![NIDUS logo — Network for Investigation of Delirium : Unifying Scientists]

September 2021 NIDUS Newsletter

Network for Investigation of Delirium: Unifying Scientists

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NIDUS Celebrates it 5th Anniversary!

NIDUS has been funded for another 5 years by the National Institutes of Aging (Grant no. R24AG054259). More information about the goals of NIDUS for the next 5 years, its current cores and task forces and its leadership can be found at: https://deliriumnetwork.org/about/

Over the past five years, thanks to the efforts of many, the guiding principles of NIDUS have been met through a long list of initiatives and programs; all of which continue to successfully grow today:

Measurement info cards:

- 40 Adult Info Cards and 5 Pediatric Info Cards

- Delirium Item Bank and Harmonization Program: Statistical harmonization code to create crosswalks and the Delirium Item Bank.
- Delirium Severity Symptom Coverage - compares 17 commonly-used delirium severity measures based on symptoms included in each measure

Delirium Research Hub: discover studies and collaborators

- The NIDUS Research Resources Core has created the Delirium Research Hub - a searchable database of over 700 human and over 100 animal completed and ongoing delirium research studies, intended to enable research collaborations, meta-analyses, and systematic reviews
- If you have conducted a delirium study, submit your study information for inclusion in this important resource
- Join the Collaboration site to network with collaborators and join in on related studies (https://deliriumnetwork.org/deliriumresearch-hub/collaboration-communication-site/)
- Each week, a research study included in the Delirium Research Hub is highlighted on the NIDUS twitter as a part of our #DeliriumHub500 Campaign
- Delirium Research Hub Investigator Spotlight features an investigator and research study that is included in the Research Hub. Submit your study for a chance to be featured in the investigator spotlight!
- Visit https://deliriumnetwork.org/delirium-research-hub/ for more information and how to submit your study

The Delirium Boot Camp

- The annual Delirium Boot Camp is a 2.5 day intensive training course on delirium research and methodology, featuring interactive workshops led by leaders in the field
- The Boot Camp contains didactic sessions on a variety of delirium-specific research topics ranging from biomarkers to qualitative research, as well as a mock grant review, CAM training and more
- Sign up to be an attendee or NIDUS alumni-junior faculty at future Boot Camps
- Recordings from previous Boot Camp sessions are available on the NIDUS website: https://deliriumnetwork.org/career-development/delirium-boot-camp-videos/

- Junior Faculty Working Groups provide peer support, collaboration, and mentorship. Activities include peer review of manuscripts, abstracts, and grants; presentation of ongoing research progress; and participation in NIDUS activities
- Mentorship & career development webinars are ongoing and recordings of previous webinars are saved to the NIDUS website

Dissemination Task Force: publicize your work

- The NIDUS blog, featuring posts on a variety of topics related to delirium research and news, is a great way to create awareness about your new publications and grants
- NIDUS twitter and newsletters are used to disseminate research findings and delirium publications

The Delirium Bibliography

- The Delirium Bibliography allows you to quickly gain access to 4,273 indexed articles on delirium and acute care of older persons and is updated on a monthly basis
- Full text links are available for publications through PubMed Central
- Access the Bibliography at https://deliriumnetwork.org/bibliography/
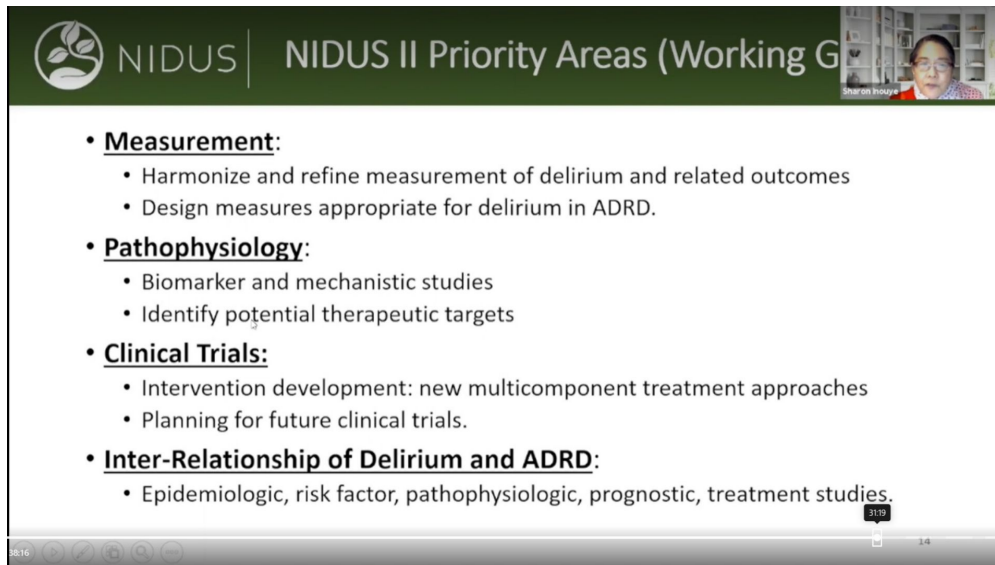
Collaboration with American Delirium Society (ADS): present your work and network

