction:** Studies in Africa have commonly shown an association between the presence of HIV infection in pregnant women and negative outcomes in their children. And while infected children, particularly those where infection has progressed to disease, may be most at risk of severe impairment of psychomotor skills, offspring of HIV infected women that do not become infected with HIV have also been shown to have significant deficits and slower growth. The wide variability in outcome observed in both infected and uninfected children suggests multiple sources of impaired development following *in utero* exposure to HIV. The current study sought to investigate variations in psychomotor development during infancy according to birth weight, gender, nutritional status, HIV exposure and area of residence.

**Method:** The study was undertaken at two study locations in Kenya, one rural and one urban. Pregnant women were enrolled into the study early in the second trimester through the district hospitals at both sites, and their offspring were followed up from birth to 24 months. Information on disease exposure *in utero* was obtained via histological tests on umbilical cord blood and placental samples at birth. Weight-for-height, weight-for-age and length-for-age z-scores were calculated with growth reference curves developed by the World Health Organisation. Using the Kilifi Developmental Inventory (KDI), a locally developed and validated tool, children's psychomotor skills were assessed at 6, 12, 18 and 24 months. Univariate and multivariate analyses were used to examine the relationships between various background characteristics and performance at each time point.

**Results:** At 6 months, children with low birth weight had significantly lower scores than their counterparts who were of normal birth weight. At 12, 18 and 24 months, these differences were not significant. Gender differences were only significant at 24 months. Nutritional status created significant differences at all ages, with those who were undernourished consistently scoring lower than their counterparts who were not. Although children who were not exposed to HIV had higher KDI scores at 12, 18 and 24 months, these differences were only significant at 12 months. At 12, 18 and 24 months, children in the rural site had significantly higher scores than those in the urban site. In the multivariate analysis, only birth weight and nutritional status were significant predictors of KDI scores at 6 months. Area of residence and wasting explained 42% of the variance observed at 12 months. Area of residence and underweight significantly predicted KDI scores at 18 months while only area of residence was a significant predictor at 24 months.

**Conclusion:** The limited variability observed in relation to some of the factors studied may point to ambiguity in scoring some items on the KDI. Nutritional status and area of residence were the only factors that were consistently and significantly associated with differences in KDI scores across all time points. The varying strength of the association of biological and environmental

factors with KDI scores during infancy suggests that strategies to mitigate the effects of modifiable risk factors should consider different factors at each time point.



Chandy John/USA

Robert Opoka/ UGANDA

**Paul Bangirana**

R01NS055349

Pathogenesis of Cognitive/Neurologic Deficits in Central Nervous System Malaria

### **ABSTRACT**

#### **Severe malarial anemia is associated with long-term neurocognitive impairment**

Paul Bangirana, Ph.D., Robert O. Opoka, M.P.H., MBChB, M.Med., Michael J. Boivin, M.P.H., Ph.D., Richard Idro, MBChB, M.Med., Ph.D., James S. Hodges, Ph.D., Regilda A. Romero, Ph.D., Elsa Shapiro, Ph.D., Chandy C. John, M.S., M.D.

From the Departments of Psychiatry (P.B.) and Paediatrics and Child Health (R.O.O., R.I.) Makerere University College of Health Sciences, Kampala, Uganda; Departments of Psychiatry and Neurology/Ophthalmology, Michigan State University, East Lansing, Michigan and Department of Psychiatry, University of Michigan, Ann Arbor, Michigan (M.J.B.); Division of Biostatistics, University of Minnesota, Minneapolis, Minnesota (J.S.H.); Clinical Psychology Associates of North Central Florida (R.A.R.) and Department of Pediatrics, University of Minnesota (E.S., C.C.J.).

**BACKGROUND:** Cerebral malaria (CM) is associated with long-term neurocognitive impairment in children aged 5 years and older. No prospective studies to date have assessed neurocognitive impairment in children with CM <5 years of age, or in children with severe malarial anemia (SMA), a form of severe malaria estimated to affect as many as 5 million children annually.

**METHODS:** Children <5 years of age presenting to Mulago Hospital, Kampala, Uganda, with CM (n=80) or SMA (n=86) were assessed for overall cognitive function, attention, and declarative memory one week after discharge and 6 and 12 months later. Age-adjusted z-scores for each domain were computed based on scores of 61 healthy community children (CC), who were also tested at enrollment and 6 and 12 months later. Groups were compared using mixed linear models.

**RESULTS:** At 12 months, children with CM had lower scores than CC in cognitive ability ( $P < 0.001$ ), attention ( $P = 0.04$ ), and declarative memory, ( $P = 0.002$ ). Children with SMA had lower scores than CC in cognitive ability ( $P < 0.001$ ) but not attention or declarative memory. Cognitive ability scores in children with CM and SMA did not differ significantly.

**CONCLUSION:** In children <5 years of age, CM is associated with impairment in general cognitive ability, attention, and declarative memory 12 months after the episode, and SMA is associated with long-term impairment in overall cognitive function similar to that seen in CM. SMA may be a major cause of long-term neurocognitive impairment in children in sub-Saharan Africa.

PI name/ PI Country: Chandy C. John, USA

Major foreign collaborator name/ Foreign Collaborating Country: Robert Opoka, Uganda

Presenter name: **John, Chandy**

Grant number: R01NS055349

Grant title: Pathogenesis of Cognitive/Neurologic Deficits in Central Nervous System Malaria

**High plasma erythropoietin levels are associated with prolonged coma duration and increased mortality in children with cerebral malaria**

Estela Shabani, Richard Idro, Robert Schmidt, Robert O. Opoka, Gregory S. Park, Paul Bangirana, Gregory M. Vercellotti, John A. Widness, Chandy C. John

Institutions: University of Minnesota, Minneapolis, MN, USA; Makerere University, Kampala, Uganda; University of Iowa, Iowa City, IA, USA

**ABSTRACT**

**Background:** Elevated plasma erythropoietin (EPO) levels were associated with protection from acute neurologic deficits in Kenyan children with cerebral malaria (CM). On the basis of these findings and animal studies, clinical trials of recombinant human EPO (rHuEPO) have been started in children with CM. Recent clinical trials in adults with acute ischemic stroke have demonstrated increased mortality with rHuEPO treatment. We conducted a study in children with CM to assess the relationship of plasma and cerebrospinal fluid (CSF) EPO levels to acute and long-term neurologic outcomes and mortality.

**Methods:** Two hundred and ten children 18 months -12 years of age with a diagnosis of CM were enrolled at Mulago Hospital, Kampala, Uganda. Plasma (n=204) and CSF (n=147) EPO levels at admission were measured by radioimmunoassay. Surviving children were assessed for neurological deficits at discharge and six months later..

**Findings:** Plasma and CSF EPO levels did not differ in children with acute or long-term neurologic deficits as compared to those without deficits ( $P > 0.29$  for all). Prolonged coma, and younger age were risk factors for neurologic deficits at discharge, and prolonged coma, and lower Blantyre coma scores were risk factors for neurologic deficits at six months. Plasma and CSF levels of EPO correlated positively with coma duration ( $P=0.01$  for both). After adjustment for age and hemoglobin level, a one-log increase in plasma EPO level was associated with a 1.7 fold increase in mortality (95% confidence interval, 1.1-2.8,  $P=0.019$ ).

**Conclusions:** High plasma EPO levels are associated with prolonged coma duration and increased mortality. The study findings suggest that recombinant human erythropoietin therapy could lead to adverse outcomes in children with cerebral malaria.

PIs: Chandy John (USA) & Robert O. Opoka (Uganda)

Presenter: **Michael J. Boivin, PhD, MPH**

Co-Presenters: Paul Bangirana, Robert O. Opoka, Alla Sikorskii, Richard Idro, Chandy C. John

Grant Number: RO1NS055349

Grant Title: *Pathogenesis of cognitive/neurologic deficits in central nervous system malaria (Uganda).*

**PRESENTATION TITLE:** The correspondence between early and middle childhood neurodevelopmental assessments in Ugandan children recovering from severe malaria.

**OBJECTIVES:** Tracking the developmental trajectory of children at-risk for brain injury allows investigators to evaluate how core brain/behavior domains are affected by disease, prevention, and treatment interventions from very early childhood through adolescence. Assessing neurodevelopmental outcomes for common core brain/behavior domains, from infancy through middle childhood and into adolescence, makes possible longitudinal risk analysis for exposure to brain injury (e.g., CNS infectious disease, malnutrition, perinatal complications). A consistent brain/behavior impairment metric for such exposures then allows investigators to evaluate the most strategic points of rehabilitative intervention for brain injury exposures throughout the lifespan in the developing world. Such validated longitudinal assessment tools also allows us to characterize the most critical features of risk and resilience within public health, in brain/behavior development across the lifespan in low-resource settings.

**Principal Study Aim:** *To evaluate the correspondence between a neurocognitive assessment battery for children in early childhood, and a neuropsychological assessment battery in middle childhood administered to the same cohorts of Ugandan children in the aftermath of severe malaria (severe malaria anemia and cerebral malaria).*

**METHODS:** 65 children with hospitalized with either severe malaria anemia or cerebral malaria and 61 community controls (no history of severe malaria or other know brain injury) were evaluated 1 year following hospitalization (3 to 4 yrs of age, Mean 3.9 yrs) and again at 2 years following hospitalization (5 to 7 yrs of age; Mean 5.5 yrs). The 1-yr assessment consisted of the Mullen Scales of Early Learning (MSEL) (Gross Motor, Fine Motor, Visual Reception, Receptive Language, Expressive Language), the Color Object Association Test (COAT; visual-spatial memory and learning measure), the Early Childhood Vigilance Test (ECVT; attention measure), and the Achenbach Child Behavior Checklist (CBCL) for psychiatric symptoms (administered to the principal caregiver for evaluating the child). The 2-yr assessment consisted of the Kaufman Assessment Battery for Children, 2<sup>nd</sup> edition (KABC-II), Tests of Variables of Attention (TOVA; visual attention and impulsivity), and the CBCL (school-age). In assessing the correspondence between the 1-yr (preschool) and 2-yr (school age) battery of tests, all models are adjusted for age at testing, MUAC/height ratio, gender, and SES.

**RESULTS:** Predictive Validity: The preschool MSEL Cognitive Composite score (one-yr follow-up) was predictive of all principal school-age (2-yr follow-up) KABC-II and TOVA neuropsychological performance domains. The preschool ECVT (attention) total performance was predictive of school-age overall TOVA (attention) performance and CBCL externalizing (behavioral) problems. The preschool COAT (memory) score was predictive of school-age KABC-II nonverbal cognitive and learning ability, and overall TOVA (attention) performance.

Construct Validity: KABC-II global development domains of Simultaneous Processing and

Learning were significantly lower for CM-R survivors compared to Controls. This substantiates earlier findings from our R21 NIH/FIC Brain Disorders cerebral malaria study. Congruent Validity: The corresponding neurocognitive and behavioral domains for the preschool and school-age batteries were highly correlated with one another for both the community control and severe malaria cohorts tested at 1- and 2-yr follow-ups. These included corresponding performance measures between pre- and school-age assessments for global cognitive ability, memory, attention, and CBCL internalizing (emotional) and externalizing (behavioral) problems. **CONCLUSIONS**: Our preschool and school-age neurocognitive/neuropsychological assessment batteries provide a valid way to track the brain/behavior trajectory of Ugandan children at-risk for brain injury from infectious disease in early childhood. Batteries validated in this manner for predictive, construct, and congruent validity from early childhood through adolescence are of vital importance in studying risk and resilience factors related to brain disorders in the developing world.

PI name/ PI Country: Chandy John - USA

Major foreign collaborator name/ Foreign Collaborating: Robert O Opoka - Uganda

Presenter name in BOLD: **Robert O Opoka**

Grant number: RO1NS055349

Grant title: Pathogenesis and neurocognitive sequelae of central nervous system malaria

**Title: Ugandan children with severe malarial anemia and cerebral malaria**

Robert O. Opoka<sup>1</sup>, Karen Hamre<sup>3</sup>, Nathan Brand<sup>3</sup>, Paul Bangirana<sup>2</sup>, Richard Idro<sup>1</sup>, Chandy C. John<sup>3</sup>

<sup>1</sup>Department of Paediatrics, Makerere University, Kampala, Uganda, <sup>2</sup>Department of Psychiatry, Makerere University, Kampala, Uganda, <sup>3</sup>Division of Global Pediatrics, University of Minnesota, Minneapolis, USA.

**Introduction:** Cerebral malaria (CM) and severe malarial anemia (SMA) are the two most important manifestations of severe malaria. Together CM and SMA account for nearly two thirds of malaria related admissions and mortality in children in malaria endemic regions of Sub Saharan Africa. The risk of hospital readmission for children with CM and SMA is however not well established.

**Methodology:** A cohort of children aged 18 mo - 12 y who were treated for CM or SMA were followed for 6 months after initial admission. Incidence of hospitalization or outpatient clinic visits for illness in these children was compared incidence to a cohort of healthy community children (CC) from the same neighborhoods.

**Results:** 154 children with CM, 131 children with SMA and 132 CC were followed over 6 months. Incidence of hospitalizations (hospitalizations per 100 person-years) was higher in children with CM (6.3) or SMA (16.7) than CC (0,  $P=0.045$ , CM vs. CC,  $P=0.0004$ , SMA vs. CC). Incidence of outpatient clinic visits for illness was also higher in children with CM (50.3) or SMA (53.1) than for CC (21.9,  $P=0.004$ , CM vs. CC,  $P=0.003$ , SMA vs. CC). Malaria was the most frequent reason for hospitalization (86.7%) and clinic visits (63%).

**Conclusion:** Children with CM or SMA are at high risk for hospitalization and outpatient illness, both usually due to malaria, in the 6 months following illness. Randomized controlled trials should assess whether post-discharge malaria prophylaxis can decrease risk of hospitalization and outpatient illness.



## Conclusions

Other than achieving the initial research goals, the R21 grant has left behind a remarkable human resource, research and clinical care capacity in Mulago hospital and a thriving severe malaria research centre. Future research will build on this existing capacity, especially in basic science laboratory testing.

PI Name Johnson, David

PI Country USA

Collaborator Name Salazar-Villanea & Coto-Yglesias

Collaborator Country Costa Rica

Presenter Name Coto-Yglesias

Grant Number R21TW009665

Grant Title Epidemiology and Development of Alzheimer's Disease (EDAD)

3 Word Description Alzheimer's, APOE, & MCI

Authors Román, Boza, Calvo, Salazar, Kozakova, Sequeira, & Von Storren

## Title

**ApoE genotyping Multiplex PCR-refractory in patients with mild cognitive impairment**

## Abstract

Alzheimer's disease (AD) is the most common cause of dementia. It is a multifactorial disease in which genetic and environmental conditions interact. The genotype of apolipoprotein E e4 (ApoE4) is a risk factor for developing Alzheimer's disease. Epidemiologically the ApoE4 is present in 15-16% of the Latin American population with a greater presence in the Caucasian population. Presence ApoE4 increases the risk of developing EA from 3 to 8 times and decreases the time of onset of symptoms between 7-15 years. The risk increases significantly in homozygous form. In Costa Rica, the first prevalence study conducted in the community (Santo Domingo de Heredia) with a sample 400 people showed a prevalence of probable dementia of 4.2% (any type). In the study population of 41 were diagnosed with AD (n = 14) and mild cognitive impairment (MCI, n = 27). In the Memory and Aging Clinic Hospital San Juan de Dios (CMEC) diagnosis is made by interdisciplinary consensus (now for over 7 years), using a protocol established by our team of neurologists, geriatricians and clinical psychologists which includes a battery cognitive assessment tests and functional capacity (screening, history medical, neuropsychological assessment, neurological examination, review of records clinical studies in molecular biology and neuroimaging). In the population currently evaluated at the memory clinic we detected 41.6% of patients possessed at least 1 APOE allele, placing them at risk for dementia.

PI Name Johnson, David  
PI Country USA  
Collaborator Name Salazar-Villanea & Coto-Yglesias  
Collaborator Country Costa Rica  
Presenter Name Salazar-Villanea  
Grant Number R21TW009665  
Grant Title Epidemiology and Development of Alzheimer's Disease (EDAD)  
3 Word Description Cultural validity of clinical instruments  
Authors Garnier-Villarreal, Salazar-Villanea, Coto-Yglesias, Moncada-Jimenez & Johnson

## **Title**

**Center for Hispanic American Research Methods (CHARM)**

## **Abstract**

The Center for Hispanic American Research Methods (CHARM) is a cooperative of US and Latin American research laboratories interested in coordinating biobehavioral research. The first goal of the CHARM is to create a multilingual applied clinical research library (to-date over 400 unique instruments in 850 different applications) that can be shared widely by investigators throughout the US and Latin America to facilitate high quality biobehavioral research on medical issues germane to Hispanic Americans. It uses state-of-the-art data standards that specify a research lifecycle (the Data Documentation Initiative - version 3; DDI-3). By applying this international data standard to the clinical research instrument library, the CHARM offers participating investigators a database of well-described clinical instruments and code libraries that bootstrap the investigative process. An investigator assembles a neurocognitive battery using a flexible assessment battery approach. The selected battery can be implemented using Computer Assisted Testing (CATI), REDCap (both online data entry or email surveys), LIME Survey and its associated Optical Character Recognition (OCR) software (QueXF), or more traditional Paper-and-Pencil via PDFs. The DDI standards creates the database frame so that investigators move quickly to collect the data as well offering open source tools to facilitate data entry and verification. Finally these shared data standards provide a rational heuristic to pool data across sites, thus increasing power to detect meaningful differences while distributing the research costs, and subject burden. So long as a cooperative of multisite investigators used similar DDI standards (instrumentation, question phrasing and collection methods - all specified by the

CHARM library) then those data can be pooled to answer a shared research question. This framework promotes a coordinated, interdisciplinary approach to research while allaying some of the administrative burden of deploying a research project by an (usually) over-encumbered investigator. Although we use validated and published translations wherever possible, there are many clinical instruments that need still translation by trained clinicians (about 2/3 of the library). We are establishing an online referee process for these translations as well coordinating the translation assignments.

PI Name Johnson, David  
PI Country USA  
Collaborator Name Salazar-Villanea & Coto-Yglesias  
Collaborator Country Costa Rica  
Presenter Name Coto-Yglesias  
Grant Number R21TW009665  
Grant Title Epidemiology and Development of Alzheimer's Disease (EDAD)  
3 Word Description Health behaviors & patient education  
Authors Salazar-Villanea, Coto-Yglesias, Moncada-Jimenez & Johnson

### **Title**

**pura VIDA - The Vitality and Individual Differences in Aging study**

### **Abstract**

Costa Rican epidemiological data indicate a counter-intuitive mortality advantage for low-middle class rural dwellers compared to higher SES urban dwelling counterparts and its Latin American neighbors. This advantage may be due to environmental and lifestyle factors protective against age-related neurocognitive and physical decline. Our prospective memory and aging pilot study in Costa Rica assesses the environmental versus organismic determinants of healthy aging and dementia in Latin Americans from developed and developing areas. Using clinically sensitive health science protocols currently in use at the KU Alzheimer's Disease Center (P30AGXXXXX), our research investigates the critical interaction of cardiovascular risk factors with environmental factors in a unique and understudied population of Latin Americans. Preliminary data indicates that the San Jose urban sample and the KU ADC samples of volunteers are well matched in age, education, physical fitness, biometrics, and health literacy. US and CR urban samples differ in diet, access to health care, and specific health behaviors. We review current progress to recruit US rural older adults - both Caucasian and Hispanic American.

PI Name Johnson, David  
PI Country USA  
Collaborator Name Salazar-Villanea & Coto-Yglesias  
Collaborator Country Costa Rica  
Presenter Name Coto-Yglesias  
Grant Number R21TW009665  
Grant Title Epidemiology and Development of Alzheimer's Disease (EDAD)  
3 Word Description Pulse pressure & hypertension  
Authors Coto-Yglesias & Rosero-Bixby

## **Title**

**Pulse pressure and antihypertensive drugs to treat elderly patients with high blood pressure**

## **Abstract**

This prospective, population-based cohort study using the The Costa Rican Study of Longevity and Healthy Ageing (CRELES) sample describes the trajectory of blood pressure in old age, pharmacological treatment weight and association of systolic and pulse pressure to cardiovascular mortality. We assessed 2,900 Costa Ricans older adults. Prevalence of systolic hypertension was 56.5%. Cross-sectional analyses show that systolic pressure increases with age, until 80 years then it plateaus, different to pulse pressure that persistently increases. No significant variation in CV-death hazard was associated with stage 1 hypertension (adjusted RR=1.00, 95% CI=0.67-1.50), but stage 2 had 50% higher risk of death (adjusted RR=1.55, 95% CI=0.94-2.57). The higher adjusted risk of CV death occurs in a model where individuals have wide-PP, stage 2 hypertension, and under treatment, (RR=2.65) compared to normal range SBP, PP and no treatment. Hypertension is very prevalent in Costa Rican older adults, with 1 out of every 4 being at stage 2 hypertension. Highest cardiovascular mortality was observed in those pharmacologically treated for stage 2 hypertension that developed a wide pulse pressure.

PI Name Johnson, David  
PI Country USA  
Collaborator Name Salazar-Villanea & Coto-Yglesias  
Collaborator Country Costa Rica  
Presenter Name Salazar-Villanea  
Grant Number R21TW009665  
Grant Title Epidemiology and Development of Alzheimer's Disease (EDAD)  
3 Word Description Geriatric Depression Instrument Sensitivity  
Authors Garnier-Villarreal; Johnson; Woods; & Salazar-Villanea

### **Title**

## **The Factor Structure and Item Properties of the Geriatric Depression Scale (GDS) in a Costa Rican Sample of Older Adults**

### **Abstract**

The Geriatric Depression Scale (GDS) was specifically designed to measure depression in the older adults, primarily as a screening instrument. A major problem is the confusion of dementia with depression in the elderly. Depression in the elderly often is accompanied by subjective experiences of memory loss and cognitive impairment (Yesavage et al., 1983). This scale was developed under the theoretical assumption of unidimensionality (Yesavage et al., 1983). We seek to test this assumption. Participants were 204 older adult Costa Rican with an average age of 69.6 (SD = 8.28) and 59.7% were women, in the sample the average years of education of 11.75 (SD = 5.03). A CFA was performed with the lavaan (0.5-12) package (Rosseel, 2012) within R (3.0, R Core Team, 2013) using the WLS estimator (Christofferson, 1975; Muthen, 1978, 1984; Muthen & Satorra, 1995) with robust chi-square and standard errors (WLSMV; Muthen & Muthen, 2001). The reliability for each factor was calculated with the semTools (0.4-0) package, we are reporting the Cronbach alpha (1951) and the omega (Raykov, 2001); since the items are dichotomous the Cronbach alpha (1951) was calculated from the polychoric (polyserial) correlation. The IRT analysis was performed using the mirt (0.9.0) package (Chalmers, 2012). The two-parameter (2PL) logistic model was fitted to the scale items. Where the first parameter (a) is the discrimination, telling how well each item distinguishes between people with higher or lower levels of depression. The second parameter (b) is the threshold, is the location on depression where the item is most discriminant. We found that the GDS holds a unidimensional structure, as it was created with that intension. This structure holds in both the 30 and 15 items formats. Instead of testing Exploratory Factor Analysis, the Confirmatory Factor Analysis works with the theory behind the creating of a scale. We performed a IRT analysis to identified the psychometric properties. This showed that the GDS is a good screening scale, since it is able to discriminate when a person has high levels of depression, but it does not discriminate when somebody has only mild symptoms. When we compared the complete 30 item scale with the subset of items included in the short form, we find that they share both the structural form, as

the psychometric properties, meaning that the short form is a good representation of the complete form.

