Minneapolis VA Health Care System
Research Day 2016

Celebrating 70 years of Collaborative Research
1946 - 2016

VA U.S. Department of Veterans Affairs

University of Minnesota

Program and Abstract List
(alphabetically, by author)

May 23, 2016

☆ Program ☆

1. Oral Presentations – 1st Floor Auditorium (12:00 - 1:00 pm)

☆ **Introductions and Welcome** .....Hanna E. Bloomfield, MD, MPH, Associate Chief of Staff, Research Service

☆ **2015 Zieve Award Presentation** ..... James Johnson, MD

Recipient: *Aimee M. Merino, MD*
"A Randomized Controlled Trial of a CPR Decision Support Video for Patients Admitted to the General Medicine Service"

☆ **Keynote Address**..... Allen S. Levine, PhD

Professor of Food Science and Nutrition
Liaison for Special Initiatives, Office of the Provost University of Minnesota

"Why we can't we stop eating"

☆ *The Minnesota Veterans Medical Research and Education Foundation will be providing Free Box Lunches to the first 120 attendees.*

2. Poster and Exposition Session – 2nd Floor Flag Atrium (1:00 – 3:00 PM)

☆ *Research Findings and Innovations from the Minneapolis VA Medical Center*

☆ *Popcorn provided by the Minneapolis VA Research Office*

Author Index *(first author only)*

1. Effect of Implantable Cardioverter Defibrillator on Survival of Patients with Ejection Fraction greater than 35%

Adabag, Selcuk[1,2]; Rector, Thomas[1,2]; Ensrud, Christine[1,2]; Vakil, Kairav[1,2]; Patton, Christine[3]; Buxton, Alfred[4,5]; Poole, Jeanne[3]

1. Minneapolis VA Health Care System
2. University of Minnesota
3. University of Washington
4. Beth Israel Medical Center
5. Harvard University

Abstract: BACKGROUND: When added to optimal medical therapy, implantable cardioverter defibrillators (ICDs) improve the survival of many patients with heart failure who are at a heightened risk of sudden cardiac death (SCD) due to ejection fraction (EF) ≤ 35%. In 25% of patients with ICD, EF improves to above > 35% during follow-up. Whether ICD continues to benefit these patients is unknown. OBJECTIVE: To assess the effect of ICD on survival in patients with EF > 35% METHODS: We analyzed the The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) database, which randomized 2521 patients with New York Heart Association class II-III symptoms and EF ≤ 35% to ICD, amiodarone, or placebo for primary prevention of SCD. During follow-up 1875 (74%) patients had a repeat EF measurement and were included in this analysis. Survival of patients assigned to placebo or amiodarone were not different. We merged these two groups in to a single control group. The first follow-up EF measurement after randomization in SCD-HeFT was used to categorize patients into EF > 35% and EF ≤ 35% groups. Follow-up period started with the date of the first EF measurement after randomization. RESULTS: Of the 1,875 patients, 580 (31%) had a follow-up EF > 35% after 13.7 ± 6.2 months. In these patients, the mean EF increased from 26 ± 7% to 46 ± 8% while there was no significant change in the remaining 1,295 patients (23 ± 7% at baseline and 25 ± 7% at follow up). In total, 30% of the patients assigned to ICD and 31% of those assigned to amiodarone/placebo had a follow-up EF > 35%. A total of 360 (19%) patients died during a median follow up of 30 months (IQR 19.4 to 41.5 months). All cause mortality was lower in patients with EF > 35% than EF < 35% (3.5 vs. 9.4 per 100 person-years). The ICD was associated with an absolute reduction of 2.6 deaths per 100 person-year follow-up in patients with follow-up EF ≤ 35% and 1.3 deaths per 100 person-year follow-up in patients with a follow-up EF > 35% The adjusted hazard ratio for ICD effect on all-cause mortality was 0.65 (95% CI 0.51 to 0.84; p = 0.001) in the EF < 35% group and 0.77 (95% CI 0.39 to 1.54; p = 0.46) in the EF > 35% group. The adjusted interaction between ICD and EF category was not significant (interaction p-value=0.72). CONCLUSIONS: Compared to patients with EF < 35%, ICD is associated with a similar relative reduction but a smaller absolute reduction in mortality in patients with EF > 35%.