- Featured NIDUS sessions to present talks and posters
- Network with international delirium researchers
- Mentoring Sessions

NIDUS Highlights from the 2021 American Delirium Society Annual Meeting

During the recent American Delirium Society Annual Conference, NIDUS held an overview session and three virtual abstract sessions featuring research from former boot camp alums and pilot grant awardees. Many thanks to the meeting organizers for putting together a wonderful event!

accomplishments and what is planned over the next five years. For more information please refer to https://deliriumnetwork.org/about/

NIDUS Pilot Abstract Session 1

Dr. Michael Avidan, Co-Leader of the NIDUS Pilot and Innovation Task Force, moderated the NIDUS Pilot Abstract Session. The presentations were authored by the awardees of the NIDUS Year 4 Pilot grants! The NIDUS pilot awardees were chosen from a highly competitive group of applicants.

Biomarkers of Postoperative Delirium in Children After Cardiac Bypass Surgery – Sean Barnes, MD

Delirium is prevalent in children who undergo cardiac surgery with cardiopulmonary bypass (CPB) and is independently associated with increased ventilator days, ICU length of stay and mortality. The pathophysiology of pediatric delirium in the postoperative period is not understood. Dr. Barnes and colleagues hypothesize that plasma biomarkers reflective of pathways implicated in delirium pathogenesis (i.e., neuronal and astrocytic injury, altered neurotransmitter signaling, inflammation) can predict postoperative delirium in the perioperative period. His research to date has demonstrated the feasibility of enrolling a representative sample of pediatric cardiac patients, screening and diagnosing postoperative ICU delirium in this population, and collecting and assaying multiple biomarker samples.
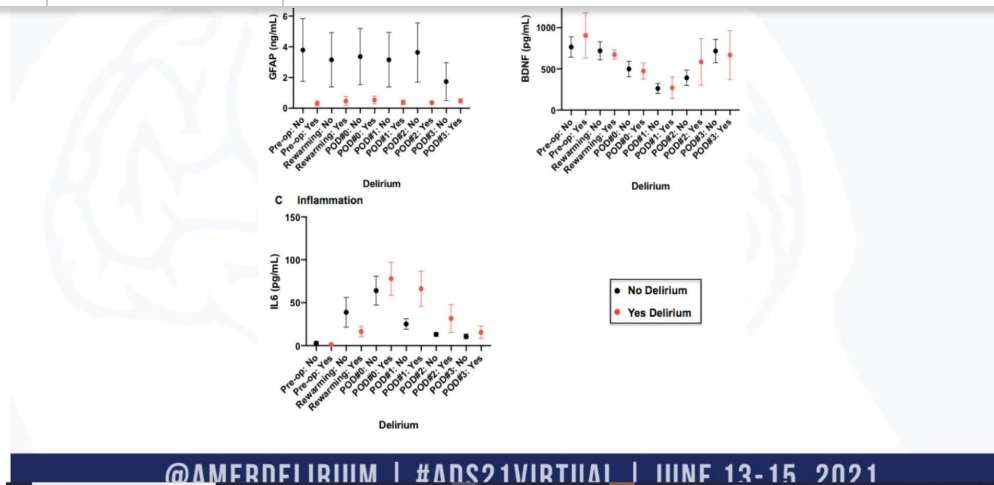
Machine Learning Algorithm to Predict from Emergency Department Data–
Sangil Lee, MD

