RESEARCH NEWS

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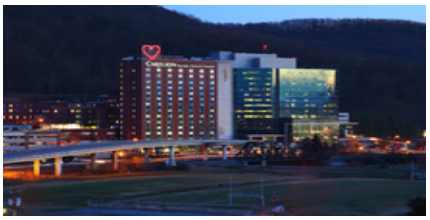

RESEARCHER SPOTLIGHT

Understanding Fundamental Mechanisms of Opioid Drugs Utilizing the Highly Powerful Resolution of Intracranial EEG to Probe Brain Function

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Neurosciences

Sujith Vijayan, PhD
VT Neural Dynamics & Neural Engineering lab

Opioid misuse is a national problem, hitting the Appalachian region particularly hard. The situation worsened during the COVID-19 pandemic with the number of opioid-related deaths climbing higher than the number of deaths from motor vehicle accidents. Increased mortality from opioids is considered a key driver of decreasing life expectancy in the United States. To tackle the problem scientifically, one first needs to understand the underpinning of the disorder. Opioids and other neuroactive compounds interact with the brain in different ways, and the various parts of the brain may be affected differently. The fundamental ways such drugs affect neuronal function can be studied using electroencephalography to probe electrical activity in the brain. This is a great tool but lacks fine resolution when recorded from the scalp. One can study neuronal activity in much finer detail using chronically implanted electrodes in the brains of epileptic patients who are undergoing invasive monitoring for clinical purposes.

Epilepsy is a common disorder characterized by recurrent unprovoked seizures. For most, the condition is treatable, and seizures are controlled with medications. However, up to a third of patients with focal epilepsy continue to suffer from seizures, even on medication. For these individuals with medically intractable focal epilepsy, surgical intervention to ablate or resect the seizure focus is an attractive alternative to eliminate seizures completely. Some of these patients require intracranial EEG (iEEG) monitoring to define the epileptogenic zone. In these patients, we routinely implant depth electrodes (small flexible plastic tubes of 1.3 mm diameter with embedded small platinum recording electrode and thin wires) and/or subdural grid electrodes into the brain under stereotactic guidance. Each depth electrode has multiple small metal electrodes, and up to 60-120 electrodes are placed in various brain regions, depending on the clinical need. Brain imaging techniques (post-op CT scan merged with pre-op MRI scans) can be used to accurately localize the location of each electrode within a specific brain region with high accuracy (see Figure 1).

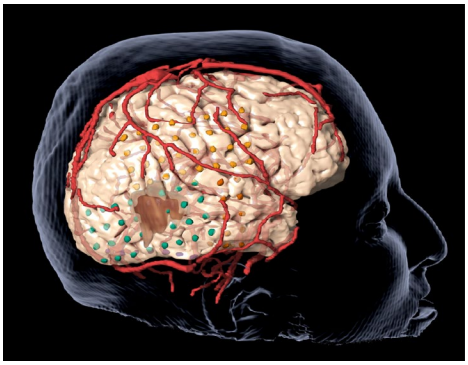

Figure 1: Reconstruction of pre-op MRI co-registered with post-op CT scan showing intracranial subdural grid electrodes (green and orange dots) over the right side of brain. Prominent venous structures are also overlaid.

A team of clinicians and researchers at Carilion Clinic and Virginia Tech, supported by an NIH iTHRIV grant[1], is using this invaluable method of iEEG recording combined with accurate anatomical information of electrode location to study the effects of various neuroactive drugs. The iEEG is usually recorded for several days from various brain regions to identify the seizure zone. During this time, the individual may take neuroactive drugs, including opioids, to control postoperative pain. The research team studies the relationships between drug administration and neural dynamics (e.g. power in a particular frequency in a given brain region) using classical standard signal processing techniques and statistical methods.