Research Topic: Heart Disease
Funding agencies: CSR&D
Grant support: None

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2. VA CSP #592 Efficacy and Safety of ICD Implantation in the Elderly

Adabag, Selcuk[1]; Eggers, Tommi[1]

1. Minneapolis VA Health Care System

Abstract: Introduction: ICDs have a single but powerful action: to prevent Sudden Cardiac Death (SCD) by restoring normal rhythm in the event of a life-threatening ventricular tachyarrhythmia. While ICD therapy is proven as an effective preventer of SCD in younger patients, its benefit to older patients is unclear. Relevance: ICD therapy is an under-utilized treatment option. The proportion of potentially eligible veterans implanted with an ICD peaks at age 67 and declines continuously thereafter. No randomized clinical trials have focused solely on an older population. Objectives: 1) to study the safety and efficacy of ICD implantation as a primary prevention strategy of SCD in patients 70 and older; 2) to compare the effectiveness of ICD + optimal medical therapy (OMT) versus OMT alone on all-cause mortality; and 3) to assess treatment efficacy in patients with high versus low co-morbidity burden. Research Plan: Participants will be randomized (1:1 ratio) to ICD + OMT, or OMT alone, stratified by participating site and co-morbidity level (Charlson score < 3 versus > 3). We postulate that ICD + OMT will result in a 25% reduction in the hazard for all-cause mortality.

Research Topic: Heart Disease
Funding agencies: CSR&D
Grant support: VA Cooperative Studies Program (VA CSP)

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3. Efficacy of Serial IV Ketamine Infusions for Comorbid Post-Traumatic Stress Disorder and Treatment-Resistant Major Depression: A Pilot Study

Albott, C. Sophia[1,2]; Shiroma, Paulo R.[1,2]; Erbes, Christopher[3]; Thuras, Paul[3]; Wels, Joseph[4]; Lim, Kelvin O.[1,2]

1. Mental Health Service Line, Minneapolis VA Health Care System
2. Department of Psychiatry, University of Minnesota Medical School
3. Mental Health Service Line, Minneapolis VA Health Care System
4. Department of Anesthesiology, Minneapolis VA Health Care System

Abstract: Background: Comorbid major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are common sequelae of trauma and associated with a more severe clinical presentation than either disorder alone. In the present study, we sought to explore whether repeated ketamine infusions would improve symptoms of depression and PTSD in a comorbid population of individuals with MDD and PTSD. Methods: 12 individuals with MDD and PTSD received six IV infusions of 0.5 mg/kg ketamine over 40 min. on a Monday-Wednesday-Friday schedule during a 12-day period. Symptoms of depression were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). PTSD symptoms were assessed using the PTSD-symptom Checklist (PCL-5) and the Clinician Administered PTSD Scale (CAPS-5). Outcomes measures were collected prior to the 1st ketamine infusion and 24-hours after the 6th ketamine infusion. Results: A significant decrease in mean MADRS scores was observed from baseline to 24-hours after the 6th ketamine infusion (mean MADRS change = 27.5, 95% CI: 22.96-32.04, $p<0.001$, paired t-test) and associated with a large effect size (Cohen's d = 3.85). PTSD symptoms were also significantly decreased over the treatment period (mean PCL-5 change = 32.29, 95% CI: 17.77-46.78, $p<0.001$, paired t-test; mean CAPS-5 change = 20.27, 95%CI: 13.16-27.38, $p<0.001$, paired t-test) and associated associated with large effect sizes on both the PCL-5 (Cohen's d = 1.5) and CAPS-5 (Cohen's d = 1.92). Conclusion: This study provides the first evidence that repeated infusions of subanesthetic ketamine are well-tolerated and effective for the rapid reduction of chronic PTSD and depression symptoms in a comorbid population of veterans. Although limited by small sample size, improvements in depression and PTSD outcomes were significant and demonstrated large effect sizes suggesting the relevance of serial ketamine treatments for depression and PTSD.

Research Topic: Mental Illness
Funding agencies: CSR&D; NIH
Grant support: Minneapolis VA Health Care System Mental Health Service Line; Career Development Award from the Center for Epidemiological and Clinical Research (CECR)-VA Clinical Research Center of Excellence to Dr. Shiroma; National Institute of Drug Abuse training grant (5T32DA037183-02) to Dr. Albott.