Delirium is frequently missed in the emergency department (ED). Dr. Lee and colleagues sought to identify a clinically valuable predictive models for prevalent delirium within the first 24 hours of hospitalization based on the available data by assessing the performance of logistic regression and a variety of machine learning models. The area under the ROC curves for their models ranged from .79 to .85. In this analysis, logistic regression, random forest, and gradient-boosted machine models demonstrated the best predictive ability with respective AUCs of .853, .853, and .854. This study demonstrated the use of machine learning algorithms to identify the combination of variables that are predictive of delirium within 24 hours of hospitalization from the ED

Validating the Fluctuating Mental Status Evaluation – Michael Reznik, MD

Fluctuating Mental Status Evaluation (FMSE) is a five-component delirium screening tool, developed by Dr. Reznik, that is specifically designed for use by clinicians in neurologically-injured patients. For each component, assessors are asked to determine if there has been any change over the nursing shift and from the prior nursing shift. In this study, Dr. Reznik and colleagues sought to validate the FMSE in population of stroke patients admitted to a neuro-ICU by evaluating the criterion validity of the FMSE, the predictive validity of the FMSE, and the real-word utility and feasibility of the FMSE. Final results are pending.

The Fluctuating Mental Status Evaluation (FMSE)

- Began developing the FMSE in 2018-2019 as part of a pilot study
- 40 patients with ICH were enrolled and assessed daily throughout their stay in the Neuro ICU & Stroke Unit
- FMSE assessments were performed by bedside clinical nurses with brief training on the use of the tool

Total FMSE score	Per assessment-day (n=306)		Per patient, ever delirious (n=40)	
	Sensitivity	Specificity	Sensitivity	Specificity
≥1	86%	74%	97%	67%
≥2	68%	83%	94%	67%
≥3	43%	93%	88%	83%

- Based on these data, plan to test FMSE score ≥ 1 as possible delirium and ≥ 2 as probabl[e]

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NIDUS Pilot Abstract Session 2
Dr. Donna Fick, Co-Leader of the NIDUS I Career Development and Mentorship Task Force and Dr. Andy Auerbach, Co-Leader of the NIDUS I Dissemination Task Force, moderated the NIDUS Pilot Abstract Session. The presentations were authored by the awardees of the NIDUS Year 4 and Year 5 Pilot grants. The NIDUS pilot awardees were chosen from a highly competitive group of applicants.

Profiling postoperative neuroinflammation in a mouse model of delirium superimposed on Parkinson's Disease – Ravikanth Velagapudi, PhD
Parkinson's disease (PD) patients often require common surgical interventions such as orthopedic surgery. These life-saving procedures often increase the risk for postoperative cognitive complications, like delirium, especially in the older and frail patients. Currently no study has attempted to model the effects of surgery-induced neuroinflammation in PD. Dr. Valagapudi and colleagues used the leucine-rich repeat kinase 2 (LRRK2) G2019S knock-in mouse to study the

by morphological changes in microglia, higher expression of CD68, as well as reactive astrocytes. These changes were not limited to the hippocampus, but were also observed in prefrontal cortex. Surgery also exacerbated the acute deposition of phosphorylated-tau in MAP2 positive cells in the dentate gyrus compared to age-matched controls. These findings suggest that mice with pre-existing PD pathology are more vulnerable to postoperative neurological complications and neuroinflammation.
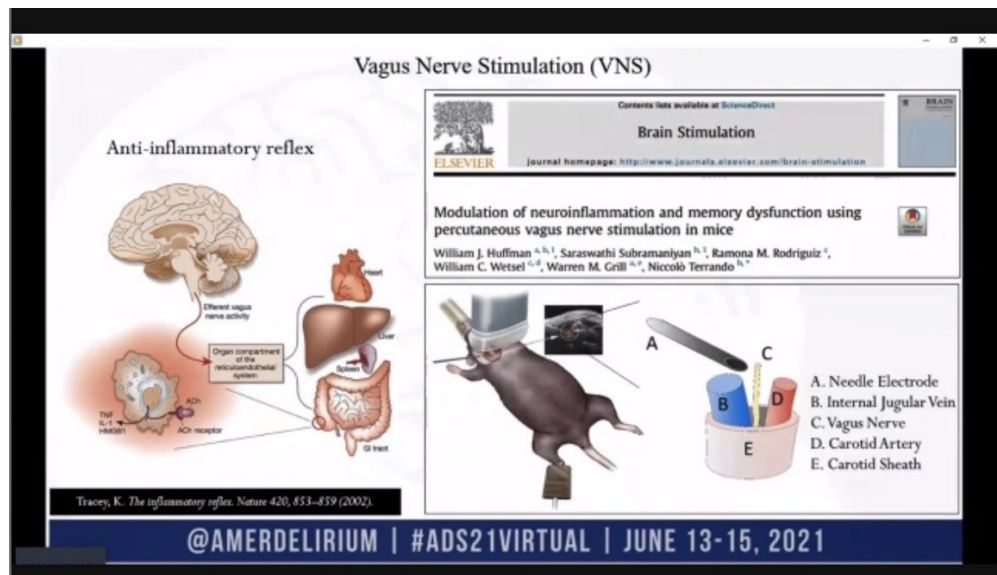