In preliminary analysis of the data, the team has shown that there is a distinct effect on the amygdala and other limbic structures following administration of hydrocodone or oxycodone (see Figure 2). This is interesting as these structures are associated with emotional experiences and memories and are also thought to be important in processing pain. The development of the techniques and tools for this investigation has the potential to be revolutionary for the study of the effects of not just opioids, but also other neuroactive compounds/medications at very high spatial resolution, helping us to understand the fundamental effects of these agents at the neuronal level.

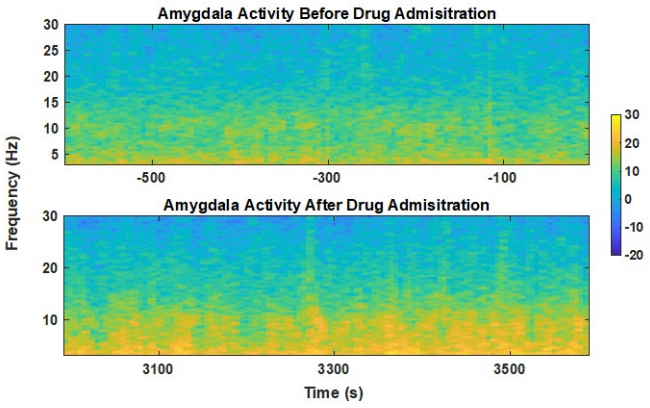

Figure 2. Hydrocodone Administration Enhances Theta (4-8 Hz) Power in the Amygdala. Top panel: Spectrogram prior to drug administration in an amygdala lead (duration: 10 minutes). The spectrogram shows power at a given frequency as a function of time. Warmer colors indicate more power. 0 is the time point of drug administration. Bottom panel: Same as top panel but after the administration of Hydrocodone, 50 to 60 minutes after Hydrocodone administration. Note the warmer colors in the theta band (4-8Hz) after the administration of the drug.

[1] The integrated Translational Health Research Institute of Virginia (iTHRIV) is a federally funded collaboration between UVA, Virginia Tech, Carilion Clinic, and Inova that facilitates clinical and translational research across Virginia. iTHRIV is funded by the National Center for Advancing Translational Science of the National Institutes of Health Awards UL1TR003015/ KL2TR003016.

ITHRIV REQUEST FOR PROPOSALS

Applications for the iTHRIV pilot grants and community grants are **due August 30**. Both types of grants will fund 12-month projects with a period of performance from 2/1/2022 through 1/31/2023. Applications are limited to 5 pages.

The goal of the iTHRIV Pilot Studies Program is to support innovative approaches to clinical and translational research to foster collaborative research across the iTHRIV partner institutions. The maximum funding amount for a project from one iTHRIV PI is $25,000. If two or more iTHRIV institutions collaborate on a project, the maximum funding amount is $50,000. iTHRIV institutions include Carilion, Virginia Tech, UVA, and INOVA.

The goal of the Community Seed Grant Program is to reduce health disparities and improve health among communities that experience poorer health outcomes and have historically been excluded from opportunities to engage in research (e.g. racial/ethnic minorities, rural communities, women, low-income families). Funding requests cannot exceed $40,000. At least 40% of all funding must directly fund the Community Organization's role in the project. Applicants are required to attend a Zoom informational session on either July 7th or August 4, 2021.

Refer to this website for complete details: https://www.ithriv.org/ithriv-request-for. Please let Vera Hollen know if you are interested in applying for either of these funding opportunities (VLHollen@CarilionClinic.org or 540-521-5284).

SPARC SECURE RESEARCH ENVIRONMENT UPDATE

After an intensive external audit, our **SPARC (Storage and Programs Accelerating Research Collaborations)** secure research environment has been approved to store **identified and sensitive information for Research, Grants and QA/QI projects**.