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4. 'Who are you and what do you do?' Improving team member role identification during emergency responses with identification stickers.

Albrecht, Kellen[1]; Del Valle, Kathryn[1]; Beard, Albertine[2]

1. University of Minnesota Medical School
2. Minneapolis VA Health Care System Department of Medicine

Abstract: Purpose: To improve code role identification through usage of adhesive name badges during code calls. Background: In code emergency response situations, team role identification is crucial in providing fast, effective patient care. Oftentimes, lack of role clarification can create confusion and frustration amongst code team members, potentially resulting in adverse patient outcomes. Our project works to improve this issue by making it convenient and easy for each member of the team to identify themselves quickly. Stickers were provided to all members of the code team to carry on their person with their role clearly printed in large font. Each healthcare profession's stickers will be a unique bright color, making them easily identifiable to not only the code team, but also to others as they arrive. Upon a SMaRT code or Code Blue being called, all members of the team put on their sticker immediately as they arrive at the code location. This allows all members of the team to easily know who all the other members of the team are and thus what their particular contributions will/can be. Methods: Sticker identification system was implemented in Nov. 2015 and continued through the end of the calendar year. At that time, we analyzed the data on SMaRT codes. In Jan. 2015, after discussion, the decision was made to expand to include Code Blue emergencies in the protocol. Additional stickers were made to make identification at codes more inclusive of all teams involved in code blues. This included the following: medicine intern and student(s) on the code team (white), IV team (pink), and floor nurse(s) (orange) in addition to the previously developed stickers for physicians (red), anesthesia (yellow), and respiratory (blue). Results: Pending. Outcomes will be analyzed based primarily on pre- and post-implementation code staff satisfaction surveys. We will also review data on patient outcomes, time to medication administration, and other common code factors to analyze for statistically significant changes.

Research Topic: Health Systems
Funding agencies: None
Grant support: None

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5. Allergy, Asthma, and Immunology Training in Internal Medicine Residents

Alpern, Mollie[1,2]; Wang, Qi[2]; Rothenberger, Meghan[2]

1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Background: Internal medicine physicians commonly encounter allergic and immunologic conditions, such as asthma, allergic rhinitis, and antibiotic allergies. However, many residency programs have limited exposure to Allergy and Immunology. Methods: We conducted a voluntary survey of University of Minnesota Internal Medicine (IM), Med-Peds, Pediatrics, and Med-Derm residents, including those training at the Minneapolis VA. We collected data on residents' self-assessed clinical competency treating common allergic conditions including rhinitis, uriticaria, contact dermatitis, antibiotic/drug allergies, anaphylaxis, and asthma. Percentages were calculated. Responses were dichotomized. Chi-square tests were used to compare between groups. Analyses were performed with Statistical Analysis Software. A two-sided p-value<0.05 was considered statistically significant. Results: There were 67 total participants (n=67), including 48 IM, 5 Med-Derm, 1 Pediatrics, and 13 Med-Peds residents. 79.1% (53/67) received no formal training in Allergy and Immunology in Medical School, and 86.6% (58/67) have not received any formal training in residency. This lack of residency training was more pronounced in the IM residents, at 91.7% (44/48), versus 73.7% (14/19) of Med-Peds, Med-Derm, and Pediatric residents. Only 38.8% (26/67) of all residents felt very or extremely prepared to treat allergic rhinitis. 14.9% (10/67) felt prepared to treat urticaria, 20.9% (14/67) felt prepared to treat contact dermatitis/skin allergies, 19.4% (13/67) felt prepared to treat antibiotic/drug allergies, and 32.8% (22/67) felt prepared to treat anaphylaxis. Regarding asthma, 56.7% of residents felt comfortable treating asthma in the inpatient setting, and 52.2% as an outpatient. There was no statistically significant difference in preparedness between IM versus Med-Peds, Med-Derm, and Pediatric residents. The majority of residents, 98.5% (66/67), thought exposure to Allergy and Immunology was an important part of IM training. 80.6% (54/67) of residents would be interested in an elective rotation, and 97.0% (65/67) would be interested in a didactic curriculum. Conclusion: Residents think training in Allergy and Immunology is an important part of Internal Medicine training. Residents do not feel adequately prepared to treat allergic rhinitis, uritcaria, contact dermatitis, antibiotic/drug allergies, or anaphylaxis. Therefore, additional clinical and/or didactic education is needed.