Potentiation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) by highly-sulfated chondroitin sulfate: a novel contributor to sepsis-associated delirium – Joseph Hippensteel, MD

Endothelial glycocalyx-derived chondroitin sulfates (CS) are shed from the vascular endothelium during sepsis; the most highly charged CS have been shown to penetrate the hippocampus. In murine models of sepsis, an association between highly charged CS concentrations in the hippocampus has been found but the underlying pathobiology of this relationship remains unclear. Dr. Hippensteel and colleagues found that a strong relationship between highly-sulfated hippocampal CS concentrations and hippocampal excitability (a potential mechanism for delirium). He is currently investigating whether blocking hippocampal penetration of CS early in sepsis will effect hippocampal excitability and murine cognition.
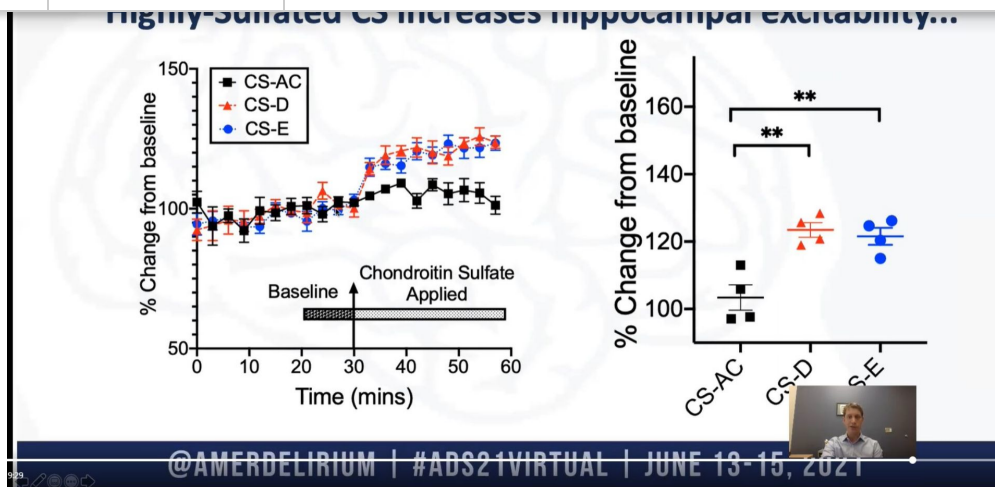
A Step Towards Building a Computable Delirium Phenotype: Analyzing Unstructured EHR Data – Kimberly Oosterhouse, PhD