SPARC is an innovative and HIPAA compliant tool for **data storage, access, analysis, and use**. Since it continuously maintains the regulatory mandated privacy and security protections for protected health information (PHI), it is a great option for research that relies on information from medical records. Moreover, SPARC allows data to be safely stored in a cloud environment and securely accessed from anywhere for ultimate convenience. With appropriate approvals, researchers can access this environment across institutions using their respective log in credentials rather than needing a Carilion Clinic account, which makes SPARC especially useful for **inter-institutional collaborations**. What makes SPARC unique to other **cloud-based** data storage programs is the ability for data analysis to occur *within* the environment. SPARC provides access to programs such as **SAS, R, Python, Microsoft Office Suite**, and **AWS tools** so data can be easily analyzed without leaving the enhanced security of Carilion Clinic's data storage ecosystem**. Coming soon - NVIVO for Qualitative Analytics!**

Contact HART@carilionclinic.org to learn more about SPARC and how to incorporate it into your Research protocol, Grant or QA/QI project!

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REGULATORY AFFAIRS HIGHLIGHT

Along with groundbreaking scientific discoveries and generalizable knowledge, research comes with a deluge of rules and regulations. Investigators involved in industry sponsored clinical trials often find themselves having to answer not only to the funding source of their research projects, but are also answerable under the tutelage of institutional, local, state, and federal guidelines that can feel contradictory. Regulations are not meant to facilitate research but are not meant to hinder the process either. While some policies can feel restrictive, the objective of these guidelines is to systematically provide tools for investigators to perform ethically sound clinical research.

To help with this process, the Research & Development department has a regulatory affairs section whose focus is on managing the regulatory processes of clinical trials taking place at Carilion Clinic. Some of the responsibilities of this section include preparing IRB submissions, gathering regulatory documents required by sponsors, such as CVs, medical licenses, and Good Clinical Practice training. Regulatory training is available and provided to clinical research coordinators, research assistants, and other key research personnel upon request. Assisting with the preparation of internal audits, performing internal quality assurance reviews, as well as preparing for any external monitoring from sponsors and regulatory authorities, including the FDA, is also part of the duties of the regulatory affairs section.

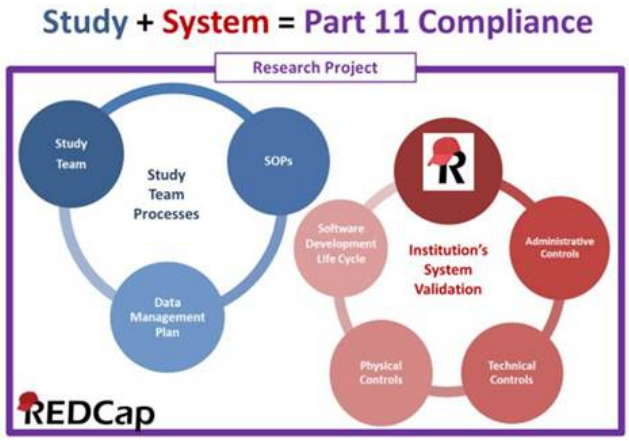
For questions involving regulatory affairs, please contact the Clinical Regulatory Affairs Manager, Kristina Cooper, at kecooper1@carilionclinic.org or 540-224-4663.

21 CFR PART 11 COMPLIANCE

Carilion Clinic Research Administration is happy to announce that we are allowing REDCap to be used for e-consent in FDA-regulated studies which require 21 CFR Part 11 compliance.

What is 21 CFR Part 11?

Title 21 of the Code of Federal Regulations (CFR) contains the rules for the U.S. Food and Drug Administration (FDA). Part 11 lies within that section of the CFR and is a guideline that describes the criteria under which the FDA considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper. This regulation, which applies to all FDA program areas, is intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.



(Source: Terri Shkuda, Systems Analyst, Lead, Penn State University)

FDA guidance on 21 CFR Part 11 compliance in the context of clinical studies is available on the FDA website here. Guidance documents are searchable, and the following are suggested:

(1) *Part 11, Electronic Records; Electronic Signatures – Scope and Application* (September 2003)

(2) *Computerized Systems Used in Clinical Trials* (May 2007)

Please note that **REDCap is 21 CFR Part 11-ready, meaning that if implemented *in conjunction with appropriate procedures, documentation, and qualification, then your study may meet Part 11 requirements.*

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However, compliance depends on the setting, which includes **BOTH** the technical aspects of the installation and maintenance, quality requirements (Carilion Clinic responsibilities), as well as the essential processes put in place by users (PI/Study Team responsibilities).