Research Topic: Autoimmune, Allergic & Hematopoietic Disorders
Funding agencies: UMN
Grant support: None

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6. Men with Urinary Tract Infections & Sub-Study about Bacterial Resistance to Antibiotics

Amundson, Carla[1]; Drekonja, Dimitri[1,2]

1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Background: Current guidelines suggest that men should be treated with 7 to 14 days of antibiotics for a urinary tract infection (UTI). This is based on prior research demonstrating that 3 days of antibiotics did not work as well as 14 days, but that 14 days worked as well as 28 days. In the VA, 9 out of 10 men are treated with the recommended 7 to 14 days of antibiotics. A recent study suggested that those receiving more than 7 days of treatment did no better than those receiving less than 7 days of treatment, but did have a higher risk of complications related to antibiotics. Specifically, those getting longer treatment had a recurrence of their UTI at the same rate as those getting shorter, and also had an increase in Clostridium difficile infection. Methods: This study is for men that have a UTI and are prescribed at least 7 but not more than 14 days of either ciprofloxacin or trimethoprim/sulfamethoxazole. Patients are randomly assigned to either 7 or 14 days of antimicrobial treatment, and followed for 1 month to determine if the UTI symptoms resolve and no not recur. The entire study can be completed via telephone and overnight mail, minimizing inconvenience and demands on patient time. There is also a sub-study exploring bacterial resistance to antibiotics. This study is being conducted to investigate the potential harms of antibiotic use. One of the potential harms is that some of the bacteria normally carried in the colon become resistant to antibiotics. These bacteria form the normal colonic microbiota and serve many useful purposes, but they can also be a source of future infections. Colonic carriage of antibiotic-resistant bacteria makes it more likely that any future infection is more difficult to treat. We are interested in studying whether longer-duration antibiotic treatment leads to increased carriage of resistant bacteria. To study this, we are conducting a voluntary sub-study that involves taking 2 stool or rectal samples, during and after treatment, and sending them to a lab here at the MVAHCS. Conclusion: This study, conducted entirely at the MVAHCS, will help to ensure that veterans receive the optimal treatment for this common condition, and help to define the potential harms of antibiotics. As of 4/15/2016, 85 patients have enrolled, with 75 opting to participate in the sub-study on antimicrobial resistance. We look forward to presenting our results at a future Research Day.

Research Topic: Infectious Diseases
Funding agencies: CSR&D
Grant support: VA Merit Review; 1I01CX000830-01A2

7. Discontinuation of Dofetilide due to QT Prolongation and Ventricular Tachycardia in the Real World

Anand, Vidhu[1]; Vakil, Kairav[2]; Tholakanahalli, Venkatakrishna[2]; Li, Jian-Ming[2]; McFalls, Edward[2]; Adabag, Selcuk [2]

1. University of Minnesota, Internal Medicine
2. Minneapolis VA Health Care System

Abstract: Objective: To determine the incidence and correlates of QT prolongation or ventricular tachycardia (VT) resulting in discontinuation of Dofetilide in a real-world setting. Background: Dofetilide is a class III anti-arrhythmic agent approved for achieving and maintaining sinus rhythm in patients with symptomatic atrial fibrillation (AF). Due to a risk of QT prolongation and VT, patients starting Dofetilide need to be hospitalized for 3 days to closely monitor telemetry and ECG. In large clinical trials < 3% of patients had to discontinue Dofetilide due to QT prolongation but data from real-world experience are lacking. Methods: We examined 114 consecutive patients with AF, hospitalized for starting Dofetilide at the Minneapolis Veterans Affairs Health Care System from 2011 to 2014. Results: The mean age of the patients was 64±8 years. Dofetilide was discontinued in 22 (19%) patients due to QT prolongation (17%) or VT (2%). A total of 32 (28%) patients were taking other QT prolonging drugs. Of these, 10 (31%) had to discontinue Dofetilide versus 12 (15%) of the 82 patients who were not taking any other QT prolonging drugs (p=0.04). Patients who were taking concomitant QT prolonging drugs were 1.9 times more likely to discontinue Dofetilide (95% confidence interval 1.1-3.4; p=0.04) compared to those who were not taking any other QT prolonging drugs. Conclusions: The incidence of QT prolongation or VT that lead to discontinuation of Dofetilide is remarkably higher in the real-world setting than in clinical trials. Concomitant use of other QT prolonging drugs was associated with discontinuation of Dofetilide.