Nurses are in a key position to prevent or identify and manage delirium, but despite increased awareness, delirium is still frequently unassessed, unrecognized, and unreported. Clinical narratives from electronic health records are a rich source of data that are not routinely being used for delirium detection. The Unified Medical Language System Meta thesaurus links independent standardized ontologies approved by the United States National Library of Medicine by health-related concepts, known as concept unique identifiers. Dr. Oosterhouse and colleagues retrospectively identified and validated concept unique identifiers for delirium in electronic health record unstructured data using a natural language processing clinical engine text analyses and knowledge extraction system(cTAKES®) to determine the positive and negative predictive values for delirium concept unique identifiers in the unstructured electronic health record data.
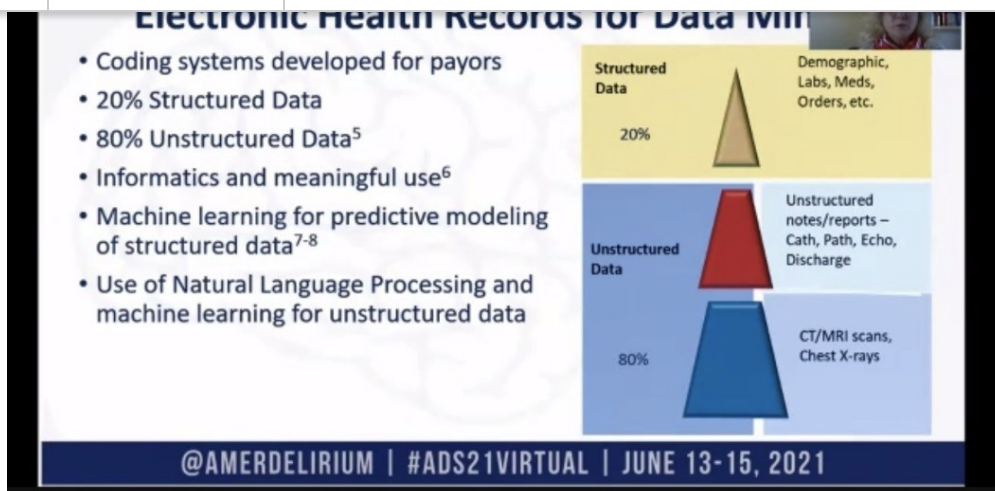
NIDUS Scientific Abstract Session

Drs. Jan Busby-Whitehead and John Devlin, Co-Leaders of the NIDUS II Career Development and Outreach Core, moderated the NIDUS Scientific Abstract Session. These excellent presentations were all authored by alumni of the Delirium Boot Camp!

Opioid Use Increases the Risk of Delirium in Critically Ill Adults – Matthew Duprey, PharmD, PhD

It remains unclear whether opioid use increases the risk of ICU delirium. Dr. Duprey and colleagues sought to evaluate the association between ICU opioid exposure (including the dose administered) and delirium occurrence The 4,075 patients (age 60.9±15.4, 63.6% male, 62.2% surgical, APACHE-IV58.5±28.0) contributed 26,250 ICU days to the cohort; an opioid was administered on 57.0% (n=14,975) days, ventilation was administered on 79.4% (n=20,852), severe pain occurred on 7.0% (n=1,829), and delirium occurred on 23.5% (n=6,176). Any opioid administered in awake patients without delirium was associated with an increased risk for delirium the next day (OR1.45; 95%CI 1.24-1.69). Each daily 10mg IV morphine equivalent dose increase was associated with a 2.4% increased risk for delirium the next day. Results were stable with respect to study year, age, ICU admission type, and whether a natural (e.g., morphine) versus synthetic (e.g. fentanyl) opioid was administered. Receipt of an opioid in the ICU increases the odds of transitioning to delirium in a dose-dependent fashion.

Methods

- Prospective cohort: August 2011 through March 2019
- Consecutive adults admitted ≥ 24 hours to the 32-bed mixed medical-surgical ICU of the University Medical Center Utrecht
- Mental status assessed by investigators using a well-validated protocol

Mental State	Characterization
1. Delirium	CAM-ICU positive or delirium-positive from algorithm
2. Coma (i.e., unarousability)	no presence of delirium, at least 1 RASS ≤ -4
3. Awake without delirium	no coma or delirium
4. Exit from the ICU	patient died or was discharged (only day t + 1)

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An Innovative Transitions Model of Care to Prevent Cascade of Problems After Delirium: "DDEFY Delirium": A Pilot Feasibility Randomized Trial – Ariba Khan, MD, MPH
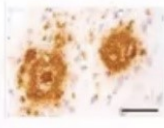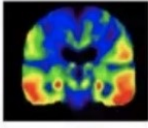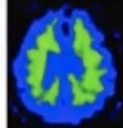
Without a structured process for delirium follow up, older individuals and their family caregivers seem to be lost, as they transitioned from hospital to home. Dr. Khan and colleagues sought to develop and pilot test a theoretical post-hospital model of care (DDEFY delirium) to mitigate the cascade of complications in patients who had delirium in the hospital. Among the 35 participants diagnosis of dementia was present in 40%. The overall recruitment rate was 44.6%, feasibility was 97% and attrition rate was 57.9%. The overall 30-day readmission rate was 21.6% and there were 2 participants who had 30-day ED visits. The intervention Group had a 44.6 % recruitment rate, 97% feasibility, 100% fidelity, 28.6% 30-day readmission rate, and no 30-day ER visit readmissions. From this pilot study, it was determined that delivering DDEFY intervention to delirium patients is feasible. The lessons learned from conducting this study will help us design a larger trial with modifications for older patients with delirium who transition from hospital to home.