PI Name Johnson, David  
PI Country USA  
Collaborator Name Salazar-Villanea & Coto-Yglesias  
Collaborator Country Costa Rica  
Presenter Name Salazar-Villanea  
Grant Number R21TW009665  
Grant Title Epidemiology and Development of Alzheimer's Disease (EDAD)  
3 Word Description Autobiographical memory & reminiscence  
Authors Garnier-Villarreal, Salazar-Villanea, Montenegro & Johnson

### **Title**

**Autobiographical memory relates to emotion and cognition in a sample of Costa Rican older adults**

### **Abstract**

Encoding, storage, and recall of autobiographical memories are relatively maintained in dementia (Piolino, Giffard-Quillon, Desgranges, Chételat et al., 2004). Clinical therapies research indicates that autobiographical memories form a core component of reminiscence therapy: The analysis of the characteristics of personal memory, the evocation of past events within a subject (Brewer in Rubin, 1986). Reminiscence therapy has been successful in people with memory problems. Our goal is to understand the temporal or thematic organization of autobiographical memory, its function, and its potential as a psychosocial intervention for age-related memory loss and dementia. In the current study we investigate whether autobiographical memories are associated with clinical indicators of depression and affect. This study focuses on the relationship between two components of autobiographical memory (semantic, and episodic) and three emotional constructs (depression, positive and negative affect), a general component of verbal memory, and executive functions. Further we show how the two components relate when the effect of the general component of memory is taken into account. Results indicate that more traditional indices of verbal memory are strong components of autobiographic memory and that autobiographic memory performance is not dependent on clinical mental health indicators. The semantic component of the current measures correlates with executive function (-0.18); participants with better executive functions had better semantic memory.

PI Name Johnson, David  
PI Country USA  
Collaborator Name Salazar-Villanea & Coto-Yglesias  
Collaborator Country Costa Rica  
Presenter Name Johnson  
Grant Number R21TW009665  
Grant Title Epidemiology and Development of Alzheimer's Disease (EDAD)  
3 Word Description Functional ability & cognition  
Authors Johnson, Salazar-Villanea, Garnier-Villarreal, & Watts

**Title**

**ADLs and Cognitive Status in Rural and Urban Costa Ricans**

**Abstract**

Costa Rican epidemiological data indicate a counter-intuitive mortality advantage for low-middle class rural dwellers compared to higher SES urban dwelling counterparts and its Latin American neighbors. This advantage may be due to environmental and lifestyle factors protective against age-related neurocognitive and physical decline. Our prospective memory and aging pilot study in Costa Rica assesses the environmental versus organismic determinants of healthy aging and dementia in Latin Americans from developed and developing areas. Our research investigates the critical interaction of cardiovascular risk factors with environmental factors in a unique and understudied population of Latin Americans.

**PI: Kanmogne, Georgette**  
**Foreign Collaborator: Njamnshi, Alfred**  
**Grant Number: R01MH094160-01A1**

**Title: Peripheral neuropathy in a group of HIV patients in Yaoundé-Cameroon: Preliminary**

AK Njamnshi, JY Fonsah, CT Kuate, GY Tatah, Nfor L. Njamnshi, R Doh, R Ngamaleu, AM Kengne, DM Njamnshi, L. Kenmogne, E Nchindap, C Tayou, P Ongolo-zogo, D Mbanya, GD Kanmogne

### **Abstract**

**Introduction:** HIV-associated peripheral sensory neuropathy (HIV-SN) includes distal sensory polyneuropathy (DSP) and ARV toxic neuropathy. Peripheral neuropathy is the most common neurological complication of human immunodeficiency virus (HIV) infection but is widely under-diagnosed in resource-limited settings. In Cameroon, the prevalence of this HIV-SN is unknown, as few unpublished studies have focused on the condition. Patients frequently have impaired sensation and vibratory sense without pain. Screening for numbness and reduced or absent ankle reflexes has the highest sensitivity and specificity among the clinical evaluation tools. It has been shown that screening tests administered by nonphysician healthcare workers (HCW) have excellent negative predictive values and are promising tools for scale-up in resource-limited settings whilst quantitative sensory tests such as electroneuromyography (ENMG) show promise for research use. We here report the preliminary results for clinically assessed peripheral neuropathy in HIV patients currently enrolled in the ‘NeuroAIDS’ study in Yaoundé-Cameroon.

**Methods:** All HIV-positive patients received consecutively were assessed clinically by a neurologist for signs and symptoms of peripheral neuropathy. They were screened for paresthesiae, dysesthesiae, ankle hyporeflexia, pallesthesia and distal motor weakness during a neurology examination. Data was analyzed using SPSS version 20.0. Categorical variables were compared using the Chi square test while means of continuous variables were compared using the unpaired t test. All p-values < 0.05 were considered statistically significant.

**Results:** 190 HIV patients were enrolled in the study. The mean age was 36.98(±9.583) with 74.2% female and 25.8% male. The prevalence of peripheral neuropathy was 18.4%. The mean

age amongst patients with peripheral neuropathy was higher than those without although this was not statistically significant (36.65 vs. 39.74  $p=0.09$ ). The main symptoms/signs observed were pallesthesia, paresthesia and ankle hyporeflexia. Patients on ART presented more with peripheral neuropathy than those naïve to treatment ( $p=0.03$ ) with a 1.79 risk of developing PN. The prevalence of peripheral neuropathy was not significantly different for sex, age, CD4 count, history of Anti-TB treatment as well as the current ART regimen type.

**Comment/Conclusion:** HIV-associated peripheral neuropathy may be more frequent in the Cameroonian population than is suspected. There is need for further assessment of these patients using ENMG for better characterization of the disorder in our context.

Key words: HIV, Neuropathy, NeuroAIDS, Cameroon.

**PI: Kanmogne, Georgette**

**Foreign Collaborator: Njamnshi, Alfred**

**Grant Number: R01MH094160-01A1**

Differential effects of Tat proteins derived from HIV-1 subtypes B and recombinant CRF02\_AG on human brain microvascular endothelial cells: implications for blood-brain barrier dysfunction  
Woollard S.,<sup>1</sup> Bhargavan B.,<sup>1</sup> Yu F., PhD,<sup>2</sup> and Kanmogne GD, PhD.<sup>1</sup>

<sup>1</sup>Department of Pharmacology and Experimental Neuroscience, and <sup>2</sup>Department of Biostatistics, University of Nebraska Medical Center, Omaha, Nebraska 68198-5800, USA.

### **Abstract**

HIV-1 genetic differences influence viral replication and progression to AIDS. HIV-1 CRF02\_AG is the predominant viral subtype infecting humans in West and Central Africa, but its effects on HIV neuropathogenesis are not known. In the present study, we investigated the effects of Tat proteins from HIV-1 subtype-B (Tat.B) and HIV-1 CRF02\_AG (Tat.AG) on primary human brain microvascular endothelial cells (HBMEC), the major component of the blood-brain barrier. Using Affymetrix GeneChip® Human Gene 1.0.ST arrays, we demonstrated that Tat.AG had minimal effects while Tat.B induced transcriptional upregulation of 90 genes in HBMEC, including proinflammatory chemokines, complement components C3, C7, and complement factor-B, matrix metalloproteinases (MMP)-3, MMP-10, MMP-12. These results were confirmed by real-time PCR. Compared to Tat.AG, Tat.B significantly increased MMP-3, MMP-10, and MMP-12 activities in HBMEC, and the MMPs tissue inhibitor of metalloproteinase-2 blocked Tat-induced increase in MMPs activity. Western blot analyses also showed that Tat increased the expression of C3 and its cleaved fragment C3b in HBMEC. These data suggest that genetic differences between HIV-1 subtype-B and CRF02\_AG influence the effects of Tat proteins from these two clades on HBMEC, including molecular and cellular functions, and canonical pathways, which would affect blood-brain barrier dysfunction and viral neuropathogenesis

**Source of support:** This work was supported by grants from the National Institute of Health, the Fogarty International Center and National Institute of Mental Health, to G.D.K (MH081780 and MH094160).

**Abstract for Poster Presentation for NIH Symposium [Non-Grantee Submission]**

Name and Country of PI: Naila Z. Khan, PhD, MBBS/Bangladesh

*Naila Z. Khan, Humaira Muslima, Asma Begum Shilpi, Shamim Ferdous, Helen McConachie, Gary Darmstadt*

*Presenting Author: Adaline Z Muyeed, PhD, MSc.*

**Title:** Findings and lessons from the use a large scale epidemiologic survey to determine the prevalence and associated risk factors of neurodevelopmental impairments (NDIs) and neurodevelopmental disabilities (NDDs) for children (aged 0 to 9 years) in Bangladesh.

**Background:** Rates of children with neurodevelopmental disorders has been rising steadily in Bangladesh, inversely proportional to declining child mortality rates. This trend may be across majority of LAMICs. UNICEF has determined that while home-based screening tools, such as the Ten Questions Plus (TQP) are being used among many countries to identify the child at-risk, in-depth assessment and profile of these children's functional limitations, traditionally determined by multi-professionals such as physicians and psychologists, have not occurred.

**Objective:** To field test an assessment tool, the Rapid Neurodevelopmental Assessment (RNDA), for use by generic child-care professionals (teachers, therapists, nurses etc) and paraprofessionals (health care workers) for determining neurodevelopmental impairments (NDIs) and neurodevelopmental disabilities (NDDs) in eight major functional domains primitive reflexes (only for neonates); gross motor; fine motor; vision; hearing; expressive language; cognition; behavior and seizures) and by grades of severity; in various settings across Bangladesh; and it's replicability in other countries.

**Methods:** An epidemiological survey (N=7,280) was conducted by the government of Bangladesh in 2013 ([http://www.hsmdghs-bd.org/Documents/SKB\\_Report\\_2013.pdf](http://www.hsmdghs-bd.org/Documents/SKB_Report_2013.pdf)) where a three-stage (screening followed by assessment followed by diagnostic workout) survey design method was applied for determining the prevalence and associated risk factors of NDIs and NDDs. The government of Bhutan also conducted a similar large scale survey using a two-stage

survey method (screening followed by assessment) in 2009-2010 (UNICEF Bhutan, 2010). In both of these surveys, the RNDA was used prominently to determine the prevalence of NDIs and NDDs, and allows for some comparison in terms of issues surrounding effectiveness of the survey design methods used and ease of implementation.

**Results:** The results present the mean screen positivity (by selected age-groups), the prevalence of (and specific types of) NDIs/NDDs, prevalence by diagnostic groups of children, as well as the frequency and prevalence of Autistic Spectrum Disorder (ASD). Other relevant findings focus on risk factor estimates (including poverty and wealth) and issues relevant for access to treatment including emerging systems of referral. This is critical given the need for appropriate access to services that are cost-effective and that can be scaled up.

**Conclusion:** It is possible to apply a two-stage (screening followed by assessment) or three-stage (screening followed by assessment followed by diagnostic workout) survey design method to determine the prevalence of NDIs/NDDs which allow a country to develop a larger umbrella of developmental surveillance and a tiered system of referral which may be cost effective and applicable for all children born within a country. The challenge in global mental health is investing in large-scale implementation of affordable, practical, innovative and sustainable solutions for evidence-based health service delivery.

PI name/PI Country: Kordas. K (USA).

Major foreign collaborator name/ Foreign collaborating country: Queirolo.E.I.

Presenter Name: **BARG, G.**

Grant number: R21 ES016523

Grant title: Nutritional and Heavy Metals: effects on child learning and behavior in Uruguay

## SUMMARY

### **Blood lead, iron deficiency, and cognition in Uruguayan children**

Barg G, Queirolo E, Mañay N, Roy A, Kordas K

*Faculty of Psychology, Catholic University of Uruguay, Montevideo, Uruguay; Faculty of Chemistry, University of the Republic of Uruguay, Montevideo, Uruguay; Nutritional Sciences, Pennsylvania State University, University Park PA.*

Cognition in children with both iron deficiency (ID) and elevated blood lead levels (BLL) is not well studied. In 1<sup>st</sup>-grade children (n=150, age 6.4±0.6 y, 56.7% boys) from Montevideo, Uruguay we investigated associations among BLL ≥5µg/dL, serum ferritin (SF) <12µg/L, IQ and two executive function (EF) tasks (Internal/External Dimensional Shift—the IED shift—and Stockings of Cambridge—the SOC—both part of the CANTAB testing battery). Mean ± SD IQ was 92.9±17.0 points. Two of the EF task outcomes were 1) the IED shift errors (mean ± SD 19.2 ±10.5, range 0-36) and 2) initial thinking time on the SOC (mean ± SD 3.1 ± 5.8 sec, 0 – 46.4 sec). Mean SF and BLL were 15.0±14.1 µg/L, 4.7±2.2 µg/dL, respectively, with 48.8 and 30.2% of study children having BLL ≥5µg/dL and ID, respectively, and 13.4% having both conditions. BLL and SF were not correlated. In unadjusted linear regressions, BLL and SF were not independently associated with IQ or the two EF tasks; neither were BLL ≥5µg/dL nor ID. However, children with both elevated BLL and ID had lower IQ 11.7 points lower than their ID-only peers (p=0.07). Preliminary analyses suggest that elevated BLL and ID may result in poor general cognitive function in school children.

PI name/PI Country: **Kordas, K. USA**

Major foreign collaborator name/ Foreign collaborating country: Queirolo, E. Uruguay  
QUEIROLO, E.I.

R21 ES016523 ; “Nutritional and Heavy Metals: Effects on Child Learning and Behavior in Uruguay.”

R21 ES019949 : “Is Low-Level Arsenic Exposure Related to Neurobehavioral Defects in Children?”

1) SUMMARY : “*Line of research: Effects of multiple metals on cognitive ability and behavior in children from Montevideo Uruguay*”

Since 2006 an interdisciplinary and collaborative group formed by the Catholic University of Uruguay, Pennsylvania State University and the Republic University of Uruguay is studying the effects of nutrition and heavy metals on development, behavior and learning of children. We present a review of studies: In 2007 the authors screened lead and hemoglobin levels in capillary blood of 222 preschool children from Montevideo, Uruguay. In 2008 the authors examined metal exposures in 109 young children from Montevideo, Uruguay and their mothers participating in a community-based study. In 2009, 150 children from first grade were enrolled. Underwent psychological and clinical assessments (blood, urine and hair was collected for measuring metals), information was requested from teachers and parents. The mothers were interviewed nutritional and psychological. There was also a home visit and sampled water, soil and household dust. This year we are investigating the relationship between exposure to low levels of arsenic and neurobehavioral disorders in children.

## RESULTS

### Study 1

Older child age, hemoglobin <10.5g/dL, and putting fingers/toys in the mouth were associated with higher blood lead level (BLLs). Young maternal age, less education, father's job with potential risk of lead exposure, and fewer family possessions were also associated with higher BLLs.

### Study 2

[BLLs](#)  $\geq 5$   $\mu\text{g/dL}$  in mother or child were associated with lower maternal perceptions of being skilled at discipline ( $p < 0.05$ ). Maternal [anemia](#) was associated with lower likelihood that mothers would let their children explore and play ( $p < 0.05$ ), whereas child [anemia](#) was associated with maternal perception of lower emotional support ( $p < 0.01$ ).

### Study 3

Mean IQ, SF and BLL were  $92.9 \pm 17.0$  points,  $15.0 \pm 14.1$   $\mu\text{g/L}$ ,  $4.7 \pm 2.2$   $\mu\text{g/dL}$ , respectively. 48.8% and 30.2% of children had  $\text{BLL} \geq 5 \mu\text{g/dL}$  and ID respectively, 13.4% had both. 31% of children had  $\text{IQ} \leq 85$  points.

### CONCLUSIONS

The consolidation of an interdisciplinary group specializing in environmental pollution and the experience of a collaborative work between different universities and institutes is a significant step in understanding the problem and finding solutions to the most vulnerable populations: children and reproductive-age women.

PI: **Gloria Patricia Cardona-Gomez**/Colombia/ University of Antioquia

Co-PI: **Kenneth S Kosik**/ USA/UCSB

Grant numbers: R21 AG024024063-01 NIH-FOGARTY- 2004-20071 R01 AG029802-01 NIA/NIH. 2007-2012

Grant title: Development of RNAi as treatment for neurodegeneration.

Oral presentation:

**Gene therapy using CDK5 RNAi reverses and prevents histopathological hallmarks and cognitive function impairment in triple transgenic Alzheimer's mice**

CDK5 plays an important role in neurotransmission and synaptic plasticity in the normal function of the adult brain, and dysregulation can lead to Tau hyperphosphorylation and cognitive impairment. We designed a CDK5 shRNAmiR carried into adeno-associated viral vector (AAV), and stereotactically injected into the hippocampi of triple transgenic Alzheimer's disease mice (3xTgAD). AAV.shCDK5miR treatment for a month (Short-term) reversed neuronal loss, Tau and  $\beta$ A aggregation in the hippocampi and improved spatial memory performance in old 3xTgAD mice (18 months old). Also, at 18 month of age 3xTg-AD mice were sacrificed after one year (long term) of CDK5 knockdown. CDK5 knockdown showed persistent reduction of CDK5, prevented Tau and  $\beta$ A aggregation, and prevented spatial memory impairment compared to controls mice treated with scrambled version. These findings further validate CDK5 as a target for Alzheimer's disease both as a preventive measure and after the onset of symptoms.

In addition, shCDK5miR protected against glutamate-mediated excitotoxicity in cortical primary cultures. Protection was dependent upon a concomitant increase in p35 and p120 catenin (p120ctn), a synaptic-adherents junction proteins, and was reversed using p35 and p120ctn RNAi, which affect down-stream Rho GTPase activity. CDK5 knock-down induced dendritic filopodium spines in a Rac activity-dependent manner and blocked memory dysfunction in triple transgenic Alzheimer's mice, confirming the increased up-regulation of p35, p120ctn, and Rac activity. In summary, our data suggest that the p35/p120ctn complex acts as an up-stream

mediator of Rho GTPases and contributes to neuronal plasticity and protection induced through shCDK5miR.

**PI: Gloria Patricia Cardona-Gomez/Colombia/ University of Antioquia**

**Co-PI: Kenneth S Kosik/ USA/UCSB**

**Grant numbers:** R21 AG024024063-01 NIH-FOGARTY- 2004-20071 R01 AG029802-01 NIA/NIH. 2007-2012

**Grant title:** Development of RNAi as treatment for neurodegeneration.

**Poster 1:**

**BACE1 knock-down avoid neurodegeneration in Alzheimer's disease mice model**

Alzheimer disease is the most common cause of dementia and has a great public health concern. It is characterized by neuritic plaques and neurofibrillary tangles. The main hypothesis on its cause is the amyloid cascade, where there's disequilibrium among the yield and removal of  $\beta$ A peptide being  $\beta$ -Secretase 1 (BACE1) an interesting therapeutic target because it is a key enzyme at the  $\beta$ A formation. In this study we design shRNAmiR against Beta-secretase 1, BACE1 (BACE1miR); RNAi were delivered by Adeno-Associated Viral Vectors (AAV) and analyzed the results *in vivo* in C57BL/6 and triple transgenic Alzheimer Disease mice-3xTg-AD. Our results show that the gene silencing of BACE1 improves memory and learning conditions of 3xTg-AD old mice, reducing amyloidosis and tauopathy through the reduction of MAP kinase and mTOR activities and modulation of the signaling pathway related to neuronal survival.

**Poster 2:**

**Implementation and strengthening of neurobiology research in Colombia: SPF vivarium and other facilities**

Protected by a clear policy of support for scientific research from the University of Antioquia, funding from NIH/Fogarty/NIA, and logistical and administrative support of Faculty of Medicine and Research Headquarters University (SIU), has allowed, the Cellular and Molecular Neurobiology (NBIOL) Area, of Neuroscience Group of Antioquia, has built and strengthened infrastructure necessary for the development of neurobiology research frontline in Latin-America, networking and scientific advising. Importation of the first genetically modified organism to the country, as the triple transgenic mice for Alzheimer's disease (3xTgAD) and

corresponding controls non-Tg approved by the Health Ministry. This colony has been growing up in specific pathogen free (SPF) Vivarium at the SIU-UdeA, under controlled genotypification, survival of 2 years old and treatments prolonged up to 1 year. Also, it has allowed strength experimental facilities using microaislator for long staying during long therapy, surgical room (with anesthesia equipment, surgical stereoscopes, thermal blankets, measuring rectal temperature, CO2 chamber, guillotine, and measurement equipment physiological parameters (Power Lab), sterilizers, microsurgical instrumentation and other partners) accessories. Finally, the SPF animal facility has the necessary equipment for the analysis of motor behavior, emotional and cognitive software's. In conclusion, NIH and institutional support has allowed during 9 years the development of research on pathogenesis and pharmacological and gene therapy of Alzheimer 's disease and stroke with high quality standards and national and international scientific competitiveness.

PI: Krister Kristensson, Sweden

Major foreign collaborators:

Alfred K Njamnshi, Cameroon

Marina Bentivoglio, Italy

Grant number: 1R21NS064888-01A1

**Grant title: Neural dysfunction and neuroinflammation in African brain disorders**

The research objectives of this project (April 2010-May 2012) focused on nervous system involvement in the neglected tropical disease human African trypanosomiasis (HAT) or sleeping sickness caused by *Trypanosoma brucei* (*T.b.*) parasites. During the project, pathogenetic mechanisms of parasite invasion of the central nervous system (CNS) have been explored, sleep-wake and rest-activity alterations in the rat model of the disease have been defined as a basis for the definition of functional biomarkers with a translational perspective. Accordingly, a pilot study on the use of a non-invasive technique, wrist actigraphy, has been performed in HAT patients to assess sleep-wake alterations by rest-activity monitoring. This has been done concomitantly and in comparison with polysomnography, the gold standard for sleep studies. The project was also aimed at establishing a network for capacity building of African investigators, and has achieved the first steps in the establishment of a research center in basic and translational neuroscience at the University of Yaoundé 1 (Yaoundé, Cameroon), and the creation of a neuroscience lab to contribute to regional networking and partnerships with a broader international perspective. The Ministry of Public Health of Cameroon has also recognized the Clinical Neurology Department of Yaoundé for referring all HAT cases in the country. Regional collaborations have been established with the Democratic Republic of Congo (DRC). In the follow-up of the R21 project, the PI and collaborators have engaged in the preparation of an R01 grant proposal. During the submission procedures, difficulties have been encountered in obtaining some administrative papers from DRC and getting through the NIH system but lessons have been learned for the future. As important preparatory activity, the PI and collaborators have also engaged in the preparation of a volume on “Neglected Tropical Diseases and Conditions of the Nervous System” (see below, the list of publications). The volume, which presents the state-of-the-art of neglected tropical diseases (NTDs) and relevant societal severe problems (such as stigma), is aimed at fostering attention of the basic and clinical neuroscience community on the limited state of knowledge of nervous system involvement in NTDs and their severe consequences and sequels, such as epilepsy and cognitive impairment. Capacity-building activities derived from the R21 project have also included, in 2013, an initiative (funded by the International Brain Research Organization and the Rita Levi-Montalcini Foundation) aimed at assisting young African investigators in the preparation of scientific manuscripts for submission to indexed journals, with the objective to sustain African neuroscience initiatives and help raise a new generation of neuroscientists. Capacity-building efforts also saw the defense of the PhD thesis of an Ethiopian student (Jickssa M. Gemechu) at the University of Verona, focusing on neuroinflammation. Several members of Prof. Njamnshi’s Cameroonian team are now pursuing training within the research field. Furthermore, research activities have been pursued, despite limited resources. The role of dendritic cells in the pathogenesis of *T.b.* infection has been investigated in a murine model. This represents a novel approach given the very limited

knowledge on the role of brain dendritic cells in neuroinflammation. With a specific focus on the pathogenesis of the sleep-wake disturbances characteristic of the rodent *T.b.* infection and of HAT, and of high clinical relevance, synaptic changes in the input to peptidergic hypothalamic neurons involved in sleep-wake regulation are currently under investigation in a murine model of *T.b.* infection. As for the definition of molecules that open the blood-brain barrier (BBB) for entry of *T. b.* into the brain, we have identified molecules that restore the BBB after the passage, enabling the parasites to become insensitive to stage 1 drugs. Better biomarkers in relation to sleep disturbances and drug therapy for this crucial event are under evaluation.