Research Topic: Heart Disease
Funding agencies: None
Grant support: unfunded

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8. A large cohort study on the risk of chronic subdural hematoma from the long term use of antiaggregation or anticoagulation agents

Balser, David[1]; Bin Zahid, Abdullah[1]; Samadani, Uzma[1]

1. Minneapolis VA Health Care System

Abstract: Introduction: Chronic subdural hematoma (cSDH) is a debilitating and costly condition that primarily affects the elderly. Increased longevity and increased use of antiplatelet / anticoagulation agents contribute to its rising incidence which is four-fold greater in VA patients than civilians. Several observational studies have demonstrated a relationship between antiplatelet / anticoagulation use and cSDH, but none measure the use of these agents on a quantifiable, long term scale: each study assumes that only recent antiplatelet / anticoagulant use is relevant. As the etiology of non-traumatic cSDH is likely the slow deterioration of subdural bridging veins, tracking the frequency of usage of agents that can cause microbleeds and venous endothelial damage may better evaluate the long term risk of cSDH and improve clinical decision making for patients who require antiplatelet / anticoagulation therapy for other conditions and need modulation rather than cessation. In addition, since the veteran population is at much higher risk of cSDH than the general population, these risks need to be quantified independently in veteran focused studies. Methods: This is a retrospective cohort study of 10,351 veterans in a neurosurgery-capable region that follows the frequency of their anticoagulant / antiplatelet use for seven years or until the development of cSDH. 10,304 patients had records accessible with the VA Informatics and Computing Infrastructure (VINCI) with no cSDH diagnosis on record prior to the study. Results: Patients were divided into five cohorts based on the frequency of their anticoagulant / antiplatelet use during the 7 year study period. The incidence of cSDH per person/year in the study is as follows (in units of incidence / 1000 person years): 0 months use = 1.53 (95% CI [1.01, 2.05]), 1-5 months use = 1.64 (95% CI [1.00, 2.30]), 6-10 months use = 1.26 (95% CI [.389, 2.14]), 11-20 months use = 2.85 (95% CI [1.60, 4.10]), and 21 or more months use = .926 (95% CI [.520, 1.33]). The linear trend between the incidence of SDH and anticoagulant use was not significant (p = 0.997). Conclusion: In this large scale cohort study, no trend could be found showing a relationship between the amount of time on anticoagulant / antiplatelet therapy and the risk for development of cSDH. Any relationship between anticoagulant / antiplatelet therapy and cSDH incidence is likely non-linear and significantly complicated by other related factors.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: CSR&D
Grant support: I01-CX000887: Cerebral Atrophy, Anticoagulants, and the Risk for Chronic Subdural Hematoma

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9. Randomized, double-blind, placebo control study of a single versus repeated intravenous sub-anesthetic ketamine treatment in refractory depression

Batres-y-Carr, Tegan[1]; Zadini, Maximiliano[1]; Fleming, Cassandra[1]; Albott, C. Sophia[1]; Thuras, Paul[1]; Wels, Joseph[1]; Shiroma, Paulo[1]