DDEFY Delirium Intervention

Stage of Intervention	Time Frame	D: Drugs	D:Diagnosis	E:Educate patient and family	F:Functional assessment and treatment	Y:Your goals
Goal		Which medications could affect cognition	Assess for: delirium, dementia and depression. Reduce modifiable risk factors.	Educate family to prevent future episodes and recognize delirium.	Ensure independence and maintain function. Reduce modifiable risk factors.	Establish patients' and families' preferences.
Tasks		Review polypharmacy, anticholinergic burden, Beer's high-risk medications, opioids, sedatives and antipsychotic medications.	Assess cognition, establish baseline to treat and prevent future episodes.	Provide family with reading material and do teach back to ensure they understand the material.	Assess function, assess for need for equipment and recommend interventions.	Assess patient's understanding and goals. Provide resources for patients to stay independent at home. Assess for caregiver burn out. Provide community resources.
First contact in the hospital	Before discharge	Introduction to the program and obtain informed consent by delirium nurse navigator.				
Home visit	Within 48 hours discharge	Do they have medications and who manages medications?	FAM CAM, 3D CAM, and MoCA, PHQ 9 and GAD. Virtual intervention: 6 item screener	Provide delirium education	Katz ADLs, IADLs, Rockwood frailty scale, timed get up and go.	Caregiver burn out (DEL-B). Establish goals "What is one personal goal that is important for you to achieve in the next month?"
Interdisciplinary team meeting: DDEFY delirium team and Clinic team	Within 7 days of discharge and after the home visit	Medication assessment and recommendations	Review chart for cause of delirium, previous cognitive problems	Review chart for gait, mobility, PT/OT/ST, equipment ordered.	Advance directives and code status.	Recommendations regarding caregiver burden
Plan of care and follow up phone calls as needed	Within one month	Community resources for caregiver burn out, advance directives, and code status. Communicate plan of care with primary care and get the orders placed for the team recommendations. Assess understanding of intervention and answer questions. Assess goals of care.				

Post-Operative Delirium and Its Relationship with AT(N)-X Biomarkers: A Meta-Analysis – Sophia Wang, MD

The pathophysiology connecting post-operative delirium (POD) and Alzheimer's and other related dementias (ADRD) is not well understood. Dr. Wang and colleagues sought to identify ADRD biomarkers associated with POD. A total of 28 studies were included in this meta-analysis. Studies focused on inflammatory and neuronal injury biomarkers; there were an insufficient number of studies for amyloid and tau biomarker analysis. Two inflammatory biomarkers (IL-6 and CRP) showed a significant relationship with POD (IL-6 n=10, SMD: 0.53, 95% CI: 0.36 to 0.70; CRP n=14, SMD: 0.53, 95% CI: 0.33 to 0.74). Two neuronal injury biomarkers (blood based S100B and NfL) were positively associated with POD (S100B n =5, SMD: 0.40, 95% CI:0.11 to 0.69; NFL n =2, SMD: 0.93, 95% CI: 0.28 to 1.57). Of note, a majority of analyses were impacted by significant study heterogeneity. This meta-analysis identified an association between certain inflammatory and neuronal injury biomarkers and POD.

2018 NIA-AA Research Framework

	Amyloid (A)	Tau (T)	Neurodegeneration/ neuronal injury (N)
Modality			
Fluid	CSF Aβ$_{42}$ or Aβ$_{42}$/Aβ$_{40}$	CSF P-tau	CSF T-tau
Neuroimaging	amyloid PET	Tau PET	Anatomic MRI FDG-PET

Jack et al. 2018

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Prevalence of Delirium in Older Adults Living with Dementia Receiving Home Health Care – Shih-Yin Lin, MPH, PhD

Our knowledge about the prevalence of DSD in home healthcare settings is limited. Dr. Lin and colleagues assessed the prevalence of delirium and features of delirium in older adults living with dementia admitted to home healthcare. A total of 126 participant had at least one 3D-CAM administered (427 total screens across the 4 visits). The prevalence of 3D-CAM Feature 1 (acute change/fluctuating course) was 6.3%, Feature 2 (inattention) 78.9%, Feature 3 (disorganized thinking) 69.7%; and Feature 4 (altered level of consciousness) 16%. The point prevalence of a positive screen was 6.3% (8/126) at Visit 1; 2.9% (3/104) at Visit 2; 1.9% (2/103) at Visit 3; and 2.1% (2/94) at Visit 4. Delirium is prevalent in older adults living with dementia receiving home healthcare.