PI: SUE LEVKOFF/ USA  
Foreign Collaborator: Huali Wang / China  
**Presenter: Sue Levkoff**  
Grant Number: 1R21AG028180-01A2  
Grant Title: Chinese Dementia Care Research Center

**Abstract:**

As China faces the consequences of an increasing aging population, it is critical to develop research infrastructure that supports the development of research programs on dementia, and research training capacity that supports the improvement of dementia care. This R21 project formed a unique collaboration dedicated to enhancing the capacity for dementia research and care in China, by building upon and expanding existing collaborations between the Peking University Institute of Mental Health, Wuhan University, and the Brigham and Women's Hospital/Harvard Medical School, and West Virginia University.

There are three basic assumptions upon which the specific aims were derived:

Assumption 1: An international collaborative research infrastructure can play an important role in facilitating research initiatives (Aim 1: *Develop a **research infrastructure*** by establishing the interdisciplinary Dementia Care and Research Center (DCRC) at the PKU-IMH)

Assumption 2: It is more important to develop local training capability than providing training to local people (Aim 2: Enable sustainable ***research training capacity*** on dementia care, and transfer primary responsibility for training to WHO/Beijing Collaborating Center for Research and Training on Mental Health, the National Center for Mental Health, China Center for Disease Control, and Wuhan University Mental Health Center).

Assumption 3: The evidence-based intervention protocols that are based on research in Western populations must be culturally adapted in order to become a feasible and successful intervention for local population (Aim 3: Conduct ***research studies*** to explore explanatory models of dementia in Chinese culture and examine the influence of cultural beliefs and values on caregiving experience and care-seeking modalities in China; Aim 4. Design a culturally appropriate intervention study for Chinese caregivers).

The major accomplishments of the R21 project include:

1. Developed the Dementia Care & Research Center at Peking University Institute of Mental Health, which becomes a standing infrastructure for dementia care research in China.
2. Developed a research assessment protocol with a panel of questionnaires for collecting quantitative and qualitative data on home-based care for the Chinese elderly with dementia.
3. Helped local collaborating partner develop research training capacity: Add the research training course into the partner training institution's existing dementia awareness and clinical skill training. The research training course was implemented for training 10 researchers for conducting qualitative interviews, 5 long-term trainees at Peking University Institute of Mental Health, and 115 short-term trainees.
4. Conducted qualitative research: The trained research staff conducted over 50 interviews with both patients and family caregivers in Beijing and Wuhan.

5. Based on the information and experience obtained from this and other projects, the research team developed an intervention to improve the overall wellness of dementia patient-caregiver dyads through participating community-based group Tai Chi exercise classes.

6. In addition, the research project also helped establish the Global Initiative on Caregiving for the Elderly at Harvard University Asia Center, and also supported two Harvard undergraduate students to accomplish two international research projects conducted at Wuhan and Beijing sites that were established through this project.

**PI Name/ PI Country: Huijun Li, Ph.D., USA; Larry Seidman, Ph.D., USA**

**Major Foreign Collaborator name/ Foreign Collaborating COUNTRY: Min Zhao, MD, PR China**

**Presenter name: Huijun Li**

Grant number: 1R21MH093294-01A1 (award period, April 2012 to April 2014)

Grant title: Broadening the Investigation of Psychosis Prodrome to Different Cultural Groups

The purposes of our proposed project are to: 1. Assess potential research needs of, Shanghai Mental Health Center [SMHC], a World Health Organization designated researcher center for mental health, and build its research capacity to develop a sustainable program of research on the progression of schizophrenia from prodrome to psychosis. 2. Provide training to SMHC research team to carry out a preliminary study. This poster will highlight the major accomplishments, research needs, and challenges since the project started in April 2012.

### **Major Accomplishments**

Three on-site trainings were provided. First, we finalized clinical instruments (Structured Interview for Prodromal Syndromes-SIPS) and Prodrome Questionnaire-Brief (PQB). Second, we provided training on the administration of SIPS and MATRCIS as well as ERP and genetic sampling procedures. Third, we provided guidance on recruitment and data collection, data storage, and protection of participants. We have Fourth, we identified two funding opportunities, with one being funded (Validating Biomarkers for the Prodrome and Transition to Psychosis in Shanghai. 1 R01 MH 101052-01, 2013 to 2015, \$600,000). The R21 grant serves as a springboard to expand our research collaboration, and contributing significantly to investigate the social and biological factors contributing to psychosis, thereby enhancing global effort to fight this debilitating mental illness. In addition, the research teams collaboratively wrote three manuscripts based on preliminary data yielded from the R21 project. Among them one was published and two are under review.

### **Needs Assessment**

The needs assessment has been an on-going. The US and SMHC have identified the following major research and logistic needs: research integrity, research coordination effort among different research components, clinical and assessment skills training to identify prodromal individuals, coordinated recruitment effort, data storage and record keeping, and English manuscript writing skills.

### **Challenges**

Our preliminary project is going well. The clinicians and researchers are able to make reliable diagnosis of cases. They are eager to get training to provide intervention to patients who are identified as at risk for psychosis. However, the funding mechanism from Fogarty International Institute has expired and we are desperately waiting for its reinstatement.

PI: Daniel Mamah, MD, MPE / U.S.A.

Co-I: David Ndeti, MD, PhD, DSc./Kenya

**Presenter: Daniel Mamah, MD, MPE**

Grant No.: R21MH095645

Grant Title: Identification of Psychosis-Risk Traits in Africa

Background: The lifetime prevalence of schizophrenia and related psychotic disorders exceeds 3%, and these disorders are a major cause of disability worldwide. Treatment of schizophrenia early in the course of illness is linked to improved outcomes, and accurately identifying individuals before the onset of psychotic illness holds promise for developing preventative interventions and reducing the burden of schizophrenia. This has particular relevance to sub-Saharan Africa, where financial and health care resources are extremely limited. Despite this fact, there is a scarcity of studies exploring psychosis-risk traits in the continent.

Method: Six focus groups were conducted to evaluate knowledge of psychiatric concepts among Kenyan youth, and assessment instruments were culturally modified. We assessed the prevalence of psychotic experiences suggestive of risk for developing psychotic illness in Kenyan youth, including in: 1) primary and secondary school student (N=1,971); 2) tertiary school students (N=2,963); and 3) community youth (14-29 yrs; N=2,758), using two different psychosis screening instruments (i.e. the Prime Screen and the psychosis section of the CIDI). Recently, we evaluated 2,806 secondary school students using more detailed screening assessments for psychosis- and bipolar-risk. In addition, we are evaluating cognition, psychiatric diagnoses, anthropometry, dyskinesia and perceived stress burden in a subset of these youth as part of an ongoing longitudinal study over 18 months.

Results: The prevalence of psychotic experiences in Kenyan youth was between 22.1%-45.5%, varying with the screening tools used. A validation of the results using the Prime-Screen suggests that the larger prevalence figures may overestimate prevalence rates. The distribution of symptoms obtained using the CIDI were similar in primary/secondary school and tertiary school populations, with the majority of youth exhibiting predominantly hallucinatory symptoms (9.6%-12.7%; “Type 1 psychosis”) over pan-psychotic symptoms (3.5%-7.2%; “Type 2 psychosis”). Analyses using newer and more detailed assessment tools are ongoing.

Conclusions & Future Directions: These results suggest a high prevalence of psychotic-risk symptoms in Kenyan youth. Our ongoing cross-sectional and longitudinal studies will shed light on the correlates of risk symptoms, and will improve our ability to predict symptom progression and conversion to psychotic disorder. Capacity building efforts will continue with teaching the application of new assessment tools to Kenyan researchers. We are also obtaining additional prevalence data on psychosis/bipolar risk symptoms from Rwanda. Together, our data will inform early intervention strategies for high-risk youth in Africa, for future studies.



**Principal Investigators:** Vishwajit L Nimgaonkar MD, PhD (USA), Hader Mansour MD, PhD (Egypt)

**Major foreign collaborator:** Hader Mansour MD, PhD (Egypt)

**Presenter:** Hader Mansour MD, PhD (Egypt)

**Grant Number:** 1R01MH093246-01A1

**Grant title:** Multi-pronged genetic studies of schizophrenia in an inbred population

**SPECIFIC AIMS:** Across the world, schizophrenia (SZ) is a common, severe and debilitating disorder. Its etiology and pathogenesis are unknown, but genetic factors are a likely source of risk. Ongoing efforts have confirmed several genetic risk variants, but many remain to be discovered. With new tools and designs we expect to identify far more of the genes involved.

In response to an increasing desire in the Middle East to reap the benefits of genomics, we initiated SZ genetics research in Egypt through a Fogarty R21 grant under the BRAINS program. We found that inbreeding substantially increases SZ risk (odds ratio, OR ~ 3.53). We have improved the research infrastructure at Mansoura University (MU), our Egyptian collaborating institution, by establishing a productive molecular genetics lab. We have also trained laboratory/clinical investigators, published peer reviewed papers and spawned research in several related areas.

**Aim 1. Homozygosity by descent (HBD) analysis to identify schizophrenia risk polymorphisms**

We will attempt to identify recessively acting risk variants by HBD analysis, which uses the fact that chromosomal fragments flanking a recessive risk allele can be passed down from the same ancestor to cases through multiple lines of inheritance in inbred populations. Population-level HBD analysis has been successful for several complex genetic disorders such as intellectual disability and autism.

**Aim 2. Follow up sequencing and bioinformatics analysis**

To further localize SZ susceptibility variants, we will prioritize HBD chromosomal segments analyzed in Aim 1 and select individuals harboring the HBD segments. Through targeted capture and Next Generation sequencing, we will evaluate the HBD segments intensively. Using state of the art bioinformatics tools, we will identify SZ risk variants and their functional relationships.

**Aim 3. Phenotypic expression of identified SZ risk variants among multi-generational families:**

To understand the range of expression of the identified risk variants, we will select patients with SZ from Aim 3 who are HBD for SZ risk mutations. We will consent and assess all of their available relatives. We will genotype these participants and evaluate their psychiatric diagnoses, cognitive function and physical abnormalities.

**Aim 4. Continue sustainable research infrastructure and capacity building:** We will build research capacity for bioinformatics and statistical analysis through training and purchase of software/hardware, and extend clinical and laboratory expertise. Egyptian collaborators will lead the entire research by grant end.

## **STUDIES AND RESULTS**

Following ethical approval from MU and the University of Pittsburgh, we have recruited more than 300 participants so far. We have been holding internet training sessions in bioinformatics

and genetic analysis techniques for overseas trainees. Additional training is being planned in January 2014 at the University of Pittsburgh to selected colleagues specializing in bioinformatics, data management and analysis, as well as molecular genetic techniques. We have already purchased dedicated computer equipment that will be transferred to Mansoura when our colleagues return to Egypt. Our collaborators in Egypt have scheduled a public symposium in Mansoura Egypt on Dec 18-20. PI Dr. Vishwajit Nimgaonkar will participate in the symposium. He will also provide individualized trainee mentorship and monitor progress of research.

We have continued HBD analysis of the samples collected under the completed R21 grant. We are currently collaborating with Dr Alasdair Cardno, Leeds University, UK who has conducted linkage analysis in an immigrant family of Pakistani origin that has multiple members with SZ. We are also collaborating with investigators in South India who are using HBD analyses to map genes for SZ in Hindu communities.

Joanna Maselko / United States  
Bilesha Perera / Sri Lanka  
Truls Østbye  
1R21TW009151  
The Sri Lanka Healthy Minds Study

Caregiving expectations and challenges among the elderly and their adult children in Southern Sri Lanka

Melissa H. Watt, Bilesha Perera, Truls Østbye, Shyama Ranabahu, Harshini Rajapakse, Joanna Maselko

The Sri Lanka Healthy Minds Study is a mixed methods study that examines how individual, caregiver, and other family level factors impact risk of depression and cognitive impairment among the elderly.

This presentation describes a key part of our qualitative findings on caregiving expectations and challenges as perceived both by elderly and their adult children. Data were based on 4 focus group discussions and 5 in-depth interviews with elderly in the Galle area of Southern Sri Lanka., and 10 in-depth interviews with adult children of the same elderly. Both elders and caregivers felt strongly that elders should be taken care of in the home by their children. They pointed to a sense of duty and role modeling of parental caregiving that is passed down through generations. Even as elders desired support from their children, they also feared losing their independence, and saw financial autonomy as important for maintaining relationship balance. Caregiving challenges included: households where both the adult child and his/her spouse worked outside the home; households where elders had a disproportionate amount of household work; economically stressed households; and lack of direct communication between elders and caregivers regarding conflicts. The results point to strong values around caring for elderly in the home, but identify current and future challenges to this arrangement.

Joanna Maselko / United States  
Bilesha Perera / Sri Lanka  
Harshini Rajapakse  
1R21TW009151  
The Sri Lanka Healthy Minds Study

Impact of and coping strategies for cognitive impairment in the elderly Sri Lankans

Harshini Rajapakse, Bilesha Perera, Shyama Ranabahu, Truls Ostbye, Joanna Maselko, Melissa H. Watt

#### Background

Sri Lanka has a rapidly aging population. There is no organized system of social care. Elders are dependent on an intergenerational care system. A changing economic landscape with children migrating for work and with dual earning households is threatening the viability of this network.

#### Objectives

This qualitative study sought to gain an in-depth understanding among elders and caregivers of what cognitive impairment means to them, its impact, coping strategies and family related modifiable protective and risk influences.

#### Methods

Four focus group discussions with 20 elders from rural and urban settings and fifteen in depth interviews with caregivers were conducted. Purposive sampling was used to obtain the widest range of views.

#### Results

Participants had a vague notion of cognitive impairment. Many felt it was a 'normal' aspect of aging. As it was not considered an illness, medical treatment was not sought early in the course when symptoms were mild. Late in the illness, treatment was sought when the cognitive impairment became an issue giving rise to conflicts within the family or when the behaviour of the elder became a socially embarrassing to the care givers. The decision to take treatment and from whom was made by the intergenerational care givers. Treatment was initially sought from religion related sources. The caregivers found it easiest to discuss the problems with the priests. When problems were continuing they turned to astrologers, indigenous herbal specialists, ritual healers and then to ayurvedic practitioners. It was only failure at all these that directed patients to allopathic medical practitioners. Even in this instance, mental health services were only rarely utilized. The reason for underutilization seemed to be partly contributed for by the general ignorance prevalent about the nature of cognitive impairment and the deeply rooted stigma and prejudices towards mental illness.

#### Conclusions

The understanding among elders and care givers about cognitive impairment was vague. Often it was not appreciated as an illness requiring treatment. Family conflicts arose and the quality of

life of elders deteriorated when they developed cognitive impairment. A better understanding of the nature of the illness and early utilization of mental health services need to be promoted to meet up with the challenge of caring for an ever increasing elderly population with proportionate increase in prevalence of cognitive impairment.

Joanna Maselko / United States  
Bilesha Perera / Sri Lanka  
Harshini Rajapakse  
1R21TW009151  
The Sri Lanka Healthy Minds Study

Successful aging: a qualitative study of Sri Lankan older people

Bilesha Perera, Shyama Ranabahu, Harshini Rajapakse, Melissa Watt, Truls Ostbye, Joanna Maselko

**Background:** Sri Lanka has the fastest aging population in South Asia. Due to this unprecedented population aging trend, health and socio-economic implications in Sri Lanka will evolve a different picture in the coming decades. This study explores the opinions and views of older people about successful aging and barriers to achieving this ideal.

**Methods:** Eight focus groups were conducted in urban and rural settings in southern Sri Lanka, with a total of 58 participants. Participants were older people (aged above 60 years) who were purposively selected to achieve diversity in socioeconomic status. Focus groups were audio recorded and transcribed. Analytic memos were prepared and common themes were identified.

**Results:** Four central characteristics of successful aging were identified: (i) being physically active and healthy; (ii) having freedom from burdens and responsibilities; (iii) having fulfilling family relationships; and (iv) pursuing spiritual development. A living environment conducive to physical activity and charitable work, and living with children were identified as facilitators of successful aging. Economic hardships, having unsettled and vulnerable children, disrespect from the community, limited access to health care, and negative attitudes of service providers towards older people were identified as important barriers to successful aging.

**Conclusions:** These findings point to strategies to improve the quality of life of Sri Lankan older people. These include increased community awareness of population aging and expectations of older people, a strengthened primary health care system catering to their future demands, and development of support systems for home based care.

Joanna Maselko / United States  
Bilesha Perera / Sri Lanka  
Joanna Maselko  
1R21TW009151  
The Sri Lanka Healthy Minds Study

The Contribution of Generative Leisure Activities to Cognitive Function Among Sri Lankan Elderly.

Joanna Maselko, Matthew Sebranek, Mirna Hodzic Mun, Bilesha Perera, Vijitha DeSilva, Jill Ahs, Truls Ostbye

Although it is acknowledged that leisure activities protect against cognitive decline associated with aging, it remains unclear which specific types of activities are most important to prevent or delay cognitive decline. Anchored in lifecourse developmental theory, we examine the contribution of generative activities, defined as “activities borne out of a concern for others and a need to contribute something to the next generation” (Erikson and Erikson 1997), on elder cognitive function. Data were collected through a cross-sectional community based survey of elderly (60+) residing in a peri-urban and rural area in Southern Sri Lanka. Combining data from questions about frequency of engagement in various leisure activities, we assessed the extent to which generative leisure activities, as well as solitary and other social leisure activities, contribute to cognitive function. Cognitive function was measured using the Montreal Cognitive Assessment (MoCA) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). We find that more engagement in generative leisure activities are associated with higher levels of cognitive function, independent of the impact of other social and solitary activities, and after adjusting for other potential confounders. These results corroborate the value of the generativity construct in the study of leisure activities and cognitive function.

**PI: Ana-Claire Meyer (U.S.A./Kenya)**

Foreign Collaborator: Judith Kwasa (Kenya)

Presenter: Unable to attend

Grant Number: 5R21NS077858-02

Grant Title: Targeted Treatment of Early Cryptococcal Infection in HIV-infected Patients

In sub-Saharan Africa and southeast Asia, invasive cryptococcal disease is the second most common life-threatening HIV-associated opportunistic infection after tuberculosis and is responsible for up to 20% of deaths. Since invasive cryptococcal disease primarily affects HIV-infected individuals with advanced immunosuppression, one potential strategy to detect early cryptococcal infection in resource-limited settings is to screen asymptomatic individuals with advanced HIV-related immunosuppression for serum cryptococcal antigen (CrAg) as they enter outpatient HIV care and treatment programs. Several observational cohort studies have demonstrated that this approach clearly identifies a population at high risk of cryptococcal meningitis and death and is a feasible screening method for resource-limited settings. However, screening using serum CrAg alone identifies a heterogeneous clinical population, many of whom already have sub-clinical meningeal infection or fungemia. Preliminary evidence suggests that fluconazole monotherapy is not an effective treatment in a heterogeneous population of individuals with early cryptococcal infection. Thus, there is a critical need for potent therapies which can be safely administered in resource-limited settings. Combination therapy with oral high-dose fluconazole and flucytosine has shown promise in small clinical trials for the treatment of cryptococcal meningitis but has not been tested for early cryptococcal infection.

The major goal of this study is to determine the safety and estimate the efficacy of fluconazole plus flucytosine as compared to fluconazole alone in HIV infected asymptomatic outpatients with serum cryptococcal antigenemia and severe immunocompromise in an open-label randomized controlled trial. A secondary aim is to define the clinical predictors of survival in this population. We have obtained ethical and regulatory approvals from the various institutions involved, trained our staff, and recruitment began in September 2013. We anticipate study recruitment will take 12-18 months.

Our secondary goal is to expand the human resources necessary for the conduct of clinical research of neurological disorders in Kenya in partnership with our colleagues at the Kenya Medical Research Institute (KEMRI) and the University of Nairobi (UON). We completed a research symposium for Masters in Medicine candidates at UON, and additional activities are planned for early 2014 for junior faculty and research officers at KEMRI and UON.

This study will provide important preliminary data on safety, efficacy, and outcomes such as mortality and incidence of cryptococcal immune reconstitution inflammatory syndrome (IRIS) which will help us power a planned R01 to follow—an open-label Phase III factorial randomized trial to test the efficacy of combination therapy with fluconazole and flucytosine, as well as to determine the optimal timing for initiation of antiretroviral therapy in early cryptococcal infection. We will also develop efficient and effective study procedures and an integrated

research team so that our group will be poised to conduct a larger clinical trial.

The most significant barrier we have encountered to initiating our research was the timeliness of ethical review by one of the foreign country ethical review boards. Sustainability of research in Kenya is limited because of few career development opportunities for junior faculty in Kenya to develop their own independent research questions and careers.

**PI name/ PI Country: Dr. MKC Nair; Dr. Narendra K. Arora, India**

**Major foreign collaborator name/ Foreign Collaborating COUNTRY:**

**Prof. Donald Silberberg, University of Pennsylvania, USA**

**Prof. Maureen Durkin, University of Wisconsin, USA**

**Prof. Jennifer M. Pinto, University of Pennsylvania, USA**

**Prof. Vinod Bhutani University of Stanford, USA**

**Presenter name in BOLD: Prof Narendra Arora**

**Grant number: 1-R21HD053057-01A1**

**Grant title: Neuro-developmental Disabilities among Children in India: An INCLEN Study.**

**Title: Neuro-Developmental Disorders in India: From Epidemiology to Public Policy**

Narendra Arora,MD,MKCNair,MD,DonaldSilberberg,MD,FAAN,  
VinodBhutani,MD,MaureenDurkin,PhD,DrPH,ShefalliGulati,MD,JenniferPinto-  
Martin,MPH,PhD

**Background:** In India, there was no nation-representative study reporting epidemiologic data on neuro-developmental disorders and disabilities (NDDs) viz., Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorders (ASD), Intellectual Disability, Epilepsy, Learning Disability, Neuromuscular Impairments including Cerebral Palsy (NMI-CP), Speech and Language Disorders, and Hearing and Vision Impairments. Consequently, these have been under-recognized for policy making.

**Objective:** The main objectives of our research were: 1) to estimate the prevalence of Neuro-Developmental Disorders (NDDs) among children aged 2-9 years among urban, rural, hilly areas, and tribal groups in India; 2) to disseminate research experience and finding in India and other countries where individuals with NDDs have been under-recognized.

**Design/Methods:** Indian culture and context relevant validated diagnostic tools were identified for the ten NDDs mentioned above; four tools had to be developed and validated *de novo* by the group viz., for epilepsy, NMI-CP, ASD and ADHD. A total of 4,000 households in five regions of India were sampled using multi-stage cluster random sampling. Sample prevalence data was weighted against the National Census of 2011 for 2-9 year old children to calculate population weighted prevalence. In the process, a 39-question Neuro-developmental Disorders Screening Tool (NDST) was also tested. The research experience and findings were presented in various forums to technical experts and policy makers.