1. Minneapolis VA Health Care System

Abstract: 1. Objectives: Primary Aim 1: To determine the efficacy of a single versus six IV ketamine infusions among patients with TRD over a 12-day treatment phase. H1: Veterans who complete six ketamine infusions will have greater reduction of depression severity than those who received a single ketamine infusion (preceded by 5 midazolam infusions). Aim 2: To determine the durability of antidepressant effect after completion of a single versus six ketamine infusions. H2: Veterans treated with six ketamine infusions will sustain antidepressant effect for longer period than those who received a single ketamine infusion (preceded by 5 midazolam infusions) over a 6-month follow-up period. 2. Research Plan and Methods: The proposed study is a one-center, interventional, efficacy trial designed to determine antidepressant outcomes of serial ketamine infusions compared to a single ketamine infusion among veterans with TRD. Participants will be randomly assigned to one of two parallel treatment conditions: 1) six ketamine infusions at 0.5 mg/kg or 2) single ketamine infusion at 0.5 mg/kg preceded by five midazolam infusions at 0.045 mg/kg. Midazolam was chosen as an active placebo given similar pharmacokinetics and dissociative effect profile to ketamine. Each intervention will be provided for a total of 12-day infusion-phase on a Monday-Wednesday-Friday schedule. The follow-up visits will occur at weekly intervals for the first 4 weeks, at 2-week intervals for the next 8 weeks, and at 4-week intervals for the remaining 12 weeks. The primary end point is the Montgomery-Åsberg Depression Rating Scale (MADRS) score 24 hours following the last infusion where the peak antidepressant effects of ketamine occur. 4. Preliminary Results: M1 Baseline: m 24.08, variance 46.27; W2 T+24: m 16.01, variance 154.69; F2 T+24: m 7.83, variance 61.33; 3 Week FU: m 13.11, variance 195.91. Discussion: Preliminary data remain blinded. Based on mean and variance, these data appear to be consistent with hypothesis 1. Results show high mean scores with low variance at baseline, and low scores with low variance at F2 T+24. Mean and variance increases at Week 3 post-treatment, which is consistent with our expectations that single infusion scores return towards baseline while six-infusion scores remain significantly lower. W2 T+24 data suggest an immediate drop in six-infusion group scores as well as a small placebo effect in the single-infusion group.

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: None

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10. Subchondral Bone Structure and Pain Behaviors in Complete Freund's Adjuvant Monoarthritis in Mice Treated with Intra-Articular (IA) Neurotoxin

Bert, Joseph[1]; Krug, Hollis[2]; Abbass, Fakhar[2]; Dorman, Christopher[2]; Frizelle, Sandra[2]; Mahowald, Maren[2]

1. University of Minnesota
2. Minneapolis VA Health Care System

Abstract: We produced painful inflammatory monoarthritis in mouse knees with IA CFA. IA Neurotoxins reduced pain behaviors in murine CFA Arthritis. Treatment with anti-nerve growth factor in humans rarely produced rapid joint destruction requiring arthroplasty. We used micro CT of knees to correlate pain behaviors with histomorphometric bone changes and to determine whether IA Neurotoxin treatment worsened changes. Methods: Chronic inflammatory arthritis was produced by IA injection of 30 µl CFA into the left knee of C57BL6 male mice 3 weeks prior to pain behavior testing using evoked pain score and automated dynamic weight bearing device. EPS was a tally of fights and vocalizations/ min with knee palpations at 15.6 psi. Percent weight and time on each limb was measured with ADWB apparatus. IA vanilloids resiniferatoxin and capsaicin were given 7 days prior to pain testing. IA botulinum toxin A was injected 3 days before testing. Knees were imaged on a micro-CT scanner. Subchondral trabecular bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular spacing (Tb.s), and number (Tb.N) were cacluated from coronal CT Slices. Results: Arthritis pain behavior was low in na¥ve mice - EPS (0.5) and ADWB proportions for weight (40.9%) and time (97.4%) were normal. IA CFA arthritis significantly increased EPS (2.5) and decreased ADWB for weight (34.1) and time (92.3). Arthritic knees had significantly reduced BV/TV (42.4 vs 50.3%), Tb.Th (252 vs 352 µm), and increased Tb.S (183 vs 112 µm) compared to naive knees. There was a significant negative linear relationship between EPS and BV/TV (R2= 0.626, pti.05) with higher EPS when BV/TV was lower. IA neurotoxin treatments did not decrease BV/TV or Tb.Th or increase Tb.S. High dose IA-RTX in CFA mice normalized Tb.Th but not Tb.S or BV/TV. Conclusion: We confirmed that IA CFA monoarthritis increased evoked and spontaneous pain behaviors. MicroCT measured significant changes in BV/TV proportion, Tb.Th and Tb.Sp in CFA inflammatory arthritis. IA neurotoxins treatments with BOT, RTX and CAP did not worsen these subchondral changes. Interestingly high dose IA-RTX actually normalized Tb.Th. The negative relationship between BV/TV proportion and pain behaviors (ie increased pain with lowest BV/TV) suggests that more severe arthritic subchondral structural changes may be associated with increased pain behaviors.