3D-CAM Feature 2 & Feature 3 Questions

Feature 2 Inattention (Code 'Yes' if any of the items 4,5,6,7, 16 and 17 are incorrect/present)

4. Now I am going to read some numbers, but I want you to repeat them in backwards order from the way I read them to you. For example, if I said 6-4, you would say 4-6.

The first one is 7-5-1.

5. The second is 8-2-4-3

6. Please tell me the days of the week backwards, starting with Saturday.

7. Please tell me the months of the year backwards, starting with December.

16. Did the patient have trouble keeping track of what was being said during the interview? (repeatedly asking the interviewer to repeat questions)

17. Did the patient appear inappropriately distracted by environmental stimuli? (such as television, people outside the room, roommate's conversations)

Feature 3 Disorganized Thinking (Code 'Yes' if any of the items 1, 2, 3, 13, 14 and 15 are incorrect/present)

1. Please tell me the year we are in right now.

2. Please tell me the day of the week.

3. Please tell me what type of place is this? [hospital]

13. Was the patient's flow of ideas unclear or illogical? (nonsensical speech, inappropriate answers to questions, contradictory statements or shifting unpredictably from subject to subject)

14. Was the patient's conversation rambling, inappropriately verbose, or tangential? (off target responses or telling a story unrelated to the interview)

15. Was the patient's speech unusually limited or sparse? (inappropriately brief or stereotyped answers)

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NIDUS II Collaborative Happy Hours !

The 2021 NIDUS Happy Hours are off to a great start!
The goal of the NIDUS Happy Hours is to catalyze **collaborative working groups** who will work together to design projects and to compete for the NIDUS II Pilot Awards.
Each happy hour, moderated by a NIDUS faculty, will:

- Provide an overview of NIDUS resources and how researchers can utilize them to accomplish their scholarship
- Review requirements for NIDUS pilot proposals
- Create a forum to enhance and launch new collaborations

Future Happy Hours are Scheduled for:
September: 9th (1:30-2:30pm EST), 14th (5:30-6:30pm EST), 23rd (12-1pm EST) & 28th (5-6pm EST)
October: 6th (12-1pm EST), 12th (5-6pm EST), 19th (12-1pm EST) and 28th (12-1pm EST)
November: 4th (12-1pm EST) and 18th (5-6pm EST)

Happy Hour Registration: https://redcap.link/f2d807l0

Why form a collaborative group?

- Compete for <u>one of the ten $1,000 NIDUS II Collaborative Awards</u>!
  - One-page letters of intent (LOI) are due November 15, 2021. Letters of intent must involve a collaborative group, but must be submitted by a single principal investigator.
  - LOI instructions here: https://deliriumnetwork.org/pilots/nidus-ii-pilots-loi/
- Move ahead to a pilot grant: Qualifying pre-applications (1 page letter of intent) will be eligible for:
  - Methods consultation to refine your pilot grant (up to 10 in Year 1)
  - Research Hub may help you find other investigators to launch your working group
  - Measurement Core may help you harmonize targeted measures

More information at https://deliriumnetwork.org/delirium-research-hub/nidus-happy-hours/

2021 NIDUS Boot Camp Nov 7-9 at Chapel Hill, NC

The 2021 NIDUS Boot Camp will be held in Chapel Hill, North Carolina on November 7-9. Twelve junior delirium researchers will be attending this year's bootcamp. The Boot Camp will include didactic sessions on a variety of delirium-specific research topics, as well as a mock grant review, CAM training and more. Applications for the fall 2022 Bootcamp will open in early 2022. More information on the NIDUS bootcamp can be found at https://deliriumnetwork.org/career-development/

Join NIDUS!

We encourage your mentees and colleagues to sign up and become a NIDUS member or just to receive our announcements/newsletter.

For more information on NIDUS, please
visit our website.

Follow NIDUS on Twitter: @NIDUS_delirium

About NIDUS

measurement resources, training opportunities, pilot funding and dissemination of information. It is funded through an award from the National Institutes of Health/National Institute on Aging (grant no. R24AG054259).

Find Out More

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