**Results:** Country wide results revealed that 14.7% [95%CI=13.0-16.7] of children ages 2-9 yrs had one or more NDDs. The region-wise prevalence was 10.0% (Hilly areas), 12.7% (Urban areas) to 18.1% (Rural areas). The tribal prevalence was 4.9%, perhaps reflecting lower infant survival. Analysis of the data derived from the original 39-question Neuro-developmental Screening Tool (NDST) utilized in gathering data from 4,000 families revealed that optimal sensitivity and specificity was achieved by utilizing only 12 questions: Sensitivity–72.0%; Specificity–63.1%.

**Conclusions:** The study has contributed to highlight the burden of NDDs in India to policy makers: (1) the questionnaire on disability in Census of 2011 has been expanded; (2) a national program for screening, diagnosis and treatment of NDD's, Rashtriya Bal Swasthya Karyakram (RBSK), has been developed.

**Seth O’Neal, USA**  
**Armando Gonzalez, Peru**  
**Seth O’Neal**  
**5R21NS069275 – 02**  
**Targeted screening for *Taenia solium* tapeworms**

## **ABSTRACT**

### **Ring screening for taeniasis to control endemic transmission of *Taenia solium*.**

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### **Background**

Neurocysticercosis is a major cause of preventable epilepsy across Asia, Africa and Latin America. Screening and treatment of the causative parasite (*Taenia solium* taeniasis, a.k.a. the pork tapeworm) within sub-populations at increased risk may reduce parasite transmission and prevent epilepsy by limiting human exposure to tapeworm eggs. We piloted ring-screening strategy which involves screening and treatment for taeniasis among households located nearby pigs that are heavily-infected with cysticercosis. These pigs mark areas of increased transmission and can be identified by tongue examination.

### **Methods**

We selected two villages in northern Peru for our non-randomized controlled community trial. In the intervention village (population 1058) we examined tongues of all pigs every 4 months for nodules characteristic of cysticercosis. We then screened all residents living within 100-meters

of any tongue-positive pig using ELISA to detect *Taenia* antigens in stool. Residents with taeniasis were treated with niclosamide. In both control (population 753) and intervention villages we conducted an education campaign about reducing risk of infection. We measured exposure incidence by sampling the pig population in both villages every 4 months for serum antibodies against cysticercosis using EITB LLGP.

### Findings

Baseline seroincidence among pigs born during the study was 19.9 cases per 100 pigs per-month (95% CI 16.3-24.4) in the intervention and 13.8 (95% CI 10.6-17.9) in the control. There was significant 12% reduction in seroincidence with each successive 4-month period in the intervention community (IRR 0.88, 95% CI 0.82-0.95) while seroincidence in the control remained statistically unchanged (IRR 0.95, 95% CI 0.86-1.04). After one year of intervention there was 54% overall reduction in seroincidence in the intervention community compared to baseline (IRR 0.46, 95% CI 0.34-0.61).

### Conclusions

Ring-screening was highly effective in reducing *T. solium* transmission in this pilot study and may be an effective and practical community-based strategy for regions where resources are limited. We will optimize and validate this strategy in a larger community-based clinical trial to begin in 2014 under the Brain Disorders in the Developing World R01 program. Our research capacity building efforts in this program have focused on training Peruvian health professionals in structured local Master's degree programs. We will expand the training program under the new award by continuing to support local Master's candidates as well as by supporting Peruvian PhD candidates in Epidemiology through Johns Hopkins Bloomberg School of Public Health.

## **Modern techniques contributing to the Diagnosis of Tropical Neurological Disorders: HTLV-1 Infection in Central Nervous System**

**(R21)/ 1 R21 NS058293-01A1**

Marzia Puccioni-Sohler, Emerson Gasparetto, Romeu Domingues Cortes, Bruce R. Rosen, Caterina Mainero

Lymphotropic virus human T-cell type 1 (HTLV-1) was the first retrovirus to be isolated in humans. It is endemic in southeastern Japan, the Central and South America, including Brazil and parts of Africa, and also in Melanesia and the Middle East. There are approximately 20 million people infected worldwide. Approximately 1-2% develop a chronic progressive disease of the central nervous system termed HTLV-1 associated myelopathy/ tropical spastic paraparesis (HAM/TSP). It causes an great social impact and financial costs on infected individuals, their families, and health care systems. We investigate the association between clinical data, white matter lesions in magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings in HAM/TSP. The disease leads to demyelination and axonal loss in central nervous system.

**Method:** We studied brain and cervical spinal cord on MRI and CSF examinations of 28 Brazilian HAM/TSP patients. **Results:** The majority of patients had severe neurological incapacity (support to walk or restricted to wheelchair). The brain MRI showed white matter lesions (75%), and atrophy (14%). The preferential brain location was periventricular. Cervical demyelination lesions occurred in 11% of the cases, and cervical atrophy in 3.5%. One patient had enhancement lesions on T1 cervical spinal cord MRI. Cases with spinal cord lesions had signs of acute CSF inflammation (pleocytosis, hyperproteinorrachia, blood-CSF barrier dysfunction, intrathecal synthesis of total and HTLV-1 antibodies). The brain white matter lesions predominated in the patients with higher age. **Conclusion:** Our data suggest that an active inflammatory process is associated with the cervical spinal cord lesions in HAM/TSP. The brain abnormalities are not related to the clinical and CSF findings of HAM/TSP. The study contributed to a better knowledge about the disease.

**PI: Dushyant P. Purohit, M.D. /USA**

**PIs/Co-PIs: Drs. C. Pinto, J. Deshpande, A.B. Shah, J. Jashnani/ INDIA**

**Presenters: Dr. D. Purohit, with Dr. M. Sano**

**Grants: R21-AG1-0124065 and R01-AG028188 “Age-Related Cognitive Loss in Mumbai, India”**

Dementia research is just beginning to expand in developing countries, which is a timely response to the rising concern about aging brain health and dementia. There are some key trends that have resulted in the need to conduct research on cognitive loss in aging in the developing countries. First, with increasing life span, more people reach old age and be susceptible to cognitive loss and dementia. Second, the functional impact of cognitive loss in a developing society will be huge due to changing socio-economical structure. Technologies used in daily life are accelerating in the developing countries at an astronomical pace and the cognitive loss of the current aging population with low education or literacy could cause them to be highly disadvantaged. Thus the decline in activities of daily living caused by cognitive loss and aging are further magnified. The health care services are not prepared for providing necessary support due to shortage of personnel and a dearth of training programs that would expand that workforce. Considering potentially huge number of cognitively impaired older population that would require clinical care and support in daily living, there will be a need to identify cognitive impairment earlier before the loss of function becomes critical. This will require the development and implementation of methodologies for early detection, both with cognitive testing instrument and with biomarkers. Teaching skills to local investigators will allow them to develop and employ these tools and carry out research for advancement of knowledge and stay abreast with international research collaborations.

In our experience the Fogarty award permitted us to train a wide range of researchers in areas critical to brain aging and disease. First, we trained physician/investigators to integrate standardized evaluations and research diagnostic criteria in the clinical setting. This provided a uniform method for distinct categories of individuals that could be used to direct care and management of patients. We trained psychometricians to use standardized, quantitative measures to assess cognition that provides a basis on which to evaluate change and to tests hypotheses about cause and effect relationships of the brain behavior relationships. Our program also established clinical diagnostic ability for different types of dementia while studying over 300 recruited subjects and others who sought clinical care at our clinic. Pathology component also contributed in developing a previously lacking laboratory infrastructure for dementia studies and the skill among pathologists in the morphologic, quantitative and diagnostic study methods while examining over 200 brain specimens obtained in our project’s brain bank/neuropathology lab from pathology autopsy services.

The result of this was lecture presentations and manuscripts describing the clinical and pathological findings and the study details. Our program trained more than 20 early and late stage researchers in studies on dementia, some of whom have continued locally into research and clinical interests and in pathology, and some have continued work overseas. In terms of the local infrastructure, the door to supporting research was opened through the Deans of the participating medical colleges who shared our objectives for research development.

The program generated unexpected benefits: Increased awareness among clinical practitioners through workshops and meetings at a wide number of venues to meet other professionals, talks at professional organizations and presentations to organizations doing advocacy for aging populations. Community outreach directly to the elderly population was carried out at senior centers which also help recruit controls for our study attended. Engagement and trust among the target community is essential to being able to conduct this research and the support of the local investigators allowed the community to understand the research mission from their own investigators. Thus, the presence and imprimatur of NIH support can move the local community to support the continuation of research. One example is the commitment of significant research funds made by four local philanthropies to supplement NIH funding secured by us in the future.

Principal Investigator: Mohammad H. Rahbar, PhD / USA  
Professor of Epidemiology & Biostatistics, The University of Texas School of Public Health at Houston

Presenter: **Mohammad H. Rahbar, PhD**

Maureen Samms-Vaughan, MD, PhD / Jamaica

Professor of Child Health, The University of the West Indies (UWI), Mona Campus, Kingston, Jamaica

Grant Number: R21HD057808 /R01ES022165

## **Epidemiological Research on Autism in Jamaica**

Autism Spectrum Disorders (ASD) are complicated neurodevelopmental and behavioral disorders that manifest in early childhood and continue into later life. Although the causes of ASD are unknown, the evidence suggests that the origins are likely the result of environmental factors, either directly or through interaction with certain genes.

During the past 4 years, with funding from NICHD/FIC (R21, PI: Rahbar) our research team at the University of Texas Health Science Center at Houston (UTHealth) has collaborated with Dr. Maureen Samms-Vaughan and her colleagues at the UWI in Jamaica to investigate the role of the glutathione-S-transferase (GST) genes (GSTM1, GSTP1 and GSTT1) and five heavy metals (lead, mercury, arsenic, cadmium, manganese) in relation to ASD in Jamaica. We conducted an age- and sex-matched case-control study and enrolled 300 children 2-8 years of age (150 pairs of ASD cases and typically developing (TD) controls and their parents). To date we have published three manuscripts and have made seven presentations at scientific meetings and conferences. In our first published manuscript<sup>1</sup>, we showed that older paternal and maternal ages are jointly associated with having a child with ASD. In the second published manuscript, we reported no associations between blood mercury concentrations and ASD<sup>2</sup>. In the third published manuscript, we reported no associations between blood arsenic concentrations and ASD<sup>3</sup>. Currently, we are in the process of revising a manuscript focused on manganese and ASD which is under review by Autism Research<sup>4</sup>. Recently, we have submitted another manuscript focused on cadmium and ASD to PLOS-ONE<sup>5</sup> for review and possible publication. Recently, after receiving the genetic data, we explored potential interactions between lead and GST genes. However, we neither found a significant association between ASD and blood lead concentrations nor a significant interaction between the blood lead concentrations and GST genes in relation to ASD.

The long-term goal of this project is to develop capacity for conducting large-scale population-based ASD studies in Jamaica. During the past 4 years, we have developed a very strong collaboration with our colleagues at the UWI. We have focused on capacity building activities that included conducting a week-long biostatistics workshop at the UWI, training of our UWI colleagues in the administration of ASD assessments, provision of opportunities for UWI researchers and students to gain additional research training in the US, provision of interview instruments, and biologic sampling protocols for this study. In March 2011, our collaborators at the UWI obtained funding through a grant from the Japanese Special Fund administered through the Inter-American Development Bank titled, JA Kids: The Jamaican Birth Cohort Study 2011. Dr. Samms-Vaughan, the PI of the subcontract to the UWI in Jamaica, serves as the PI of the JA Kids study. She has offered us the unique opportunity to collaborate with her team on the JA Kids study. The JA Kids study has enrolled over 5,500 pregnant women who were interviewed at

delivery. Children will be followed initially to at least 2 years of age. We have already collected n=144 cord-blood serum/blood samples for the assessment of fetal exposure to polychlorinated biphenyls (PCBs), organochlorine (OC) pesticides, and six heavy metals (lead, mercury, arsenic, cadmium, manganese, and aluminum) during pregnancy. Our R01 grant which was funded by NIEHS on September 12, 2013, will provide an opportunity to investigate the role of PCBs, OC pesticides, and six aforementioned heavy metals and their potential interactions with GST genes involved in contaminant metabolism in relation to ASD. We look forward to continuing this successful collaboration with our colleagues at the UWI, in Jamaica for at least another five years.

Principal Investigator: Mohammad H. Rahbar, PhD / USA  
Professor of Epidemiology & Biostatistics, The University of Texas School of Public Health at Houston

Presenter: **Mohammad H. Rahbar, PhD**

Maureen Samms-Vaughan, MD, PhD / Jamaica

Professor of Child Health, The University of the West Indies (UWI), Mona Campus, Kingston, Jamaica

Grant Number: R21HD057808 /R01ES022165

**TITLE: Role of fruits, vegetables, and seafood consumption in blood heavy metal concentrations among Jamaican children with and without autism spectrum disorders**

The etiology of Autism Spectrum Disorders (ASD) is complex and not fully understood. Several studies have investigated the possible association between exposure to several heavy metals (e.g., lead, mercury, arsenic, cadmium, and manganese) and ASD, but their findings are conflicting. As an island nation, Jamaica has very specific sources of exposure to environmental contaminants, including heavy metals. We investigated whether environmental exposures to mercury, lead, arsenic, manganese, and cadmium have a role in the etiology of ASD. In addition, we explored the role of the drinking water source, fruits, vegetables, grains, and seafood consumption in relation to blood heavy metal concentrations among Jamaican children for the aforementioned five heavy metals.

During the past 4 years, our research team conducted an age- and sex-matched case-control study that began enrollment in 2009. Based on available data from 110 Jamaican-born matched pairs (220 children) ages 2-8 years, we used General Linear Models (GLM) to test the association of ASD status with blood lead, mercury, arsenic, cadmium, and manganese concentrations. In addition, we used Conditional Logistic Regression (CLR) to assess associations between potential confounders and ASD case status. Furthermore, we assessed the role of the drinking water source, fruits, vegetables, grains, and seafood consumption in blood heavy metal concentrations among Jamaican children.

In our sample, 84.5% of the cases and controls were male, which is consistent with the usual gender distribution seen in children with ASD. As expected, age distribution between cases and controls were comparable. We observed that parental education levels were significantly higher for ASD cases in comparison to typically developing (TD) controls ( $P < 0.01$ ). Dietary intake differed significantly between ASD cases and TD controls, including the frequency of seafood, vegetables, and grains consumed. Specifically, parents of TD controls reported that their children had a significantly higher consumption of many fruits and vegetables, compared to that of ASD cases. For example, parents of cases were less likely to report that their children consumed “yam, sweet potato, or dasheen” than parents of controls (MOR=0.50; 95% CI: 0.26, 0.97;  $P = 0.04$ ). We also found that children who ate more than 6 meals of seafood per week had a significantly higher geometric mean blood mercury concentration than children who ate  $\leq 6$  meals of seafood per week (1.25 vs. 0.62 $\mu\text{g/L}$ ;  $P < 0.01$ ). Furthermore, we observed significant differences between cases and TD controls with respect to geometric mean blood mercury and lead concentrations ( $P < 0.04$ ,  $P < 0.03$ , respectively), but no significant differences were observed between ASD cases and TD controls with respect to arithmetic mean blood arsenic, cadmium, and manganese concentrations. However, after controlling for potential confounding variables in our final multivariable models for each of the five aforementioned heavy metals, we

observed no significant differences between ASD cases and TD controls with respect to adjusted geometric mean blood mercury and lead concentrations and arithmetic mean blood arsenic, cadmium, and manganese concentrations.

After adjusting for the potential confounding variables, our results do not support an association between blood mercury, lead, arsenic, manganese, and cadmium concentrations in Jamaican children 2-8 years of age and ASD. However, our data suggest that some Jamaican children may still be exposed to lead, mercury, arsenic, cadmium, and manganese through other sources such as consumption of fruits, vegetables, and seafood.

PI name/ PI Country: John M. Ringman, M.D., M.S./USA- POSTER ONLY  
Major foreign collaborator name/ Foreign Collaborating Country:  
Miguel Angel Macias-Islas, M.D., Ph.D./Mexico  
Esmeralda Matute, Ph.D./Mexico  
Presenter name: John M. Ringman, M.D., M.S.  
Grant number: 1R21TW009787-01  
Grant title: Establishing Infrastructure for Prevention of familial AD in Mexico

### Project Summary/Abstract

Alzheimer's disease (AD) is a growing health problem worldwide and currently available treatments are of limited efficacy. Prevention of AD may be a more relevant goal, particularly in lower and middle-income countries. Studies of AD prevention however, are challenging, in part because of the unpredictable onset of the disease in elderly individuals. Persons inheriting mutations causing fully-penetrant autosomal dominant familial AD (FAD) provide an informative and motivated population for assessing the efficacy of AD prevention strategies. The PI has been working with clinician investigators in Mexico for over 10 years, characterizing multiple families with FAD due to PSEN1 or APP mutations. Multi-center collaborative efforts to perform prevention

trials in preclinical persons carrying FAD mutations are underway (the Dominantly Inherited Alzheimer Network in which the PI is a site investigator and the Alzheimer Prevention Initiative) but such efforts have not reached Mexico. The capacity to perform FAD prevention trials in Mexico is limited due to lack of understanding among families and physicians of the disease and its genetic nature as well as by the availability of infrastructure including personnel appropriately trained to perform such studies. The goal of this project is to enhance the ability of Mexican investigators to perform such studies through the following specific aims:

Aim #1: Enhance local capacity to perform quality cognitive, clinical, imaging, and biochemical assessments as outcome measures for prevention trials in Mexico. This project will be the planning stage in which the possibility of exchange programs wherein health professionals from Mexico come to the UCLA to receive specialty training in genetic counseling, dementia diagnosis, management, and research will be explored.

Aim #2: Investigate attitudes towards and promote education regarding AD, genetics, FAD, and prevention trial procedures among members of families with FAD in Mexico.

Aim #3: Establish a registry of persons eligible for participation in prevention trials for FAD.

**Diane Rohlman**/USA and Gaafar Abdel Rasoul/Egypt

*R21 ES017223 and R01 ES022163-01*

Vulnerability of the Adolescent Brain to Organophosphorus Pesticides

### **Longitudinal Assessment of Exposures, Symptoms and Neurobehavioral Performance in Egyptian Adolescent Pesticide Applicators**

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**Introduction:** Chlorpyrifos (CPF), an organophosphorus (OP) pesticide, is applied seasonally in Egypt by adolescent agricultural workers, however, the extent of occupational exposure and the potential for environmental CPF exposure in this population is poorly understood. In addition, while there is compelling evidence that repeated low-level occupational and environmental OP exposures are associated with neurobehavioral performance deficits in adults, little is known about potential effects in adolescents, who have a developing nervous system.

**Purpose:** To assess biomarkers of exposure to CPF and the impact of exposure on neurological symptoms and neurobehavioral performance among adolescents.

**Methods:** Adolescent male pesticide applicators (N=57) and age-matched male non-applicators (n=38), recruited from Menoufia Governorate (Nile Delta), Egypt, completed symptom questionnaires and neurobehavioral tests across a 10-month period prior to, during and after pesticide application in 2010. Spot urine samples were collected at multiple time-points to measure trichloro-2-pyridinol (TCPy) in urine, a CPF-specific metabolite (exposure biomarker) and blood acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) provided biomarkers of effect.

**Results:** Applicators demonstrated significantly higher TCPy concentration and BChE depression than non-applicators throughout CPF application. This difference persisted for 4-7 weeks after the cessation of agricultural spraying. However, both groups exhibited significantly elevated TCPy and depressed BChE, compared to their respective baseline. Applicators reported significantly more neurological symptoms relative to baseline than non-applicators at time-points during and after the pesticide application season. Cumulative TCPy level was a significant predictor for the average percentage of neurological symptoms only among the applicators.

Neurobehavioral performance showed initial learning effects and then deficits in performance for the pesticide applicators during the pesticide application season.

**Conclusions:** The longitudinal assessment of CPF biomarkers provided robust measures of exposure and effect and revealed noteworthy exposures in both applicators and non-applicators. Biomarker levels in the non-applicators, which mirrored that of the applicators, indicated that the non-applicators received environmental CPF exposures. The number of symptoms reported by both the applicators and non-applicators follow the same pattern as the urinary TCPy levels, with applicators demonstrating deficits in neurobehavioral performance during the application season. Larger, long-term studies are needed to more fully characterize the exposure and effects in adolescent applicators; furthermore, non-applicators appear to have environmental exposures that need to be addressed because of the potential public health concern.

**Diane Rohlman/USA and Gaafar Abdel Rasoul/Egypt**

*R21 ES017223 and R01 ES022163-01*

Vulnerability of the Adolescent Brain to Organophosphorus Pesticides

### **Building Research Capacity through Education and Training**

Diane S. Rohlman<sup>1, 2</sup>, Gaafar Abdel Rasoul<sup>3</sup>, Ahmed A. Ismail<sup>3</sup>, Matthew R. Bonner<sup>4</sup>, Olfat Hendy<sup>5</sup>, Lamy Hamad<sup>4</sup>, and James R. Olson<sup>4, 6</sup>

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**Introduction:** Many children throughout the world are engaged in agricultural work, either for pay or on family farms, which has the potential for exposures to pesticides. Even subtle changes in health outcomes due to pesticide exposures could result in large social and economic consequences. This project is conducting research on pesticide exposures and resulting health effects in adolescents that are hired seasonally to apply pesticides on the Egyptian cotton crop. While it is ideal to conduct this research at a local level, universities in Egypt do not have resources, training or experience to carry out comprehensive exposure assessments or to effectively evaluate subtle neurotoxic (neurobehavioral) changes. Furthermore, Egyptian researchers have little training on writing competitive applications to obtain these resources. There is a need to increase capacity at a local level and to provide training to Egyptian researchers to be competitive at a national level in order to address these important health concerns.

**Purpose:** To build and enhance the research culture at Menoufia University, Shebin El-Kom, Egypt.

**Methods:** We aim to achieve this goal through education, including lectures and seminars, skills training on analytical methods and epidemiological research design, mentoring, including onsite opportunities for training in international laboratories, and a pilot project program to create a competitive research culture within the University.

**Results:** These activities will build on the success of the previous R21 grant, which expanded the research capacity at Menoufia University through both training and education. Staff were trained and certified on both the analysis of cholinesterase (ChE) activity in blood samples and administration of the neurobehavioral test battery and a Neurobehavioral Testing Laboratory was formed. To date, these methods have been incorporated into 5 additional projects.

Furthermore, during our initial collaborations with Menoufia, we identified a need to provide training on developing fundable research ideas and writing grant applications that express those ideas effectively. A needs assessment revealed that although faculty are interested in applying for funding (93%) or training opportunities (83%), the majority are not aware of available opportunities, much less what is required to apply for these opportunities. A series of seminars and videoconferences were presented to over 120 researchers to provide an overview of grant funding.

The needs assessment also revealed a major challenge at Menoufia is the lack of institutional support for grant activities. Currently, there is no office at the University responsible for research and development, although they do have a functioning IRB (set up at our request). There is limited funding available for basic laboratory and office supplies, much less for materials needed for research. Researchers often independently fund their thesis or research projects. Furthermore, there is limited recognition for research endeavors. In order to begin to change this culture, arrangements were made with the Dean of the School of Medicine to recognize faculty who participated in the videoconferences. Certificates were awarded and a copy placed in their file. Traditionally, funding for research in Egypt is quite limited and poses significant challenges for Egyptian researchers resulting in a non-productive research culture at Menoufia University. Thus the goal of the current R01 project is to build and enhance the research culture at Menoufia.