Carilion HART offers a secure environment for REDCap instances, which are frequently upgraded and backed up to a secure site. Login accounts to these instances are provided and monitored by HART and Organizational Integrity & Compliance (OIC) personnel. Logins are also provided to personnel of Carilion collaborators and organizations affiliated with Carilion or its collaborators.

Individual users or study teams are also responsible for ensuring the establishment/documentation of appropriate SOPs for both technical and procedural compliance. The actions recommended by Part 11 are general good practices in research and include: clear definition of study team roles and responsibilities, training corresponding to personnel responsibilities, database change control and documentation, and record retention.

Again, Carilion's REDCap cannot be considered Part 11 compliant without **BOTH** administration **AND** study team SOPs. **It is ultimately the Principal Investigator's responsibility to ensure this occurs for their research projects.** Please see the diagram from Penn State to illustrate the necessary steps for REDCap Part 11 compliance.

If you have any additional questions about REDCap and e-consent, please reach out to HART (Mattie Tenzer at mmtenzer@carilionclinic.org) or Research Compliance (Allison McKell at aomckell@carilionclinic.org).

NEW EMPLOYEES

Jordan Hughes, BS, Clinical Research Coordinator – Cardiology
Jordan received her bachelor's degree in Health and Exercise Science from Jefferson College of Health Science and has worked on COVID research in the NRV area through Velocity Care. We are excited to have her join our Cardiology group and support our ever-growing Cardiology research portfolio.

Maryann Hollen, BS, Clinical Research Coordinator – Radiology
Maryann received her bachelor's degree from Shenandoah University in Public Health and Psychology and has worked closely with Carilion's Psychiatry Department on their ED Bridge to Clinic project. We are thrilled to have her join us in the Department of Radiology and help grow the research program in that area.

Jadon Beck, BA, Clinical Research Assistant – Orthopaedic Hand Clinic
Jadon Beck is a new clinical research assistant that will be supporting Dr. Peter Apel's research in the Orthopaedic Hand Clinic. Jadon graduated from the University of Kansas in 2017 with a B.A. in sociology and also earned a post-baccalaureate certificate in pre-medical graduate health sciences from VCU. Jadon has worked in several clinical positions and joins R&D after working as a clinical assistant at Carilion Clinic Velocity Care in Lexington.

JP Rader, BA, Clinical Research Assistant – Surgery
JP is a new Clinical Research Assistant that will be supporting research within the Department of Surgery. JP is a recent graduate of the University of Virginia where he received a B.A. in biology. While completing his undergraduate coursework, JP worked on amphiphilic compounds testing for antibiotic resistance to S. aureus and E. coli. Prior to coming to Carilion, JP served as a medical scribe for Shenandoah Valley Orthopedics.

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Christina Dowdy, BA, Regulatory Affairs Specialist

Christina Dowdy will be joining the Research & Development team in mid-July as the newly appointed Regulatory Affairs Specialist. Christina received her B.A. in Speech & Hearing Science with a Research Distinction from Ohio State University. Most recently, Christina held the position of Clinical Research Project Manager – Neurology at the University of Cincinnati Health. In her new role, Christina will work closely with the clinical research coordinators and external agencies in the submission of IRB documentation and preparation and maintenance of regulatory documentation for industry-sponsored clinical trials. We are excited to have someone with her knowledge and experience in clinical research regulations join our team.

RESOURCE LINKS

Research and Development

Human Research Protections Office

CITI

Health Analytics Research Team

TriNetX

iTHRIV

PRIS3M Online IRB Submission System

iTHRIV UPDATES:

Upcoming Workshops and general information: https://portal.ithriv.org/#/home