Research Topic: Autoimmune, Allergic & Hematopoietic Disorders
Funding agencies: RR&D
Grant support: 2 I01 RX000379, Bone Histomorphometry can define OA Changes in rodents and in Antigen-induced arthritis (AIA) in rats

11. Brain atrophy in chronic subdural patients is higher than controls but lower than in Alzheimer's

Bin Zahid, Abdullah[1]; Balser, David[2]; Mikheev, Artem[3]; Dammavalam, Vikalpa[1]; Thomas, Rebekah[2]; Rusinek, Henry[3]; Samadani, Uzma[2]

1. Hennepin County Medical Center
2. Minneapolis VA Health Care System
3. New York University Langone Medical Center

Abstract: INTRODUCTION: Chronic subdural hematoma (SDH) will become the most common adult cranial neurosurgical indication by 2030. Little is known about the long-term effects of SDH. Atrophy is an independent predictor of cognitive decline and risk factor for both SDH and dementia. Here, we compare long-term brain atrophy rates in SDH, Alzheimer's disease (AD) and controls in 168 veterans who underwent 1416 CT-scans from 2004-2014. METHODS: We retrospectively analyzed multiple CT-scans over time (t) for each patient in three groups (AD, SDH, or controls) using a fully automated algorithm that calculated whole brain, intra-cranial and CSF volumes. Serial atrophy measurements A(t) = VolBrain(t) were correlated to age and pathology using a mixed linear model. RESULTS: A total of 1416 CT-scans for 168 patients (50 SDH, 48 AD and 70 controls; ages 19 to 95 yrs) with an average of 8.4 exams over 5.2 yrs were analyzed. The atrophy rate dA/dt differed significantly across three groups (overall p-value<0.001). The average dA/dt in AD was 7.59ml/yr, 3-fold higher than in controls (2.34ml/yr; intergroup p-value<0.001). In SDH patients mean dA/dt was 4.93ml/yr, about twice that of controls (p-value=0.015). CONCLUSION: This is the first large study to demonstrate higher long term atrophy rates in SDH versus control population. It also demonstrates that cSDH patients have less atrophy than AD patients. Further research is needed to understand whether the increased atrophy rate begins before or after development of the cSDH.

Research Topic: Dementia & Neuronal Degeneration
Funding agencies: CSR&D
Grant support: I01-CX000887: Cerebral Atrophy, Anticoagulants, and the Risk for Chronic Subdural Hematoma

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12. Benefits and Harms of the Mediterranean Diet Compared to Other Diets

Bloomfield, Hanna E[1,2]; Kane, Robert[3]; Koeller, Eva[1]; Greer, Nancy[1]; MacDonald, Roderick[1]; Wilt, Timothy J[1,2]

1. Minneapolis VA Health Care System, Center for Chronic Disease Outcomes Research
2. University of Minnesota School of Medicine
3. University of Minnesota School of Public Health

Abstract: Background: The Mediterranean diet may be a healthier diet than typical Western diets. Purpose: To summarize the literature on the effect of the Mediterranean diet on health outcomes. Data Sources: Ovid MEDLINE, CINAHL and the Cochrane library for articles in English from 1990 through August 2015. Study Selection: Controlled trials or cohort studies with at least 100 subjects followed for at least one year. Data Extraction: Study characteristics and outcomes were extracted onto evidence tables by one investigator and verified by another. Data Synthesis: One large primary prevention randomized trial found that a Mediterranean diet resulted in lower incidence of major cardiovascular events (HR 0.71, 95%CI 0.56, 0.90), breast cancer (HR 0.32, 95%CI 0.13, 0.79), and diabetes (HR 0.60, 95%CI 0.43, 0.85). A second found no difference in CVD or Diabetes outcomes. Pooled analyses of primary prevention cohort studies showed that compared to the lowest quantile, the highest quantile of adherence to a Mediterranean diet was associated with reductions in total cancer mortality (RR 0.86, 95%CI 0.82, 0.91), incidence of total cancer (RR 0.96, 95%CI 0.95, 0.97) and colorectal cancer (RR 0.91, 95%CI 0.84, 0.98). In 3 secondary prevention trials, a Mediterranean diet reduced the risk of myocardial infarction (RR 0.32, 95%CI 0.15, 0.67). We found inconsistent or minimal evidence pertaining to any other outcome, including hypertension, kidney disease, cognitive impairment, rheumatoid arthritis, and quality of life. Limitations: There were few controlled trials and the strength of evidence was low for primary prevention outcomes (all-cause mortality, major cardiovascular events, all cancer incidence, incidence of breast and colorectal cancer, and cognitive functioning) and insufficient for all-cause mortality in secondary prevention studies. Conclusions: Consumption of a Mediterranean diet may be associated with primary prevention of major cardiovascular events, breast cancer, and type 2 diabetes mellitus as well as secondary prevention of myocardial infarction.