Dr. MaryAnn Romski/UNITED STATES

Dr. Juan Bornman/SOUTH AFRICA

**Dr. MARY ANN ROMSKI**

Grant Number: 1R21TW008999

Grant Title: Speech and Language Delays in Children with Neurodevelopmental Disorders in South Africa

Speech and language skills provide a child with the ability to express wants and needs, interact socially, and gain information about the complex world in which we live. A significant impairment in the development of speech and language has far reaching consequences for a child's long-term development including education and employment. Children with neurodevelopmental disorders are at extremely high risk for speech and language disorders secondary to their primary condition. This project brings together researchers from the United States and South Africa to examine the patterns of language disorders in children with neurodevelopmental disorders in South Africa. Post-apartheid South Africa provides a unique setting for the study of this issue. It is a country where 11 national languages are immersed within a range of socio-economic contexts. This study will extend the knowledge related to speech and language delays in children with neurodevelopmental disorders from different language backgrounds. This planning grant's aim is to develop measurement tools to identify speech and language delays in children with neurodevelopmental disorders within specific language contexts so that appropriate behavioral interventions can be provided to the children.

We have developed linguistic and cultural adaptations of the *Mullen Scales of Early Learning* into four languages spoken in northern South Africa: (i.e., Afrikaans, English, Sotho, and Zulu) and have piloted the measure with a sample of typically developing children speaking each of the languages. We have collected assessment data on 80 children with neuro-developmental disorders in South Africa (20 who reside in families who speak one of the four languages). We will report on the speech and language performance of the children with neuro-developmental disorders across all the languages and describe patterns of language strengths and weaknesses in relation to language and specific etiology. Given the substantial need to develop qualified behavioral investigators in South Africa, we have also provided training for University of Pretoria staff to develop expertise about measurement and research design. Institutional partnerships between Pretoria and colleagues at hospitals and other universities have been developed to enhance participant recruitment and research training with respect to measurement design and methodology for neuro-developmental disorders.

PI: Ned Sacktor/Maria Wawer USA  
Foreign Collaborators: Ronald Galiwango, Noeline Nakasujja, Uganda

**Presenter: Ned Sacktor**

Grant Number: RO1 MH099733

Grant Title: Neurologic sequelae of HIV subtype A and D infection and antiretroviral therapy, Rakai, Uganda

Grant dates : 4/13-2/18

Prior Grant Number : R21 MH083465

Prior Grant Title: HIV dementia and sensory neuropathy in Uganda

Prior Foreign Collaborator: Noeline Nakasujja, Uganda

Prior Grant dates: 9/08-5/11

Abstract title: The Rakai HIV Neurology Cohort: A New Study to Assess HIV Subtype and Risk of Dementia in Uganda

Ned Sacktor<sup>1</sup>, Ronald Galiwango<sup>2</sup>, Richard Skolasky<sup>1</sup>, Gertrude Nakigozi<sup>2</sup>, Noeline Nakasujja<sup>3</sup>, Kevin Robertson<sup>4</sup>, Ronald Gray<sup>5</sup>, Maria J. Wawer<sup>5</sup>

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**Background:** HIV dementia was seen in 31-41% of antiretroviral (ARV) naïve HIV+ individuals in previous studies in Kampala, Uganda, but prior data are inconsistent regarding associations between HIV subtype and risk of dementia. One study suggested that HIV subtype D may be associated with an increased risk of dementia compared to subtype A in HIV+ individuals with advanced immunosuppression. However, another study (R21 MH083465) suggested that HIV subtype D and subtype A had an equal risk for dementia among HIV+ individuals with moderate immunosuppression. As a result of these prior studies, Ugandan researchers are now trained in neurological assessment, neuropsychological test administration, and clinical research methods. The Rakai Health Sciences Program in rural southwestern Uganda conducts the population-based Rakai Community Cohort Study (RCCS): HIV prevalence is 13%, with a subtype distribution of HIV-1 17% A, 70% D and 13% AD recombinants, (a more equal distribution of HIV subtypes D and A than in our prior studies). We are currently recruiting 400 RCCS participants into a new neurological cohort to evaluate the frequency and risk factors for dementia among HIV+ individuals with both moderate (CD4 350-500 cells/ $\mu$ L) and advanced (CD4 < 200 cells/ $\mu$ L) immunosuppression, and by subtype. We will also enroll a comparison group of 400 HIV negative individuals.

**Methodology:** To date, 23 ARV naïve HIV+ individuals with CD4 < 200 and 52 ARV naïve HIV+ individuals with CD4 350-500, (all with age > 20 years), received detailed neurological history, examination, neuropsychological tests (including tests of verbal memory, motor, psychomotor speed, executive function, and verbal fluency), functional assessments, CD4 count, and plasma viral load. HIV associated neurocognitive disorders (HAND) stage was determined

using Frascati criteria combining clinical, neurological, functional and neuropsychological test data and compared to HIV- normative data obtained from a prior study in Uganda.

**Results:** Recruitment began on July 12, 2013. Demographics to date include: Age [Mean(SD)]=35.4(8.7) years, Gender=54% male, CD4 count in advanced immunosuppression subgroup [Mean(SD)]=118(52) cells/ $\mu$ L, CD4 count in the moderate immunosuppression subgroup [Mean(SD)]=412(41) cells/ $\mu$ L. 74% of those HIV+ individuals with advanced immunosuppression had HAND. Advanced age ( $p=0.003$ ) and low education ( $p=0.004$ ) were risk factors for symptomatic HAND (mild neurocognitive disorder and dementia).

**Conclusion:** In ART naïve HIV+ individuals in rural Uganda, HAND and HIV dementia are common. Future studies will evaluate the association of HIV subtype and dementia (and neuropathy), and response to antiretroviral treatment.

**PI name/ PI Country:** Apinun Aramrattana, Thailand

**PI name and country:** Napapon Sailasuta (Contact), USA

**Major foreign collaborator name/ Foreign Collaborating**

**Country:** Huntington Medical Research Institute, USA, Chiang Mai University, Thailand and Westat, USA.

**Author and Presenter name in Bold:** Napapon Sailasuta, **Apinun Aramrattana**, Suwit Seakho, and Mekkla Thompson

**Grant number:** 1R21DA033024-01A1

**Grant title:** A Chiang Mai University – HMRI MRI/MRS project: A neurobiology study of methamphetamine abuse and HIV infection in Thai adults

**Abstract:**

The methamphetamine (MA) epidemic in Thailand, in particular in the northern part of the country, Chiang Mai, remains a major problem despite aggressive prevention efforts by local authorities. Low cost, availability and longer drug action are major reasons for using the drug among surveyed Thai methamphetamine users. On top of the widespread methamphetamine tablets (around 20% each tablet), methamphetamine crystal of more than 90% purity has been sharply increasing. The drug treatment system has not been able to effectively respond to the epidemic. High prevalence of depression, psychoses and sexually transmitted infections, including HIV, among MA users were reported in Chiang Mai. About 9% of MA psychotic patients in Chiang Mai died within 5 years from suicide, accidents and AIDS. Damage to several parts of the brain has been demonstrated in both HIV patients and MA abusers. The extent and gravity of health problems among younger Thai adults has increased the demand for reliable means to reduce the epidemic and to effectively guide and evaluate prevention/treatment programs.

This project was made possible because of the availability of state-of-the-art MR technology through its newly installed 1.5T Philips MR scanner at the Department of Radiological Technology, Chiang Mai University, Thailand and the mission of advancing and expanding local expertise in MRI/MRS technology. MRS and MRI are two non-invasive complementing approaches for studying the dysfunction in the brain CNS. Lack of local knowledge of these methods in clinical research setting is proving to be a major barrier for the current interest in clinical research in HIV/AIDS and drug abuse. The overarching goal of this exploratory phase is to take advantage of the newly installed magnetic resonance imaging scanner at the CMU to build clinical research capacity suitable for conducting research focusing on CNS dysfunction and neuro-development in drug abusers with HIV infection in Northern Thailand. Understanding the impact of HIV and MA use on the brain central nervous system (CNS) may lead to new approaches in the effort to reduce HIV infection and effective treatment of drug addiction. We will focus on magnetic resonance imaging and spectroscopy technology as our primary research tools. The specific aims of this project are 1) to build local expertise in MR technology suitable for long term clinical research by conducting training and mentoring of local MR physicists, healthcare professionals and technicians in Northern Thailand;. 2) to generate preliminary MRI and MRS data in HIV-infected, MA users and MA users who also HIV-infected population **and then moving on to the next step** which is studying a much larger subject population **and apply for R01 grant**. We will collect normative brain MRI and MRS data along with a small number of subjects who are HIV infected, methamphetamine abusers, and MA subjects with HIV-infection.

Results from this project may lead to new approaches in the effort to reduce HIV infection and drug abuse worldwide.

**PI Name/ PI Country:** Napapon Sailasuta (Contact), USA, Apinun Aramrattana, Thailand

**Major Foreign Collaborator Name/ Foreign Collaborating Country:** Huntington Medical Research Institute(HMRI), USA, Chiang Mai University, Thailand and Westat, USA.

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**Grant number:** 1R21DA033024-01A1

**Grant title:** A Chiang Mai University – HMRI MRI/MRS project: A neurobiology study of methamphetamine abuse and HIV infection in Thai adults

**Abstract: Co-morbidity of Methamphetamine Abuse and HIV infection in Thai Adolescents:**

#### **A MRI/MRS Clinical study**

Methamphetamine (MA) abuse is a major health issue worldwide including in Thailand. Despite aggressive efforts by the local governments, MA usage among Thai adolescent remains high. The 2009 seizure record for Thailand showed 86% of amphetamine type stimulant (ATS) related offences arrested are MA-related offenses. In northern Thailand, high purity MA is readily available in the crystalline form (more than 90% pure), whereas the pill form is approximately 25% pure. The recent trend of high purity MA being produced and sold on the streets in Chiang Mai, the second largest city in Thailand, has created an urgent situation for health professionals to provide means of reducing the epidemic. In the Thai society, comorbidity of Ya-ba (another form of methamphetamine) usage and HIV infection is also significant among Thai adolescents.

Cerebral injury from MA use and HIV infection are well established. Frontal, or the executive brain functions, are most affected in MA abusers with development neurological conditions of inability to attend and concentrate slowness in thinking and moving. HIV infection, on the other hand, is thought to be indirect process due as neurons are not infected by the virus. Cells including brain microphages, microglia is infected and a reactive astrocytosis is often present. Little is known of the cerebral injury in MA use and HIV infection comorbidity.

Our main aim of this study is to determine the extent of cerebral injury in MA abusers who are also HIV infected among Thai adolescents. We use magnetic resonance imaging to determine changes in brain volume (MRI), white matter integrity (DTI) and single voxel proton MRS. We will recruit 15 healthy volunteers, 15 HIV seropositive patients with no history of MA use, 15 MA users with no HIV infection and 15 MA users who are HIV infected during the next 15 months. In this cross-sectional study, each participant will undergo MRI/MRS scans and neuropsychological evaluation. **We will present preliminary results of gray-white matter volume and single voxel proton MRS from white and gray matter in MA users.**

**PI name/ PI Country:** Apinun Aramrattana, Thailand; Napapon Sailasuta (Contact), USA  
**Major Foreign Collaborator Name/ Foreign Collaborating Country:** Huntington Medical Research Institute, USA, Chiang Mai University, Thailand and Westat, USA.

**Author and Presenter (name in bold):** **Apinun Aramrattana**<sup>1</sup>, Kanok Uttawichai<sup>2</sup>, Suwit Seakho<sup>3</sup>, Napapon Sailasuta<sup>4</sup>, Mekkla Thompson<sup>5</sup>, Bangorn Sirirojn<sup>1</sup> and Daralak Tavornprasit<sup>1</sup>

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**Grant number:** 1R21DA033024-01A1

**Grant title:** A Chiang Mai University – HMRI MRI/MRS project: A neurobiology study of methamphetamine abuse and HIV infection in Thai adults

**Abstract: Increase of methamphetamine use and its comorbidity in Thailand.**

Amphetamine-type stimulants (ATS) are the world's second most widely used drugs and methamphetamine is the most common. In 2012, reported use of methamphetamine increased in Cambodia, China, Japan, Lao PDR, Myanmar, the Republic of Korea, Thailand and Viet Nam, according to experts in those countries. Methamphetamine pill use continues to rise while crystalline methamphetamine use has rapidly become more prevalent throughout the region. The methamphetamine (MA) epidemic in Thailand, in particular in the northern part of the country (Chiang Mai) remains a major problem despite aggressive prevention efforts by local authorities. Low cost, availability and longer drug action are major reasons for using the drug among surveyed Thai methamphetamine users. On top of the widespread methamphetamine tablets (around 20% each tablet), methamphetamine crystal of more than 90% purity has been sharply increasing. The drug treatment system has not been able to effectively respond to the epidemics. Methamphetamine use related to works is found among sex workers, truck drivers, farmers, factory shifted-workers and students. Young users use them for socialization, entertainment and sexual purposes. Sexual risk behaviors including multiple sex partners, unwanted pregnancy and sexually transmitted infection are common among methamphetamine users. Methamphetamine psychoses, alcohol dependence and depression as well as involvement with drug sale and incarceration are not uncommon. Methamphetamine injection is also increasing. A long-term study among 1,116 methamphetamine psychotic patients in Thailand reported about 92 (8.2%) deaths during 2001-2007. Main causes of death (64%) were suicide, HIV/AIDS and accidents. Damage to several parts of the brain has been demonstrated in both HIV patients and MA abusers. The extent and gravity of health problems among younger Thai adults has increased the demand for reliable means to reduce the epidemic and to effectively guide and evaluate prevention/treatment programs.

Urgent investigations on the methamphetamine effects to the brain and its interaction with HIV infection among methamphetamine dependence are needed for guiding possible early interventions among these populations. Therefore, the aims of this R21 pilot clinical translational research project using MRI and MRS approaches are: 1). characterize neuronal abnormalities in Thai adolescents MA abusers, 2). determine the extent of HIV co-infection to the neuronal dysfunction, and 3). correlate the MRI/MRS results with neuropsychological evaluation.

**PI name, institute and country:** Sathiakumar, Nalini, University of Alabama at Birmingham, United States

**MFC name, institute and country:** Dr. Rajitha Wickremesinghe, University of Kelaniya at Sri Lanka

**Presenter name in BOLD:** Sumal Nandasena, MD

**Grant number:** 5R21ES018730-02

**Grant title:** Prenatal Exposure to Solid Fuel Smoke and Infant Neurodevelopment

#### **ABSTRACT.**

**Background:** Household air pollution (HAP) from combustion of solid fuels used for cooking and heating is the third leading contributor to the global burden of disease causing over 3.5 million deaths and the loss of 4.3% of Disability-Adjusted Life Years. The evidence that HAP causes acute lower respiratory infections in children and chronic obstructive pulmonary disease or chronic bronchitis in women is compelling, while evidence of effects on adverse pregnancy outcomes, low birth weight and infant neurodevelopment is limited.

**Objective:** To investigate the association between prenatal exposure to HAP and birth outcomes including neurodevelopment at birth and at six months.

**Methods:** Using a longitudinal study design, 719 pregnant mothers in their first trimester were recruited from the Ragama Ministry of Health area, in the Gampaha district of Sri Lanka; 39 of these mothers moved from the study area. Mothers were followed until delivery, and their babies were followed until six months of age. Exposure to HAP was assessed based on information from detailed HAP-related questionnaire for all subjects and on area PM<sub>2.5</sub> and CO measurements conducted during each trimester of pregnancy in two-thirds of total households (n=380). Information on covariates such as maternal socio-demographic characteristics, body mass index, diet, medical history, and lead exposure were ascertained using questionnaire and from laboratory investigations. Outcomes assessed included birth weight, length, head circumference and neurodevelopment; the latter was assessed at birth and at six months using the Brazelton Neonatal Behavioral Assessment Scale and Bayley-III Scales of Infant Development, respectively.

**Preliminary Results:** Of 719 mothers recruited, 386 (54%) use solid fuel and 333 (46%) use liquid petroleum gas or kerosene. To date, PM<sub>2.5</sub> and CO measurements have been completed in 150 households. Among solid fuel users, the mean PM<sub>2.5</sub> levels is 545 µg/m<sup>3</sup> (range, 27 µg/m<sup>3</sup>-7220 µg/m<sup>3</sup>) which is four times higher than those using clean fuels (mean, 130 µg/m<sup>3</sup>; range, 18 µg/m<sup>3</sup>-1310 µg/m<sup>3</sup>). Currently, 521 children have been delivered with male to female ratio 1:1; 478 are full term while 43 are pre-term. Neurodevelopment assessments have been completed in 454 babies at birth and for 373 at six months. Other adverse pregnancy outcomes include miscarriages (n=46), still births (n=2) and intrauterine death (n=1).

## **Cord blood lead levels and environmental lead sources: A study from an urban center in Pakistan**

**PI:** Nalini Sathiakumar, MD, DrPH, School of Public Health, University of Alabama at Birmingham, USA

**MFC:** Muhammad Masood Kadir, MD, Aga Khan University, Karachi, Pakistan

**Presenter name in BOLD: Meghan Tipre, BDS, MSPH**

**Grant number:** 5 R21 ES017226-02

**Grant title:** Prenatal Exposure to Lead- A prelude to Intervention

### **ABSTRACT**

**Background:** Lead toxicity remains a major environmental health risk. Pakistan and South Asian countries consider phasing-out of leaded gasoline as an adequate measure for control of lead. However, lead deposited in environmental media and maternal bone continues to expose fetuses and children.

**Objectives:** (1) to estimate mean umbilical cord blood lead levels and the proportion of newborns with high cord blood lead levels ( $>10\mu\text{dl}$ ); (2) to determine sources and levels of environmental lead exposure in children's homes and surroundings; (3) to identify major determinants of umbilical cord blood lead level (BLL) including environmental sources and maternal determinants.

**Methods:** We interviewed 461 mothers presenting for delivery at the study hospitals and collected their blood for assessing BLLs, serum ferritin and hemoglobin; we also collected umbilical cord blood for lead levels in the newborns. Lead in the environment was measured in mothers' homes and surrounding environment including playground, soil around the homes using a Niton lead analyzer. Information on covariates including socio-demographic factors, maternal education, diet, BMI and past medical history was assessed using a questionnaire.

**Preliminary Results:** The mean age of mothers enrolled in the study was 26 years (SD 3.96); 49.5% children delivered were male. The mean cord BLL was  $15.9\ \mu\text{gm/dl}$  (SD, 8.1) and mothers' mean BLL was  $26.1\ \mu\text{gm/dl}$  (SD, 3.9). About 75% of newborns ( $n=346$ ) and 90% of mothers ( $n=414$ ) had lead levels more than  $10\ \mu\text{gm/dl}$ ; 77 newborns and 31 mothers had lead levels between 5-10  $\mu\text{gm/dl}$  and 31 newborns and 5 mothers had lead levels less than equal to  $5\ \mu\text{gm/dl}$ . With regard to environmental sources of lead in homes, high lead levels were found in cooking utensils (mean, 6555.5 parts per million (ppm); SD, 14423.7) and surma, a traditional eye cosmetic (mean, 316726.72 ppm; SD, 57050).

**Conclusion:** This study shows that high lead levels are still present in most newborns and mothers. It provides a better understanding of the sources of lead in household environments. Results of the study provide basis for which to inform issues of lead abatement and environmental risk reduction in Pakistan and other countries in the region.

Spinoffs from BRAIN Research grants – A Cascade Effect on Research and Training in Sri Lanka, Pakistan and India

PI: Sathiakumar N.

**Presenter name in BOLD: Meghan Tipre, BDS, MSPH**

**Grant number: 5R21ES018730-02, 5 R21 ES017226-02**

### **Abstract**

Beginning in 2001, the National Institutes of Health-Fogarty International Center-sponsored University of Alabama at Birmingham (UAB)-International Training and Research in Environmental and Occupational Health (ITREOH) has focused on capacity building in environmental and occupational health (EOH) in the Indian sub-continent. In the first five-year cycle, the UAB-ITREOH program working with the Aga Khan University concentrated on building EOH capacity in Pakistan. In the second five-year cycle, beginning in 2006, the UAB-ITREOH expanded to include the University of Kelaniya (UKe) in Sri Lanka and Manipal University (MU) in India. The UAB-ITREOH has been instrumental in promoting the prominence of EOH in partner countries by EOH-related pioneer research and training. Funds from Fogarty have supported the development of in-country MPH programs; and trainee research projects. The latter has provided the foundation to successfully apply for BRAIN grants, one in Pakistan and the other in Sri Lanka. The two R21 BRAIN grants have in turn provided a training base for in-country MPH students and medical graduates in their early careers. A total of 12 medical interns and/or MPH students have worked as research assistants on these projects and were trained in data collection procedures including the conduct of surveys, air quality measurements and the use of the Niton lead analyzer. In addition, a medical student from UAB worked on the field in Sri Lanka to gain hands-on experience by assisting with the development of a monitoring tool for the project. Besides the training benefits, the BRAIN grants have spurred the development and submission of competitive research grants to expand the R21s or to incorporate innovative ancillary components. In sum, the BRAIN grants coupled with the ITREOH program have been instrumental in building in-country research training capacity in scientific excellence and to conduct pioneer research that addresses global research gaps with the ultimate aim of evidence-based science that has the potential to shape national policies.

**Title:** Overview of Environmental Exposure Estimation Strategies - A Snapshot of the UAB-South Asia Experience

**By Dr. Nalini Sathiakumar, MD, DrPH**

**(Presenters: Dr. Sumal Nandasena, MD and Meghan Tipre, BDS, MSPH)**

According to the recent report by the World Health Organization, five leading environmental exposures including household air pollution (HAP) from solid fuels (wood, crop residue, animal dung and coal) and lead account for nearly 10% of deaths and disease burden globally, and about 25% of deaths and disease burden in children under 5 years of age. HAP is the third leading contributor to the global burden of disease. Lead, an established neurotoxin, remains a major public health problem particularly in developing countries. Accurate estimation of exposure from environmental risk factors is a critical component of epidemiological studies examining the association between these factors and adverse health effects. Increasing evidence from epidemiologic studies conducted in developing countries elucidate the complexity and heterogeneity of environmental exposure patterns. Attempts to characterize personal exposure, both acute and cumulative, are often limited by financial and logistical constraints imposed by settings in developing countries.

Under the umbrella of the Fogarty-funded International Training and Research in Environmental and Occupational Health and the Global Research Initiative Programs, and the National Institutes of Environmental Health Sciences-funded BRAIN program, investigators at the University of Alabama at Birmingham (UAB) in collaboration with investigators from the University of Kelaniya in Sri Lanka, the Aga Khan University in Pakistan and the Manipal University in India, have conducted 14 studies evaluating the association between environmental exposures (HAP, lead and methyl mercury), and a range of health outcomes (birth outcomes, infant and child neurodevelopment, acute respiratory infections in children, acute coronary syndrome and diabetes). In these studies, we have used HAP exposure assessment methods that range from crude qualitative methods such as information from national demographic health surveys on fuel and stove use, to quantitative exposure assessments such as measurements of specific air pollutants (e.g., particulate matter of size 2.5 $\mu$ m and 1 $\mu$ m, black carbon and carbon monoxide) and the use of biomarkers such as methoxyphenols for woodsmoke and urinary 1-Hydroxypyrene for polycyclic aromatic hydrocarbons. In the above assessments, we used an integrated exposure assessment approach that included the identification of microenvironments and the use of time-activity patterns for each study participant. Our studies on lead included the assessment of environmental lead using questionnaires, biomarkers (maternal and cord blood lead levels) and the use of Niton Analyzer for environmental sources of lead. In our studies examining methyl mercury exposure, we used questionnaires and biomarkers (maternal and newborn hair). Using examples from the above studies conducted in Sri Lanka, Pakistan and India, we will discuss the challenges in conducting quantitative exposure assessments and solutions to address them.

## **Volumetric Brain Analysis for Hydrocephalus and Epilepsy in the Developing World**

PI names: Abhaya V. Kulkarni, Steven J. Schiff, and Benjamin C. Warf / Uganda

Major foreign collaborator name/ Dr John Mugamba / Uganda

Presenter name: **Steven J. Schiff**

Grant number: 1R21TW009612-01A1

Grant title: Neurocognitive outcomes and changes in brain and CSF volume after treatment of post infectious hydrocephalus in Ugandan infants by shunting or ETV/CPC

Brain image analysis in the developing world is largely limited to CT, as the expense of MRI scanning renders it largely inaccessible to the vast majority of people living in developing countries. We wished to develop a flexible, automated strategy for improving brain diagnostics and treatment in developing countries for both hydrocephalus and epilepsy.

We invented a novel technology that employed a particle filter to follow the boundary of the brain in the manner often used in autonomous robotic air and ground vehicle navigation. Our goal was to create a versatile tool to segment brain and fluid in MRI and CT images of the developing brain, lay the foundation for an intelligent automated edge tracker that is modality independent, and segment normative data from MRI that can be applied to both MRI and CT. Segmentation with varied levels of noise (0-9%) and spatial inhomogeneity (0-40%) resulted in percent error ranging from 0.06% to 5.38% for brain volume and 2.45% to 22.3% for fluid volume. We applied this method to the NIH Pediatric MRI database to develop the first human growth curves for brain and cerebrospinal fluid (Mandel et al 2014a).

In all countries in the world, the evaluation of hydrocephalus remains focused on ventricular size, which is directly related to CSF volume, yet the goal of treatment is to allow for healthy brain development, which is dependent on brain volume. Brain and CSF volumes were measured in 33 infants with myelomeningocele treated at the CURE Children's Hospital of Uganda (CCHU), 26 of whom required surgical treatment for hydrocephalus. Linear discrimination analysis (LDA) was used to test if age-normalized brain and fluid volumes can discriminate neurocognitive outcome. Brain volume alone, unlike fluid volume, could discriminate high from low cognitive outcome. It was further shown that a combination of age normalized brain and fluid volumes can discriminate neurocognitive outcome by 2-way LDA ( $p < 0.01$ ) and 3-way LDA ( $p < 0.01$ ). The multivariate LDA demonstrated the secondary contribution of large fluid volume to a decrement in cognition. This strategy offers a way to predictively manage such patients by tracking brain growth rates to optimize neurocognitive development (Mandel et al 2014b).

Lastly, the incidence of temporal lobe epilepsy (TLE) due to mesial temporal sclerosis (MTS) can be high in developing countries. Current diagnosis of MTS relies on structural MRI, which is generally unavailable in developing world settings. Given widespread effects on temporal lobe structure beyond hippocampal atrophy in TLE, we proposed that CT volumetric analysis can be used in patient selection to help predict outcomes following resection. Temporal lobe and whole-brain volumes in 10 epilepsy surgical patients treated at CCHU were measured from CT and contrasted with from normative temporal lobe growth curves. A multivariate measure of the

volume of each temporal lobe separated patients that were seizure-free (Engel IA) from those with incomplete seizure control (Engel IB/IIB) with LDA ( $p < 0.01$ ). Additionally, we demonstrated that age-normalized whole brain volume, in combination with temporal lobe volumes, may further improve outcome prediction ( $p < 0.01$ ). This provides strong evidence that temporal lobe and brain volume can be predictive of seizure outcome following temporal lobe resection, and that volumetric CT analysis of the temporal lobe may be feasible in lieu of structural MRI when the latter is unavailable (Mandel et al 2014c).

Our volumetric methodology has the capability to allow CT to be a more effective diagnostic tool for neurological disorders, a task of substantial importance in developing countries where CT is often the only available method of brain imaging. We are refining our volumetric algorithms to become an automated clinical rather than a research tool, and are training our colleagues in Africa to be able to perform such analysis themselves. We are archiving all of our methodology as open source algorithms with the publication of our papers on these findings.

Jeremy M. Silverman, Ph.D. / United States  
Henriette Raventos, M.D. / COSTA RICA

**Jeremy M. Silverman**

R21TW009258

Successful Cognitive Aging and Cardiovascular Risk Factors in the Central Valley of Costa Rica

For samples primarily under 75 years of age, some cardiovascular risk factors (CVRFs) have been associated with increased risk of cognitive decline, dementia, and Alzheimer's disease (AD). Although frequently interpreted as applying generally to *all* elderly, findings from our group and others suggest that such associations are greatly diminished or even reversed in more elderly samples. If, as these results suggest, the effects of some CVRFs do not reflect **stable cardiovascular risk**, but rather change as the population ages, they may reflect enduring traits possessed by some **protected survivors**. If protection refers to lower mortality as well as preserved cognitive function, the proportion of protected survivors increases as the population ages.

Our project aims to determine the applicability of these models of successful cognitive aging (SCA; living at least 90 years free of cognitive impairment) to the relationships of cardiovascular risk factors (CVRFs) with neuropsychological phenotypes. We are examining the effects of CVRFs on neuropsychological phenotypes by comparing proband and relative groups highlighted by the respective SCA model. We are currently recruiting the very elderly (age 90+ years) nondemented (VEND) probands and their offspring (O-VEND). We are also recruiting offspring of very elderly demented probands (O-VED). Subjects are being characterized for CVRFs (cholesterol, C-reactive protein, hemoglobin-A1c, blood pressure, and apolipoprotein E genotype) as well as assessed on a battery of neuropsychological tests.

The project is being performed in the Central Valley of Costa Rica (CVCR), which has high life expectancy and reduced genetic and cultural heterogeneity. Thus, differences observed between groups will tend to be less vulnerable to confounding based on cultural/environmental differences. To date, representing about one year of recruitment, we have enrolled and studied 169 subjects: 23 VENDs, 100 O-VENDs, and 46 O-VEDs. At the same time, we are building research capacity in Costa Rica upon an already existing infrastructure. We are training the experienced and dedicated Costa Rican investigators on this research team, so they can perform independent studies of SCA and aging in the CVCR based on data from this R21 and other collaborations.

Utilizing nonagenarian probands from our R21 project as well as an earlier CVCR sample, we recently examined the association of APOE-e4 with dementia in 75 VENDs and 37 VEDs. In contrast to an independently collected younger CVCR case-control sample (AD cases = 54, controls = 49; odds ratio = 6.30, 95% confidence interval [CI]=2.04, 19.50;  $p < 0.0005$ ), the association of dementia and APOE-e4 was less strong and not significant (OR=2.43, 95% CI=0.81, 7.32,  $p=0.12$ ). Furthermore, we found that increasing age was associated with a reduction in the association between APOE-e4 and dementia ( $p=0.03$ ). Dividing the nonagenarian sample at age 95 showed a group interaction ( $p=0.04$ ): APOE-e4 was more associated with dementia below 95 ( $p=0.054$ ) than above 95 ( $p=0.55$ ), in which all four APOE-

e4 carriers were VENDs. The results support the reduction in association of APOE-e4 with dementia as age increases, consistent with a protected survivor model for successful cognitive aging.

## **A randomized surgical trial in Uganda: early lessons learned**

PI names: Abhaya V. Kulkarni, Steven J. Schiff, and **Benjamin C. Warf / Uganda**

Major foreign collaborator name/country: Dr John Mugamba / Uganda

Presenter name: **Abhaya V. Kulkarni**

Grant number: 1R21TW009612-01A1

Grant title: Neurocognitive outcomes and changes in brain and CSF volume after treatment of post infectious hydrocephalus in Ugandan infants by shunting or ETV/CPC

Randomized trials of surgical interventions are fundamentally challenging, but added challenges can present themselves when conducting such trials in sub-Saharan Africa. Our group has developed a randomized trial to compare two surgical treatments for post-infectious hydrocephalus in infants treated at CURE Children's Hospital in Mbale, Uganda: cerebrospinal fluid shunt ("shunt") and endoscopic third ventriculostomy with choroid plexus cauterization ("ETV+CPC"). A novel component of this study was the use of neurocognitive outcome as the primary outcome, as measured by the Bayley Score of Infant Development (BSID-3).

Having completed the design and set-up for the trial and, now, having begun recruitment, we have identified the following anticipated and unanticipated challenges:

- **Developing local expertise in administrating and scoring the BSID-3:** The BSID is a learned skill and a fairly complicated test. In order to develop local expertise with minimal cost and time, experts in Toronto trained individuals in Mbale using remote technology. The trainees watched standardized training videos and then practiced administering the BSID on healthy children volunteers, while observing each other. Specific questions were then answered by the Toronto experts. The trainees then administered the BSID to infants, while being videotaped. The videotape was reviewed by the Toronto expert, who independently scored the session. The trainees and the expert then reviewed the session on Skype. Further issues to be fully resolved include integrating more culturally-appropriate content to the testing.
- **Language & illiteracy:** Illiteracy levels among families are high, so to aid understanding, explanations about the child's condition are carried out using pictorial aids, drawing pictures and simple illustrations since most do not understand the detailed medical language. For example, the 'Dripping tap into a blocked sink' helps explain hydrocephalus. In addition, language barrier was an anticipated challenge. With 15 major languages spoken in Eastern Uganda, we have had to translate the original English consent form into 10 major local languages.
- **Disease spectrum:** The severity of the disease and co-morbidities like malnutrition, was more extensive than anticipated. This has made us revisit our eligibility criteria.
- **Local knowledge deficit:** A knowledge deficit in clinical trial methodology among the hospital staff remains. An on-going challenge will be to build more local capacity in clinical research and data analysis so that there is continuity of future research and to encourage ingenuity. This is viewed as a longer-term goal, integral to the project as a whole.

PI: Dan J. Stein

PI Country: South Africa

Major foreign collaborator: Kerry J. Ressler

Foreign collaborating country: United States

**Presenter name: Nastassja Koen**

Grant number: NIMH 1R21MH098662-01

**Grant title: Genetic and trauma-related risk factors for PTSD and depression in South Africa**

***What is the significance of the research being conducted?*** Post-traumatic stress disorder (PTSD) is a debilitating stress-related psychiatric disorder affecting vulnerable individuals after traumatic exposure. Despite the high national trauma prevalence, studies such as the South African Stress & Health Study have found that only 2.3% of South Africans suffer from PTSD in their lifetimes. However, the rate of sub-syndromal and co-morbid PTSD is likely higher. In particular, PTSD and depression have been shown to be highly co-morbid. Given that the etiology of PTSD is not fully understood, there is a pressing need for research elucidating risk/resilience factors. Our study aims to address the gap by examining the role of key candidate vulnerability genes, and their interaction with environments, in predicting PTSD in a South African community setting. The findings of this research could potentially help to predict those who are at greater risk. Furthermore, by controlling for co-morbid depression, we may enhance the current understanding of the psychobiology of PTSD and point towards novel treatment targets.

***How is the research advancing the field?*** Various studies, predominantly in the developed world, have sought to delineate genetic or environmental risk factors associated with PTSD. However, few studies have examined specifically the role of gene x environment (G x E) interactions in PTSD, and there is a further paucity of data from low- to middle-income countries (LMICs). Our study constitutes the first African G x E project. Our approach is also novel in evaluating PTSD and co-morbid depression in a previously unstudied and highly traumatised (African) population with unique genetic ancestry and patterns of stressors. Candidate gene studies to date have been inconclusive and limited by extremely low power to detect any but the strongest genetic effects (most sample sizes are <100). Thus, our study also presents an opportunity to expand significantly on current candidate gene data with a more ambitious sample size (n = 500) and to provide a novel adjunct to existing work on G x E interactions. Ultimately, an increased understanding of the neural circuitry of fear dysregulation, and continued identification of genetic pathways contributing to PTSD and depression, could lead ultimately to improved neurobiological knowledge and management of these disorders.

***Describe efforts to build research capacity.*** We are undertaking capacity building in both phenotyping and genotyping. One key aim is to enhance the ability for complex G x E interaction analyses. Although a South African infrastructure for neurogenetics research is available, further work is needed before this is internationally competitive. Our LMIC research team includes a number of early-career investigators, all of whom are benefiting from collaboration with HIC partners. We hope to enhance our LMIC research capacity via a neurogenetics research training program conducted in the USA (under the mentorship of Dr K.

Ressler), including basic genotyping, epidemiological application and translational methods. We also have regular teleconferences between sites. Furthermore, we have built into our budget travel support for visits between South Africa and USA to co-ordinate training and research activities; to monitor for potential barriers to implementation; and to develop alternative research strategies as needed.

***What barriers have been encountered in conducting the research?*** Our screening data of trauma exposure and PTSD/depression symptomatology are participant self-reported. Thus, potential barriers to disclosure include unintentional under-reporting (eg. lack of understanding of the questionnaires) and intentional under-reporting (eg. reluctance to discuss personal issues with study staff). We have addressed these barriers by providing a private, confidential and supportive environment to encourage honest communication. Further, we allow participants not to answer certain questions and still remain in the study, as long as diagnostic status can reasonably be determined. This study is also nested within a larger birth cohort investigation in which participants are followed longitudinally. Thus, we have had to manage participant fatigue and drop-out with sample attrition. To this end, we provide reimbursement for time, effort and transport to participants; and strive to ensure their comfort during assessments. They may take breaks, if requested, to lighten the interview burden; and sessions are terminated if participants become particularly distressed by any aspect of study activity.

***Describe the sustainability of the research beyond the current grant.*** Our study will comprise genotype-based hypotheses examining the contribution of specific candidate genetic polymorphisms to PTSD/co-morbid depression. At completion, we shall, however, have sufficient DNA stored for future array-based or sequencing-based discovery or cohort-replication approaches as this application develops into an R01 submission. In collaboration with Dr. Ressler's group, which is performing a genome wide association study of 8000 primarily traumatized African-Americans using the Illumina Omni 1M chip, we shall be optimally positioned to perform replication studies in an all-African cohort. We also ask permission for participant follow-up in order to initiate a longitudinal program focussing on the development and course of PTSD/co-morbid depression in highly traumatized subjects. Thus, with this grant, we aim to develop the initial genomic infrastructure and database to support a phenotype/DNA cohort for future, more well-powered studies, which may be conducted as technology improves and costs diminish.

## **Role of CXCL10 in severe malaria immunopathogenesis**

PI Name: Jonathan Stiles/ USA,

Foreign collaborator name: Neeru Singh/ India

**Presenter: Jonathan K. Stiles Ph.D.**

Grant number: NIH/FIC/NINDS R21TW006804-01

Grant title: Cerebral Malaria Associated Neurological Disorders in India

### **Abstract**

*Plasmodium falciparum* infection can cause a diffuse encephalopathy known as cerebral malaria (CM) in 2% of malaria patients. Despite availability of anti-malaria treatments, CM-associated mortalities remain as high as 30% while 25% of survivors experience neurological complications. Accumulating evidence suggest that susceptibility to fatal CM may be due to host genetic factors. Our previous studies indicated that a subset of patients who died from CM had high plasma levels of CXCL10 compared to patients who survived CM after treatment suggesting that CXCL10 may play an important role in severity of CM. However, the direct effects of increased CXCL10 production on brain cells and genetic variation in CXCL10 gene in CM pathogenesis is unknown. In this study, the role of CXCL10 in severe malaria pathogenesis was determined. Apoptotic effects of CXCL10 on human brain microvascular endothelial cells (HBVECs) and neuroglia cells in vitro were assessed. Genetic variants of CXCL10 was investigated by screening single nucleotide polymorphisms (SNPs) in CXCL10 gene to determine their role in prognosis of CM patients among 66 CM and 69 non-CM Indian patients. Finally, the hypothesis that pharmacologically inhibiting CXCL10 during CM pathogenesis will increase survival and reduce mortality was tested. Atorvastatin, a synthetic blood cholesterol-lowering drug that specifically targets and reduces plasma CXCL10 levels in humans was used to determine its effects alone and in combination with artemether on murine experimental CM (ECM) outcome. The effect of atorvastatin treatment on immune determinants of severity, survival, and parasitemia in ECM mice receiving a combination therapy from onset of murine ECM (day 6 through 9 post-infection) was assessed and results compared with controls. The results indicate that CXCL10 induces caspase-mediated apoptosis in HBVECs and neuroglia in a dose-dependent manner. It was also determined that polymorphism -1447A>G, located in the 1.8 kb promoter region of CXCL10 was associated with susceptibility to CM (odds ratio = 2.60, P = 0.021). Overexpression of CXCL10 was observed in individuals with -1447A>G polymorphism. Treatment of ECM in mice with atorvastatin significantly reduced systemic and brain inflammation by reducing levels of CXCL10. Treatment with a combination of atorvastatin and artemether in murine ECM improved survival (100%) when compared with treatment with artemether monotherapy (70%), p<0.05. This suggest that increased level of CXCL10 in CM patients may lead to neuropathogenesis and brain injury associated with CM. Furthermore, regulatory polymorphism -1447A>G in the promoter region of CXCL10 could contribute to susceptibility of individuals to severe CM. Finally, adjunctively reducing CXCL10 levels during anti-malarial therapy may represent a novel approach to treating CM patients.

## **Chemokines in Zambian children with Cerebral Malaria**

**Monique Stins\*, David Sullivan\*\*, Carlos Pardo\* and James Chipeta #**

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Cerebral malaria (CM) is a clinical syndrome associated with *Plasmodium falciparum* infection that is associated with a high mortality of up to 30%, particular in children. Neurological symptoms and signs include impaired consciousness, coma, delirium, seizures, and increased intracranial hypertension. It has recently become apparent that in African children, persistent neurologic deficits, including recurrent seizures and learning disabilities occur after survival of CM episodes.

Central to *P. falciparum* pathophysiology is sequestration of trophozoite and schizont stages of *P. falciparum*-infected red blood cells (PRBC) to the brain blood vessel endothelium. *Plasmodium* differs from other neuropathogens that invade the brain as PRBC do NOT cross the blood-brain barrier (BBB) into the central nervous system, but are still able to elicit neuronal dysfunction, as observed in *P. falciparum* CM.

It is not known how a parasite, inside an erythrocyte and confined to the blood vessels, is able to induce the neurological signs and symptoms associated with CM. Since the BBB endothelium is located at the interface of these events, we hypothesize that activation of BBB endothelium plays a role in conferring neurological dysfunction. Our published and preliminary data with an *in vitro* human BBB model show that in CM, the BBB endothelium responds with increased transcription and release of large amounts of cyto- and chemokines towards the brain side and that this that may be responsible and/or contribute significantly to the observed neurological dysfunction in CM.

To verify and validate these *in vitro* findings for the human situation and to assess whether the BBB endothelium would be an appropriate target for adjunctive therapeutic treatment and to prevent neurologic sequelae, we initiated a collaboration with the University Hospital of Zambia, Lusaka, Zambia.

This research is part of an initial research and capacity building program and funded by the Fogarty Program “Brain Disorders in the Developing World: Research across the lifespan”.

We will initially assess a specific cyto-chemokine profile in the CSF of CM patients. This program will set the basis for an extended future collaboration that will focus on the role of chemokines in CM-mediated neurological dysfunction, how this affects a patient’s life and development. Our long term goal is to prevent the neurologic sequelae in brain diseases such as cerebral malaria.

**Leonardo Trasande/USA**

**Felipe Lozano/Mexico**

**R21ES018723**

**Grant Title: Building Capacity for Studies of Prenatal Methylmercury Exposure in Mexico**

Abstract

**Prioritizing Early Life Environmental Neurotoxic Risks in a Rural Mexican Population**  
Economic transformation in Mexico has led to a doubling in the use of pesticides between 2000 and 2009, and in increased releases of heavy metals into the environment. Since 2010, NYU School of Medicine, the Instituto Nacional de Salud Publica and the Universidad de Guadalajara have built capacity for studies of prenatal exposure to environmental neurotoxins, while collaborating in study of prenatal methylmercury (MeHg) exposure a subsistence fishing community near the largest lake in Mexico (R21ES018723). Education of women of childbearing age about healthy fish consumption resulted in hair Hg levels well below both those identified in the pilot study preceding the R21 and those found in the New Zealand and Faroe Islands, where studies detected adverse neurodevelopmental effects. Levels were closer to those identified among moderate fish consumers in the US, in whom the benefits of fish consumption outweigh the risks of MeHg exposure, suggesting that our educational effort may have prevented adverse neurodevelopmental outcomes. However, our investigation revealed a new and larger neurodevelopmental concern – the widespread home and agricultural use of hexachlorocyclohexane pesticides (HCHs), despite their being recently banned under the Stockholm Convention. Surveys of agricultural workers confirmed ongoing HCH use, and we detected HCHs in 66% of pregnant women in the pilot study of MeHg exposure. Of even greater concern is the widespread occupational exposure we identified (reported application of pesticides in the second trimester by 14%). HCHs are known to interfere with gamma-aminobutyric acid neurotransmission, disrupt thyroid hormone, and affect androgen and estrogen metabolism, yet the effects of prenatal exposure to HCHs on child neurodevelopment at levels relevant to ongoing exposure in the industrializing world have not been assessed. While substantial progress has been achieved in educational, capacity building and research efforts, we are planning further efforts in the region, which are especially needed given the reality that neurotoxic chemicals exist in mixtures, and the potential for additive and synergistic benefits to preventing multiple exposures.

**Tshala-Katumbay, Desire MD PhD (PI, USA)**

**Major Collaborators: Tamfum Muyembe, MD PhD & Mumba Ngoyi, MD PhD  
(Democratic Republic of Congo)**

**Grants ES019841: Toxicodietary and Genetic Susceptibility to Neurodegeneration**

**Cassava cyanogenesis and neurotoxicity: experimental modeling. Part I. Memory deficits associated with sublethal cyanide poisoning relative to cyanate toxicity in rodents**

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Food (cassava) linamarin is metabolized into neurotoxicants cyanide and cyanate, metabolites of which we sought to elucidate the differential toxicity effects on memory. Young 6-8 weeks old male rats were treated intraperitoneally with either 2.5 mg/kg body weight (bw) NaCN, or 50 mg/kg bw NaOCN, or 1 µl/g bw saline, daily for up to 6 weeks. Short-term and long-term memories were assessed using a radial arm maze (RAM) testing paradigm. Toxic exposures had an influence on short-term working memory with fewer correct arm entries ( $F_{2, 19} = 4.57$   $p < 0.05$ ), higher working memory errors (WME) ( $F_{2, 19} = 5.09$ ,  $p < 0.05$ ) and longer RAM navigation time ( $F_{2, 19} = 3.91$ ,  $p < 0.05$ ) for NaOCN relative to NaCN and saline treatments. The long-term working memory was significantly impaired by NaCN with fewer correct arm entries ( $F_{2, 19} = 7.45$ ,  $p < 0.01$ ) and increased working memory errors ( $F_{2, 19} = 9.35$   $p < 0.05$ ) in NaCN relative to NaOCN or vehicle treated animals. Reference memory was not affected by either cyanide or cyanate. Our study findings provide an experimental evidence for the biological plausibility that cassava cyanogens may induce cognition deficits. Differential patterns of

memory deficits may reflect the differences in toxicity mechanisms of NaOCN relative to NaCN. Cognition deficits associated with cassava cyanogenesis may reflect a dual toxicity effect of cyanide and cyanate.

### **Cassava cyanogenesis and neurotoxicity: experimental modeling. Part II. Cross species and tissue variations in cyanide detoxification rates in rodents and non-human primates on protein-restricted diet**

Kimani S.<sup>1,3</sup>, Moterroso V.<sup>2</sup>, Morales P.<sup>4</sup>, Wagner J.<sup>4</sup>, Kipruto S.<sup>3</sup>, Bukachi F.<sup>5</sup>, Maitai C.<sup>3</sup>, Tshala-Katumbay D.<sup>6\*</sup>

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We sought to elucidate the impact of a protein-restricted diet on cyanide detoxification capabilities (CDC). Male rats (~8 weeks old) (N=52) on 75% sulfur amino acid (SAA)-deficient diet were treated with sodium cyanide (NaCN, 2.5 mg/kg bw) or cyanate (NaOCN, 50 mg/kg bw) for 6 weeks. Male *macaca fascicularis* monkeys (~12 year-old) (N=12) were exclusively fed cassava for 5 weeks. CDC was assessed in plasma, spinal cord, and brain. In rodents, NaCN induced acute seizures under SAA-restricted diet whereas NaOCN induced motor deficits. No deficits were observed in non-human primates. Under normal conditions, the CDC were up to ~80X faster in the nervous system (14 milliseconds to produce one  $\mu\text{mol}$  of thiocyanate from the detoxification of cyanide) relative to plasma. Spinal cord CDC was impaired by NaCN, NaOCN, or dietary deficiency in SAA. In non-human primates, plasma CDC changed proportionally to total proteins ( $r=0.43$ ;  $p<0.001$ ). The plasma CDC was ~ twice faster compared to that of rodents. The nervous system susceptibility to food (cassava) cyanogenesis may result from a “multiple hit” process mediated through the toxicity of cyanide toxicity or cyanate or deficiency in SAA. *Macaca fascicularis* may be useful in modeling the biochemical changes associated with cassava cyanogenesis.

### **Cassava cyanogenesis and neurotoxicity: experimental modeling. Part III. Carbamoylation correlates of cyanate neuropathy and cyanide poisoning: relevance to the biomarkers of cassava cyanogenesis and motor system toxicity.**

Kimani S.<sup>1,4</sup>, Moterroso V.<sup>2</sup>, Lasarev M.<sup>3</sup>, Kipruto S.<sup>1</sup>, Bukachi F.<sup>5</sup>, Maitai C.<sup>1</sup>, David L.L.<sup>6</sup>, Tshala-Katumbay D.<sup>3,7</sup>

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We sought to elucidate the protein carbamoylation patterns associated with cyanate neuropathy relative to cyanide poisoning. We hypothesized that under a diet deficient in sulfur amino acids (SAA), the carbamoylation pattern associated with cyanide poisoning is similar to that of cyanate neuropathy. Male rats (6-8 weeks old) were fed a diet with all amino acids (AAA) or 75%-deficiency in SAA and treated with 2.5 mg/kg/body weight (bw) NaCN, or 50 mg/kg/bw NaOCN, or 1µl/g/bw saline, for up to 6 weeks. Albumin and spinal cord proteins were analyzed using liquid chromatography mass spectrometry (LC-MS/MS). Only NaOCN induced motor deficits with significant levels of carbamoylation. At Day 14, we found a diet-treatment interaction effect on albumin carbamoylation ( $p=0.07$ ). At Day 28, no effect was attributed to diet ( $p=0.71$ ). Mean number of NaCN-carbamoylated sites on albumin was 47.4% higher relative to vehicle (95% CI:16.7-86.4%). Only NaOCN carbamoylated spinal cord proteins, prominently, under SAA-restricted diet. Proteins targets included myelin basic and proteolipid proteins, neurofilament light and glial fibrillary acidic proteins, and 2', 3' cyclic-nucleotide 3'-phosphodiesterase. Under SAA deficiency, chronic but not acute cyanide toxicity may share biomarkers and pathogenetic similarities with cyanate neuropathy. Prevention of carbamoylation may protect against the neuropathic effects of cyanate.

### **Cassava cyanogenesis and neurotoxicity: experimental modeling. Part IV. Diagnostic and therapeutic potential of tetanus toxin-derivatives in neurological diseases**

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We assessed the *ex vivo* reactivity of peptidic constructs of Tet1 (analog of tetanus toxin non-virulent C fragment) with sequence homology to the cysteine-active site of thioredoxin (Tet1THO) or tetralysine (Tet1PLYS) with oxidative species or axonopathic sodium cyanate (NaOCN), respectively. We then assessed their neuronal uptake *in vivo* in laboratory animals. The reactivity of Tet1PLYS with NaOCN (1:2.5 to 1:37.5 molar ratios) or Tet1THO with hydrogen peroxide (1:0.4 to 1:6.2 molar ratios) was assessed by mass spectrometry. GFP-tagged Tet1-derivatives (3 mg/ml in artificial cerebrospinal fluid) were administered daily to rats by intramuscular injection in *latissimus dorsi at lumborum* at the dose of 1  $\mu$ l/g of body weight, for 3 days. Motor neuron uptake was assessed after double immunolabeling for GFP and choline acetyltransferase (ChAT). Mass spectrometry analysis successfully demonstrated the *ex-vivo* reactivity of Tet1 derivatives in a concentration-dependent manner. Confocal microscopy revealed localization of Tet1-derivatives in axons and motor neuron cell bodies. Intramuscular delivery of Tet1-derivatives appears to be a practical approach to circumvent the blood nerve barrier and selectively deliver small molecules to the nervous system, for diagnostic and/or treatment purposes.

### **Neuropsychological effects of konzo: a permanent neuromotor disorder from insufficiently processed Cassava**

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We sought to determine whether subjects affected by konzo are impaired in their cognition. DR Congo children with konzo (mean age 8.7 yrs) were compared to nonkonzo children (mean age 9.1 yrs) on the Kaufman Assessment Battery for Children, 2nd edition (KABC-II), and the Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition (BOT-2). Both groups were also compared to normative KABC measures from earlier studies in a nearby nonkonzo region. Using a Kruskal-Wallis test, children with konzo did worse on the KABC-II Simultaneous Processing (visual-spatial analysis) ( $K(1) = 8.78, P = 0.003$ ) and Mental Processing Index (MPI) ( $K(1) = 4.56, P = 0.03$ ). Konzo boys were significantly below nonkonzo boys, but not for the girls. Both konzo and nonkonzo groups had poorer KABC Sequential Processing (memory) and MPI relative to the normative group from a nonkonzo region ( $K(2) = 75.55, P < 0.001$ ). Konzo children were lower on BOT-2 total ( $K(1) = 83.26, P < 0.001$ ). KABC-II MPI and BOT-2 total were predictive of konzo status in a binary logistic regression model: odds ratio = 1.41,  $P < 0.013$ ; 95% confidence interval 1.13 – 1.69. Motor proficiency is dramatically affected, and both

konzo and nonkonzo children have impaired neurocognition compared to control children from a non-outbreak area. This may evidence a subclinical neurocognitive form of the disease, extending the human burden of konzo with dramatic public health implications. Novel biomarkers of konzo include elevated serum levels of F2-isoprostanes suggesting that oxidative stress may play a role in the pathogenesis of the disease.

### **Nutraceuticals: the way forward to prevent adverse health effects of a cassava-dominated diet**

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Cyanide is a mitochondrial toxin known to induce oxidative damage. We asked whether cassava poisoning induces oxidative stress and determine whether local food crops may be used as nutraceuticals (food with health benefits) to initiate the prevention against the toxic effects of cassava. We first performed a case-control study of 20 subjects severely affected by konzo vs. 20 age- and gender-matched controls from rural Bandundu, Congo-Kinshasa, the most konzo-affected region of the globe. Levels of oxidative markers F2-isoprostanes were assessed using state-of-the art proteomic methodologies (LC-tandem mass spectrometry). We also analyzed organic- and water-soluble extracts of five green vegetables widely grown in Bandundu province using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical-scavenging assay (by thin layer chromatography and ELISA). Crops of interest included *Manihot utilisima*, *Pteridium aquilinum*, *Dioscorea praehensilis*, and *Megaphrynium macroschtachyum* (concentration range 500 – 1,95 µg/ml of methanolic extracts). Extract were compared to vitamin C, vitamin E ( $\alpha$ -tocopherol), or quercetin as references for their antioxidant activities. We showed a clear correlation between levels of F-2 isoprostanes isomers (reaching up to 50-times normal reference values) and konzo-associated disability (Spearman  $r = 0.7$ ,  $P < 0.01$ ). Oxidative damage is a biological hallmark of cassava poisoning. *Pteridium aquilinum* and *Dioscorea praehensilis* showed antioxidant activities comparable to those of vitamin E. Select food crops may be used as nutraceuticals in campaigns to mitigate the health effects of cassava neurotoxicity when acceptance of modern intervention trials is not guaranteed.

## LIST OF PUBLICATIONS

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**Grants ES019841: Toxicodietary and Genetic Susceptibility to Neurodegeneration  
Biomarker-based association models for predicting cognition deficits in cassava cyanogenic  
poisoning**

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**Background.** Dietary reliance on cyanogenic cassava may be associated with paralysis (konzo) and cognition deficits of which we search for risk factors, biomarkers, and mechanisms.

**Method.** In the search for risk factors of cognition deficits, we anchored levels of serum albumin, free-thyroxine (free-T4) and thyroid-stimulating hormone (TSH), and motor proficiency (Bruininks/Oseretsky Test, 2nd Edition (BOT-2) scores) to measures of mental processing (Kaufman Assessment Battery for Children, KABC-II score) in 40 children (median age: 9 years) including 21 with konzo and 19 controls (median age: 8 years). Cyanogenic exposure was ascertained by measures of urinary thiocyanate (SCN). Multiple regression was used to determine characteristics most associated with average KABC-II score.

**Results.** Children with konzo had SCN levels as high as 1032  $\mu\text{mol/L}$ . Multiple regression analysis showed that KABC-II score was significantly associated with age ( $p=0.018$ ), gender ( $p=0.009$ ), BOT-2 score ( $p=0.008$ ), and, marginally, free-T4 ( $p=0.049$ ). There was a crude (unadjusted) association between KABC-II score and levels of serum albumin ( $p=0.029$ ). Subclinical hypothyroidism was not associated with poor cognition performance.

**Conclusion.** Mitigation of cognition deficits associated with cassava cyanide poisoning may require nutritional and physical rehabilitation as well as effective processing of cyanogenic cassava to remove motor system toxicants prior to human consumption.

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**Major foreign collaborating country** USA  
**Presenter Name** Carla Gallo  
**Grant Number:** 1R21MH095644--01A1  
**Grant Title:** Drug Discovery for Mental Disorders: Preclinical Studies of Peruvian Botanicals

Mental disorders are multidimensional and severely disabling diseases, with a strong need for pharmacotherapies with better adherence, long-term outcome and patient functionality. Unfortunately, the scientific advancements in the field have not yet led to the introduction of truly novel pharmacological approaches to treatment. One of the possible avenues to achieve this goal is to take advantage of world's ancient knowledge of healing practices to direct search of new lead compounds, with expectedly novel action mechanisms that would lead to better treatment outcomes. Drug discovery from traditional medicines add the possibility of incorporating validated traditional practices into protocols for care, especially in Low and Middle Income Countries, where access to care and treatment is limited.

This proposal is part of a long range effort directed to the discovery of new pharmaceuticals from Peruvian flora traditionally used for the treatment of mental disorders. Our main hypothesis is that plants ancestrally used by Peruvian traditional healers for treating mental illnesses are a source of novel therapeutics for these disorders. We specifically hypothesize that: 1) it is possible to isolate bioactive principles from these plants; 2) rodent behavioral models are a good start point tool for screening/validation and for further prioritization of research on those activities; 3) the isolated lead compounds will be superior to those obtained from chemical libraries in terms of better bioavailability and less secondary effects; 4) the pharmacological information obtained will help to further understand the traditional medicine conceptualization of mental disorders in Peru. Previous studies have led us to collect information on the traditional use of plants for the treatment of mental disorders in several Peruvian localities and geographical regions. We currently have extracts from 475 plant collections corresponding to 265 species from 87 different plant families. These plants are traditionally used for one or more of the following activities: antipsychotic, antidepressant, anxiolytic and sedative. Importantly, about 65% of those species have never been described in the scientific literature for their potential effects on the modulation of behavior. Forty percent of these plant extracts have been screened

so far to validate its traditional medical use with behavioral tests in mice. To date we have identified 123 extracts having one or more potential psychotropic activity (75 antipsychotic, 73 anxiolytic and 22 antidepressant). Dose-response curves have been run for 9 of these extracts. In this R21 we will run 30 additional dose-response curves and pursue the activity guided fractionation of at least 1 extract. We have especial interest in developing or testing new methods for the screening and bioassay guided fractionation of our extracts, in order to identify novel agents that could be candidate drugs or lead compounds for mental disorders. Also, we aim to get further insight on the Peruvian traditional medicine conceptualization of mental disorders, by comparing the pharmacological/behavioral results obtained in our experiments with the reported/interpreted traditional use. A multidisciplinary group of professionals, leaders in their area of expertise, has been invited to participate in this R21, which will end up in the preparation of an R01 proposal. Screening natural product extracts for mental disorders has led to the discovery of therapeutic agents in use today, and, although discovery of a new agent is obviously an ambitious goal, there are numerous factors that support the likelihood of being able to successfully identify novel agents that are candidate drugs or lead compounds for mental disorder treatment. These factors include the innovative screening approach we are aiming to devise, the uniqueness of our natural product library, the multidisciplinary nature of the project, and the expertise of the team of investigators and consultants.

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R21MH096559

Technology Development and Neuroimaging of 5-year Old Children with HIV Infection

### **Neurometabolite differences in basal ganglia in HIV-infected children receiving different ART regimens at age 5 years**

Kenneth Mbugua, Martha Holmes, Francesca Little, Aaron Hess, André van der Kouwe, Ernesta Meintjes, Barbara Laughton

**Introduction:** The use of antiretroviral therapy (ART) in young children limits HIV damage to the brain. However, little is known about the optimal ART for children born HIV-infected or how children on ART develop during childhood. MR spectroscopy (MRS) is a useful tool to investigate neurological development in children, since many neurological processes that occur during childhood are accompanied by metabolite changes. This study examines differences in metabolite levels in basal ganglia (BG) between HIV-infected children receiving different ART regimens, as well as associations with clinical measures of disease progression.

**Methods:** Single voxel 1H-MRS (SVS) was acquired in 34 HIV-infected (mean age =  $5.5 \pm 0.3$  yrs) and 15 HIV-uninfected (mean age =  $5.6 \pm 0.5$  yrs) Xhosa children from Cape Town, South Africa in a BG region with a real-time motion and B0 corrected [1] point resolved spectroscopy (PRESS) sequence (15x15x15 mm<sup>3</sup>; TR 2000 ms, TE 30 ms, 64 averages, scan time: 2.16 min) on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany). HIV-infected children were from the Children with HIV Early ART Treatment (CHER) trial [2]: 12 arm 1 (ART delayed until immunological or clinical criteria met), 11 arm 2 (ART initiated before 12 weeks of age with interruption at 40 weeks), and 11 arm 3 (ART initiated before 12 weeks of age with interruption at 96 weeks). Water reference scans were acquired for eddy current compensation,

frequency/phase correction, and to compute absolute metabolite levels. Spectra were analysed using LCModel; metabolites assessed include N-acetyl-aspartate (NAA), choline-containing compounds glycerophosphocholine plus phosphocholine (GPCPCh), creatine plus phosphocreatine (CrPCr), glutamate (Glu), glutamate plus glutamine (GluGln/Glx), and myo-Inositol (Ins). Statistical analyses included one-way between group ANOVA, regression models to control for potential confounding effects of child's age, birth weight, and gender, and Pearson correlation to examine associations with clinical measures.

**Results:** Although below conventional levels of significance, ANOVA reveals group differences in NAA ( $p=0.08$ ) and choline containing compounds (GPCPCh) ( $p=0.1$ ) in the BG. Post-hocs demonstrate that NAA in this region in children who received early treatment for 40 weeks (arm 2) tend to be higher than in uninfected controls ( $MNAA(\text{arm}2)=5.4$ ,  $MNAA(\text{ctl})=5.0$ ,  $p=0.07$ ), while the concentration of choline containing compounds (GPCPCh) tend to be higher in children who received early ART for 96 weeks (arm 3) compared to uninfected controls ( $MGPCPCh(\text{arm}3)=1.14$ ,  $MGPCPCh(\text{ctl})=1.04$ ,  $p=0.06$ ). Regression analyses reveal a significantly stronger association between age and NAA levels in children in arm 1 compared to all the other groups. After controlling for age, birth weight, and age by group interaction effects, NAA levels in BG at age 5 years tend to be lower in children in arm 1 ( $p=0.1$ ) compared to uninfected controls, with no significant differences between children in arms 2 and 3 compared to uninfected controls.

Higher CD4 count at enrolment is significantly associated with higher levels of NAA ( $r=0.34$ ,  $p=0.05$ ) and GPCPCh ( $r=0.34$ ,  $p=0.05$ ) in this region at age 5, while lower CD8 at enrolment is related to higher NAA ( $r=-0.35$ ,  $p=0.05$ ). No other clinical measures (cumulative weeks on ART, CD4 and CD8 at scan, nadir CD4, nadir CD8, and occurrence of adverse events) were significantly associated with any other metabolites in this region.

**Conclusion:** As hypothesized, children who received deferred treatment appear to exhibit a different pattern of development compared to the other children, with a stronger association of NAA levels with age in BG compared to all the other groups. This seems to suggest early brain damage, which is further supported by the association of NAA and GPCPCh levels at age 5 in this region with CD4 count at enrolment. None of the other clinical measures were associated with metabolite levels at age 5 in this region. It will be interesting to examine whether these trends are confirmed by longitudinal data when these children are re-scanned at ages 7 and 9 years.

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R01HD071664

Longitudinal Neuroimaging and Cognitive Study of HIV-Infected Children

Real-time motion and dynamic shim correction for diffusion tensor magnetic resonance imaging  
Ali Alhamud, Paul Taylor, Barbara Laughton, Ernesta Meintjes, André van der Kouwe

**Introduction:** Diffusion tensor magnetic resonance imaging (DTI) is a technique used to evaluate the integrity of white matter in the brain. In an ongoing longitudinal study we are imaging the brains of young children exposed to or infected with HIV, and controls, in the Cape Town region of South Africa. The prevalence of HIV in South Africa is amongst the highest in the world, and there is an epidemic of children born with exposure or infection. Since adoption of antiretroviral treatment (ART), HIV has become a chronic disorder with possible early and/or ongoing damage to the central nervous system due to the virus or the antiretrovirals. Using DTI and other techniques we are investigating brain development in chronically infected children on ART compared to healthy children, in a longitudinal study of children aged 5 to 9 years. Children tend to move during the long acquisitions. For ethical reasons we cannot sedate them, therefore we have developed techniques to track the brain and correct image encoding in real time during scanning, thus improving data quality and study power.

**Methods:** The Cape Universities Brain Imaging Centre (CUBIC) operates a Siemens Allegra 3 T MRI scanner. This is a research dedicated head-only scanner with powerful gradients enabling high quality DTI imaging. However, the gradient system generates eddy currents, and if the subject's head moves during scanning, artifacts result. Slices may be offset from the intended position, distorted due to eddy currents, and even lost altogether if motion occurs during the diffusion gradients. Eddy current distortions may be corrected in postprocessing but the other effects must be addressed first. By adding a 3D EPI-based navigator between repetitions times

(TRs) of the main sequence, together with online registration to a reference volume (the first navigator at the start of the scan), we are able to track and correct positioning throughout the scan. We detect volumes during which motion exceeded a preset threshold, and reacquire them, thus reducing or eliminating slices with signal drop-out. EPI-based acquisitions such as DTI are sensitive to magnetic field inhomogeneities. Shimming reduces the inhomogeneities, but the action of the shim coils is necessarily local in space and if the subject moves it is invalidated, resulting in distortions, signal dephasing and signal drop-outs in the images. Real-time motion tracking therefore does not completely correct the effects of motion without simultaneous shim correction. We added a second EPI navigator with a slightly different echo time to measure the instantaneous magnetic field at each TR [1]. By calculating the required shim for every TR we are able to correct for motion and shim throughout the DTI acquisition.

**Results:** We previously reported results of DTI motion correction with reacquisition [2]. Figure 2 shows a comparison between a representative slice of an adult volunteer's brain with and without real-time shim correction and with and without motion. In the case of no motion correction, images were corrected with retrospective offline methods. Figures 2a and 2b show more areas of blue (area of white matter from separate structural T1 scan) i.e. a smaller area of red, corresponding with a decrease in fractional anisotropy (FA, from DTI) in white matter due to retrospective correction, which blurs the images (due to resampling) and reduces the detected directionality of white matter fibers. Real-time correction and shim correction does not under-label white matter, even in the presence of motion, as seen in Figures 2c and 2d, as no resampling is needed. Dice coefficients for the overlap between white matter regions labeled using the T1 scan and white matter regions deduced from FATHresholding were 0.93, 0.94, 0.98 and 0.97, for comparisons a through d respectively.

**Conclusion:** We have shown that motion correction with reacquisition is useful in our study of HIV infected children in previous work [3]. Here we show promising provisional evidence that real-time shim correction can further improve the integrity of DTI acquisitions, especially in people who move during scanning. We will continue to develop and test the method in phantoms and healthy adult volunteers before applying it in our study. We intend also to implement real-time shimming in DTI on a regional and slice-by-slice basis.

Laughton, Barbara (South Africa); Meintjes, Ernesta (South Africa); **van der Kouwe, André (U.S.A.)**

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R01HD071664

Longitudinal Neuroimaging and Cognitive Study of HIV-Infected Children

### **Effects of HIV Exposure on MRS metabolite levels in children: at 5 and 7 years**

Martha Holmes, Kenneth Mbugua, Francesca Little, Aaron Hess, André van der Kouwe, Barbara Laughton, Ernesta Meintjes

**Study:** Single voxel 1H-MRS (SVS) data were acquired with a real-time motion and B0 corrected [1] point resolved spectroscopy (PRESS) sequence in midfrontal gray matter (MFGM) in twenty-five 5-year old (16 HIV-exposed uninfected (HIVe) and 9 HIVunexposed uninfected (HIVn)) and twenty-three 7-year old children (12 HIVe and 11 HIVn) on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa Eleven children were imaged at both ages. Spectra were analysed using the software LCModel and R was used for all statistical analyses. Where we expected to see a metabolite level increase/decrease with age, a mixed effect linear regression model was used to account for repeated measures.

**Background:** Successful programs preventing mother to child HIV transmission have created a new population of uninfected HIVexposed children. These children have an increased risk of mortality, morbidity, slower early growth [2,3] and neurological symptoms such as cognitive delay, behavioral disorders, and motor abnormalities [4,5]. Exposure to antiretroviral (ARV) drugs and environmental factors may account for the increased risk [2]. Magnetic resonance spectroscopy (MRS) is used for the non-invasive investigation of neurological development in children. Many childhood neurological processes are accompanied by metabolite changes that often correlate with demographic variables (e.g. age) throughout childhood [6,7,8]. Few studies have examined metabolite levels through childhood among healthy children, and no studies have examined the effect of HIV exposure on metabolites. The metabolite NAA is associated with neurogenesis - the steepest rate of increase is observed in gray matter in early childhood [8]. Choline is highest among infants, and remains relatively constant throughout childhood. This

study investigated the relationship between age and metabolite level in healthy children at ages 5 and 7, focused on the possible effects of HIV exposure.

**Results:** Across all children, NAA levels increased with age in the MFGM ( $p = 0.01$ ) as shown in the Figure. Within the two groups, we found that at 7 years, HIVE children have significantly lower NAA levels (t-test: HIVE vs HIVn,  $p = 0.03$ ) as well as higher choline levels (t-test: HIVE vs HIVn,  $p = 0.009$ ) in the MFGM.

**Discussion:** The significant increase in the MFGM (slope = 0.16,  $p = 0.01$ ) may be due to an increase in neuron populations and increased synaptic connections with age [7] and is likely representative of healthy neurodevelopment. HIV exposure alters the relationship between age and NAA in the MFGM: we find NAA levels increase with age among HIVn children (slope = 0.23,  $p = 0.01$ ), but the increase with age *disappears* (slope = 0.07,  $p = 0.4$ ) among the HIVE group. The group difference is a result of the significantly lower NAA levels at 7 years in HIVE children. The reduced NAA growth, as well as the lower NAA level at 7 years, suggests a possible long-term effect of HIV exposure/ARV treatment on neuron populations, axons, dendrites and synaptic terminals in gray matter. The increased choline levels observed among HIVE children at 7 years implies glial proliferation/inflammation in the MFGM, since glial cells have higher choline levels than neurons; increased choline levels are reported in the MFGM in HIV-infected children [6].

**Conclusion:** A detailed understanding of the normal age-dependent neurological metabolite changes is critical to interpreting MRS results across pediatric populations. This study adds to the existing database of MRS results in healthy children and it is the first study to use MRS techniques to investigate differences in neurological development between HIVE and HIVn children. Our results suggest HIV-exposure - *in utero* viral exposure and/or ART - has an impact on the neurological development of young children. Given the significant population - 5.6 million - of HIV infected in South Africa [9], and the subsequent children born HIVE, this research provides critical data on a largely unexplored population.

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Grant number: R01DA021421

Grant title: Varieties of Impulsivity in Opiate and Stimulant Users

Impulsivity, implicated both as an antecedent risk factor and a consequence of drug addiction, is considered one of the strongest candidate endophenotypes for addiction. However, progress in the field is hampered by the heterogeneity of the impulsivity phenotype, characterized by multiple personality, psychiatric, and neurocognitive dimensions, rarely examined concurrently within the same population; and the heterogeneity of clinical addiction phenotypes, due in part to the high rates of polysubstance dependence, which limit investigations of the common vs. specific effects of different drug classes. To circumvent these challenges, we developed a program of addiction research in Bulgaria, where drug addiction is one of the most significant public health problems, as it is a major European center for production of synthetic amphetamine-type stimulants and a key transit country for heroin trafficking, due to its strategic geographical position on the “Balkan Drug Route”. Through our 10-year collaboration with Bulgarian colleagues, we have accessed rare populations of predominantly monosubstance-dependent heroin and amphetamine users, many in protracted abstinence. This has allowed us to limit the heterogeneity of addiction phenotypes by avoiding the confounding effects of polysubstance dependence that often plague studies in North America. We have also addressed the heterogeneity of the impulsivity phenotype, by conducting one of the most comprehensive characterizations of its multiple dimensions among 102 heroin users, 104 amphetamine users and 113 healthy controls.

Our results have begun to challenge the prevailing unitary account of addiction and reveal that the addiction to opiates and that to stimulants are behaviorally and neurocognitively distinct and may be driven by different underlying mechanisms. With regards to trait measures of impulsivity, capturing its personality and psychiatric dimensions, our findings reveal that both opiates and stimulants are associated with higher levels of antisocial personality disorder (ASPD), attention deficit hyperactivity disorder (ADHD), aggression and trait impulsivity. On the other hand, opiates were uniquely associated with psychopathy, an extreme variant of ASPD;

whereas stimulants were uniquely associated with sensation seeking. In terms of neurocognitive dimensions of impulsivity, results reveal unique effects of stimulants on motor impulsivity (e.g. response inhibition) and of opiates on attentional impulsivity. With regards to more complex “cognitive” impulsivity dimensions, stimulant use was uniquely associated with increased discounting of delayed rewards, whereas opiate use was uniquely associated with increased aversion to delay on a probabilistic decision-making task. Pilot computational modeling analyses conducted to further fractionate decision-making, a central neurocognitive aspect of impulsivity, proved particularly informative in revealing that stimulant and opiate users were characterized by distinct decision-making profiles. Specifically, stimulant users showed greater sensitivity to rewards, which was related to duration of drug use, whereas opiate users evidenced reduced aversion to loss, which was related to personality characteristics such as psychopathy. Another goal of the study was to determine whether increased trait impulsivity would be associated with increased neurocognitive impulsivity in different types of drug users. Our findings indicate that whereas higher trait impulsivity is associated with neurocognitive deficits in “motor” impulsivity in stimulant users, in contrast, it is associated with better “motor” impulsivity performance in opiate users. Importantly, we also revealed that psychiatric and neurocognitive dimensions of impulsivity remain significantly associated with HIV risk behaviors in heroin and amphetamine addicts in protracted abstinence. Together, our findings underscore the utility of examining multiple and more narrowly-defined dimensions of impulsivity and contribute significantly to a growing body of literature that reveals important differences between addictions to different classes of drugs, which are observable in protracted abstinence.

Our collaboration with Bulgarian colleagues has resulted in a number of research capacity building accomplishments such as: 1) translating, adapting, and validating a number of personality, psychiatric, and neurocognitive assessment instruments into Bulgarian; 2) training Bulgarian colleagues in their administration and interpretation; 3) establishing research rotations for Bulgarian graduate students and medical residents; 4) assisting Bulgarian trainees and colleagues in applying for funding; 5) helping generate a number of smaller projects conducted locally; and 6) establishing additional multidisciplinary international collaborations.

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Foreign Collaborator: Georgi Vasilev, MD MPH, Bulgarian Addictions Institute, Sofia, Bulgaria  
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Grant: R01DA021421 “Varieties of Impulsivity in Opiate and Stimulant Users”

Increased reward sensitivity in stimulant addiction versus reduced loss aversion in opiate addiction: evidence from computational modeling with pure users

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#### Abstract

**Background:** Substance dependent individuals commonly exhibit decision-making deficits; however, it remains unclear whether the nature of the underlying decision-making processes is the same in users of different types of drugs and whether these deficits persist after discontinuation of drug use.

**Methods:** We used computational modeling to address these questions in a unique sample of relatively “pure” amphetamine-dependent (N=38) and heroin-dependent individuals (N=43) who were currently in protracted abstinence, and in 48 healthy controls.

**Results:** Computational modeling results revealed a double dissociation between amphetamine and heroin addiction on reward sensitivity and loss aversion. Amphetamine users showed increased reward sensitivity, whereas heroin users displayed reduced loss aversion relative to healthy controls. Reward sensitivity was related to number of years of drug use in amphetamine users. In contrast, loss aversion was associated with personality traits of impulsivity and psychopathy in heroin users.

**Conclusions:** Our results suggest that decision-making deficits are longstanding (or pre-existing)

and mediated by different mechanisms in stimulant and opiate users in protracted abstinence.

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Grant number: R01DA021421 “Varieties of Impulsivity in Opiate and Stimulant Users”

Psychopathy in Bulgaria: The cross-cultural generalizability of the  
Hare Psychopathy Checklist

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The generalizability of the psychopathy construct to Eastern European cultures has not been well-examined, and no prior studies have evaluated psychopathy in non-offender samples of this population. The current validation study examines the factor structure, reliability, and external validity of the Bulgarian translation of the Hare Psychopathy Checklist: Screening Version. Two hundred sixty-two non-incarcerated Bulgarian adults were assessed, of which 185 had a history of stimulant or opiate dependence. Although confirmatory factor analysis indicated good fit for the two-, three-, and four-factor models of psychopathy, exploratory factor analysis and internal reliability calculations best supported the two-factor structure. Zero-order and partial correlation analyses were conducted between the two factors of psychopathy and criterion measures of antisocial behavior, internalizing and externalizing psychopathology, personality traits, addictive disorders and demographic characteristics. Relationships to external variables provided evidence for the convergent and discriminant validity of the psychopathy construct in non-incarcerated Bulgarian adults.

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Grant: R01DA021421 “Varieties of Impulsivity in Opiate and Stimulant Users”

Relationships of trait and state indices of cognitive and motor impulsivity with HIV risk behaviors in abstinent opiate and stimulant users  
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*Background:* Identifying determinants of HIV risk behavior among Eastern European drug users is of primary public health significance. Impulsivity is an important risk factor to consider in this regard. At least two dissociable components of impulsivity--cognitive (CI) and motor (MI)--have been associated with distinct neurocognitive profiles in drug users. However, relationships between varieties of impulsivity and HIV risk behaviors have not been well-studied across users of different classes of drugs.

*Methods:* The present study examined the utility of trait-like psychiatric and state-like neurocognitive indices of CI and MI as predictors of sexual risk behaviors (SRB) among Eastern European drug users in protracted abstinence. Participants had lifetime histories of either heroin mono-dependence, amphetamine mono-dependence, or polysubstance dependence. Relationships between varieties of impulsivity and SRB were examined over varying periods of time ranging from the past 30 days to lifetime.

*Results:* Indices of CI but not MI were associated with relatively recent SRB among pure heroin and amphetamine users, with state-dependent cognitive impulsivity selectively predicting past 30-day SRB and trait-like psychiatric CI (i.e. psychopathy) predicting past six-months SRB. SRB over the lifetime was selectively associated with trait-like CI only among pure heroin users.

*Conclusions:* Our data suggest that HIV prevention efforts in Eastern European drug users--particularly heroin users--should focus on psychiatric and neurocognitive dimensions of CI as targets of intervention. MI does not appear to selectively contribute to SRB in this sample of drug users in protracted abstinence.

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Grant: R01DA021421 “Varieties of Impulsivity in Opiate and Stimulant Users”

Heroin and amphetamine users display opposite relationships between trait and neurobehavioral dimensions of impulsivity

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The multidimensional construct of impulsivity is implicated in all stages of the addiction cycle. Substance dependent individuals (SDIs) demonstrate elevated impulsivity on both trait and laboratory tests of neurobehavioral impulsivity; however our understanding of the relationship between these different aspects of impulsivity in users of different classes of drugs remains rudimentary. The goal of this study was to assess for commonalities and differences in the relationships between trait and neurobehavioral impulsivity dimensions in heroin and amphetamine addicts.

Participants included 58 amphetamine dependent (ADI) and 74 heroin dependent individuals (HDI) in protracted abstinence. We conducted principal components analyses (PCA) on two self-report trait and six neurobehavioral measures of impulsivity, which resulted in two trait

impulsivity composites (action, planning) and four neurobehavioral impulsivity composites (discriminability, response inhibition efficiency, decision-making efficiency, quality of decision-making). Multiple regression analyses were used to determine whether neurobehavioral impulsivity is predicted by trait impulsivity and drug type.

The analyses revealed a significant interaction between drug type and trait action impulsivity on response inhibition efficiency, which showed opposite relationships for ADIs and HDIs. Specifically, increased trait action impulsivity was associated with worse response inhibition efficiency in ADIs, but with better efficiency in HDIs. These results challenge the unitary account of drug addiction and contribute to a growing body of literature that reveals important behavioral, cognitive, and neurobiological differences between users of different classes of drugs.

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Grant: R01DA021421 “Varieties of Impulsivity in Opiate and Stimulant Users”

#### Reward-Based Decision-Making and Pathological Gambling in Users of Different Classes of Drugs

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Background: Pathological gambling (PG) is an addictive disorder underpinned by similar neurocognitive mechanisms to drug addiction including deficits in reward-based decision-making (RBDM). Recent studies draw a distinction between RBDM under risk versus RBDM under ambiguity. Different classes of drugs have distinct pharmacological properties which may lead to differential expression of decision-making deficits. The present study explored relationships of RBDM and PG symptoms in Eastern European adults with lifetime histories of amphetamine mono-dependence (AD), heroin mono-dependence (HD), and polysubstance dependence (PD).

Methods: Participants were 281 adults (AD = 44; HD = 61; PD = 73; healthy controls = 103). PG was assessed via the Addiction Severity Index-Lite and DSM-IV criteria. RBDM was assessed via the Iowa Gambling Task (IGT), considered a measure of RBDM under ambiguity, where the outcomes are uncertain and the outcome probabilities are unknown, hence the task requires learning of task contingencies; and the Cambridge Gambling task (CGT) a measure of RBDM under risk, where the outcomes are uncertain but the outcome probabilities are known, therefore learning is not required. Multiple linear regressions were conducted to examine the effects of drug user type and RBDM type on PG symptoms. Neurocognitive predictor variables included IGT net scores and six indices of CGT performance: overall proportion bet (OPB); risk-taking (RT); delay aversion; risk adjustment; deliberation time; quality of decision-making.

**Results:** Models containing IGT performance were not associated with PG ( $p's \geq .40$ ). CGT models explained unique variance in PG symptoms ( $p's < .05$ ), with direct main effects of OPB ( $\beta = .29, p = .02$ ) and RT ( $\beta = .35, p = .003$ ). Interaction effects indicated the relationship between OPB and PG did not differ across drug user types ( $p's > .09$ ), whereas RT predicted PG for HD and PD ( $p's > .07$ ) but not for AD ( $AD \times RT \beta = -.20, p = .02$ ).

**Conclusions:** Our findings indicate that indices of RBDM under risk represent an externally valid indicator of PG among opiate and polysubstance users, but not among amphetamine users. In contrast, indices of RBDM under ambiguity were not related to PG. Given the additional cognitive demands involved in the IGT (learning, reversal learning, working memory), these results show that a more pure measure of RBDM under risk may be more sensitive to reward-based decision-making impairments related to pathological gambling in substance users.

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**Presenter:** Anne Felicia Ambrose

**Grant number:** 5R01AG039330

**Grant title:** Kerala-Einstein Study: Healthy lifestyle, vascular disease, and cognitive decline

## **Picture Memory Impairment Screen For Dementia: Results from the Kerala-Einstein**

### **Study**

### **ABSTRACT**

**Background:** A major rate limiting factor in defining dementia burden in developing countries is the lack of brief cognitive screeners that account for cultural differences and variable literacy rates.

**Objective:** To develop and validate a picture memory impairment screen (PMIS) for the detection of dementia.

**Design:** Cross-sectional study

**Setting:** **Outpatient clinics**, Baby Memorial Hospital, Kozhikode city in the southern Indian state of Kerala.

**Participants:** **304 community-residing older adults ages 55 to 94 years and mean education level 8 years. 65 were diagnosed with dementia.**

**Main outcome measures:** **PMIS; a culture fair picture based cognitive screener designed to be administered by non-specialists.** Diagnostic accuracy estimates (sensitivity, specificity, positive and negative predictive power) of **PMIS** cut-scores in detecting dementia (range 0 to 8).

**Results:** PMIS scores were worse in participants with dementia compared to controls (1.5 vs. 7.7,  $p < 0.001$ ). **At the optimal cutscore of  $\leq 5$ , PMIS had a sensitivity of 95.4% (95% CI: 90.3% to 100%) and specificity of 99.2% (95% CI: 98.0% to 100%) for detecting dementia.** In the 167

participants with less than 10 years education, PMIS scores of  $\leq 5$  had a sensitivity of 97.8% (95% CI 93.6% to 100%) and specificity of 99.2% (95% CI 97.6 to 100%). The PMIS had better specificity than the **Mini-Mental State Examination** in detecting dementia, especially in older adults with low education.

**Conclusions: The PMIS is a brief and reliable screen for dementia in elderly populations with variable literacy rates.**

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Rahmaan A. Lawal, MBBS FMCPsych MPH / NIGERIA

**IKWUNGA WONODI**

Grant Number: 5R21MH093300

Grant Title: A Genetic Study of Schizophrenia Endophenotypes in sub-Saharan Africans

ABSTRACT

**A GENETIC STUDY OF A SCHIZOPHRENIA ENDOPHENOTYPES IN SUB-SAHARAN AFRICANS**

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Cognitive deficits severely compromise the quality of life and productivity of people with schizophrenia, exert high healthcare costs, and have no effective treatments. Uncovering the molecular substrates of cognition in schizophrenia could lead to the identification of novel molecular targets for developing rational pharmacology for cognitive dysfunction. We have demonstrated associations between genetic polymorphisms and neurocognitive impairments in schizophrenia. A logical next step after establishing SNP-phenotype associations in genetic association studies is to fine map the associated region(s). Sub-Saharan African populations, including the Yoruba and Igbo of Nigeria, have shorter LD blocks, more numerous haplotypes, and no significant population substructure, making them ideal for fine mapping analyses to identify causal variants responsible for associations initially found in European-origin populations or

populations with significant admixture (e.g., African-American). Schizophrenia has a remarkably constant global prevalence of ~1% across different cultures, ethnic groups and geographic areas, suggesting that similar etiological factors, including susceptibility genes, are at play across human populations. However, attempts to uncover the genetic basis of the illness have been hindered by clinical/genetic heterogeneity and the lack of biologically meaningful diagnostic boundaries. In the current innovative study, predictive pursuit (eyetracking) deficits, a stable quantitative trait with high heritability in schizophrenia, are used as experimental endpoints to uncover small gene effects and loci-of-interest for more extensive molecular characterization and gene mapping in a cohort of sub-Saharan Africans.

The capacity-building objectives of this study have been met with training of key members of the Nigerian research team, in the U.S. and onsite in Nigeria, on the protection of human research subjects in research, the informed consent process, the administration of structured clinical interviews (SCID), sample collection for DNA isolation and genetic analyses, and the operation and use of the EyeLink System to obtain eyetracking measurements in study participants. Participant recruitment, testing, and data acquisition are ongoing. Preliminary results will be presented at the meeting.

**Key Words:** Schizophrenia, Endophenotypes, Cognitive deficits, Genetics

Charles Wood/USA,

Victor Mudenda/ Zambia

**Presenter's Name: Victor Mudenda**

Grant number: NS074907

Grant title: Neuropathogenesis and Neuroinvasiveness of Subtype C HIV

Neuropathogenesis of end stage subtype C HIV-1 infected individuals in Zambia

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**Introduction:** As of 2011, 34 million people were infected with human immunodeficiency virus type 1 (HIV-1) globally with 22 million of these people in sub-Saharan Africa. Subtype C HIV is the most prevalent subtype that is spreading in Africa and is responsible for over 50% of new infections globally. Half of the people living with HIV-1 in sub-Saharan Africa are believed to have neurological disease associated with HIV infection (NeuroAIDS), however, little is known about Clade C HIV neuropathology in these infected individuals. In addition, opportunistic infections (OIs), common in African settings, are often neuroinvasive. The associated comorbidities in the setting may also play an important role in subtype C HIV-associated pathogenesis and needs to be further studied.

**Objective:** Our aim is to characterise subtype C HIV neuropathology and neuro-invasiveness in a Zambian cohort, determine if OIs contribute to the neuropathology and whether subtype C HIV compartmentalises in the brain.

**Methods:** Twenty-five autopsy samples (17 ART naïve HIV-1 Clade C positive, with CD4 count ranges from 4-224, and an average of 69; 8 HIV negative; 14 male: 11 female; age range 22-60

years) from Zambia, consisting of both fresh frozen and formalin-fixed samples of frontal lobe, parietal lobe, occipital lobe, temporal lobe, hippocampus, cerebellum and basal ganglia for each case examined were used in this study. Techniques used: histology, immunohistochemistry, PCR and qPCR.

**Results:** Opportunistic infections were detected in some cases as is seen in late stage ART naïve subtype B HIV infected individuals although histology showed no resulting pathology. Histology showed vasculitis with perivascular infiltration of lymphocytes, and dilated Virchow-robin spaces. Mild infiltration of macrophages into the brain was seen, but no multinucleated giant cells were seen. Microgliosis and astrogliosis were not statistically different from the control group.

**Conclusions:** From all the ART naïve subtype C HIV infected cases analysed so far, very few HIV infected cells were found in the brains, and the degree of neuronal damage appears not to be as severe as has been reported in late stage untreated HIV-1 subtype B infected AIDS patients.

**FIC-BRAIN ABSTRACT\_Russell VA\_Howells FM\_Neuronal Vulnerability\_South Africa**

Michael J Zigmond, USA

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**Fleur M Howells**

R01TW008040

Developmental Stress, Exercise and Vulnerability to Neuronal Injury: Interaction between early life stress and genetic predisposition

1) ABSTRACT

Early life stress/trauma is known to increase the risk in the development of psychiatric disorders. However limited research has assessed the role genetics play in the development of psychiatric disorders. Here we address the effects of early life stress/trauma on an established animal model of attention-deficit hyperactivity disorder (ADHD) the spontaneously hypertensive rat (SHR) and control strain(s). First we assessed the effects of maternal separation behaviourally with tests that assessed levels of arousal. Second we assessed the effects of maternal separation neurochemically with <sup>3</sup>H norepinephrine superfusion of hippocampal norepinephrine varicosities of the locus-coeruleus, a core arousal system involved in attention. Our results show that early life stress/trauma exaggerate behavioural predispositions of SHR - increased activity and novelty seeking. Second, early life stress/trauma exaggerate neurochemical predispositions of SHR – increased glutamate stimulated release of norepinephrine, via GABA<sub>A</sub> receptor antagonism. The results of these studies provide novel insight to the interaction of early life stress/trauma and genetic predisposition, and further research is warranted.

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Major foreign collaborator names: Vivienne Russell & William Daniels/ South Africa

Presenter name: **Vivienne Russell**

Grant number: R01TW008040

Grant title: Development stress, exercise and vulnerability to neuronal injury

## SUMMARY

In response to acute adversity, emotional signals shift the body into a state that permits rapid detection, identification, and appropriate response to a potential threat. The stress response involves the release of a variety of substances, including neurotransmitters, neurotrophic factors, hormones, and cytokines, that enable the body to deal with the challenges of daily life. The subsequent activation of various physiological systems can be both protective and damaging to the individual, depending on timing, intensity, and duration of the stressor. Successful recovery from stressful challenges during early life leads to strengthening of synaptic connections in health-promoting neural networks and reduced vulnerability to subsequent stressors that can be protective in later life. In contrast, chronic intense uncontrollable stress can be pathogenic and lead to disorders such as depression, anxiety, hypertension, Alzheimer's disease, Parkinson's disease, and an increased toxic response to additional stressors such as traumatic brain injury and stroke. We explored the interaction between early life stress and exercise later in life. We showed that mild pre- or postnatal stress can increase the vulnerability of dopamine neurons to toxic insult. We also showed that stress experienced in the early stages of development reduced not only the exercise-induced changes in neuron survival and behaviour, but also the exercise-induced changes in brain neuroplasticity. We found that voluntary exercise stimulated the MAPK/ERK1/2 signalling pathway in the rodent hippocampus and that this stimulation was blocked in rats that had been subjected to the early life stress of maternal separation. We argued that a full appreciation of the effects of stress and exercise – as well as their interactions –

requires a consideration of the characteristics of both conditions, including their nature, duration, intensity, and the age at which exposure takes place.