Research Topic: Other Chronic Diseases
Funding agencies: HSR&D
Grant support: Department of Veterans Affairs, Minneapolis VA Health Care System, Office of Research and Development, Quality Enhancement Research Initiative

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13. What is the optimal post-operative management for patients with refractory ascites who have undergone umbilical/inguinal hernia repair at the MVAHCS (Minneapolis VA Health Care System)?

Boster, Joshua[1]; Ramaswamy, Archana[1,2]

1. University of Minnesota
2. Minneapolis VA Health Care System

Abstract: OBJECTIVE: To assess the optimal post-operative management for patients who have undergone umbilical/inguinal hernia repair with refractory ascites at the Minneapolis VA Health Care System. BACKGROUND: The optimal post-operative management strategy for patients with refractory ascites who undergo hernia repair is unknown. Effective management of refractory ascites post operatively is crucial because inadequate management is associated with increased wound complication and hernia recurrence (1). Given the importance of effective ascites post operatively control it would be useful to know which strategies are used at the Minneapolis VA Health Care System and to compare them. PROJECT DESIGN & METHODS: Utilized Minneapolis VA Health Care System VISTA data to identify all veterans who underwent umbilical hernia repair in the setting of refractory ascites from 1998 to present. Retrospective chart review was performed to gather demographic data and to compare primary outcomes specifically hernia recurrence, mortality data, complications, and method of drainage utilized. RESULTS: A total of 43 patients were identified, 30 of those patients were managed with a Tenckhoff catheter while 13 patients had no drain. The baseline demographics were similar between the two sample populations. Hernia recurrence occurred in 30.8% of patients who were managed without a drain and 10% of patient in the Tenckhoff catheter group (p =.09, 95% CI (-.48 -.065)). The rate of complications, 30 day mortality and 3 year mortality were not significantly different between the two groups. The length of stay was significantly longer for the Tenckhoff catheter group compared to the no drain group with an average of 15.9 and 9.3 days respectively. The average time to death following the operation was 678 days for the Tenckhoff catheter group and 327 for the no drain group.

Research Topic: Other Chronic Diseases
Funding agencies: None
Grant support: None

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14. Telemedicine for Postoperative Visits at the MVAHCS (Minneapolis VA Health Care System)

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1. University of Minnesota Medical School
2. Minneapolis VA Health Care System

Abstract: BACKGROUND: Timely access to healthcare has been a recent major initiative of Minneapolis VA Health Care System. Last year we performed a feasibility study on providing telemedicine post op visits for our surgical patients (1). We found substantial interest in such a service for many of our veterans who live far away from the Twin Cities with significant potential advantages in time, money, and convenience. Thus, the purpose of this study is to measure safety, feasibility, efficacy of remote post-operative visits at the Minneapolis VA Health Care System. METHODS: All patients whose primary care was performed at a community based outpatient clinic (CBOC) were given the option to have their post-op visit performed at that CBOC, if their surgeon felt it was clinically indicated. Those who chose a face to face visit with their surgeon were scheduled a traditional appointment in Minneapolis. Data were collected by the surgeon performing the telemedicine visit at the conclusion of the visit on 95 patients. RESULTS: Patient satisfaction on a 1-10 scale with 10 being very satisfied was a mean of 9.71 + 0.80 SD. The percentage of patient that would elect to have another telemedicine post op visit was 98.9%. Mean distance to the Minneapolis VA for these patients was 115+ 71 SD miles with a mean distance of 24+ 25 SD miles to their CBOC resulting in an average savings of 91 miles. Mean estimated time to travel to the VA was 125+ 66 SD minutes with a mean time of 28+ 22 SD minutes to their CBOC resulting in an average savings of 97 minutes. Using the 2014 government reimbursement rate of $0.56 per mile an average direct cost savings of $50.96 was calculated. No complications requiring urgent evaluation at the Minneapolis VA Health Care System were discovered. CONCLUSIONS: In selected patients the routine use of telemedicine for postoperative visits shows high patient satisfaction, saves time and money, and is a safe viable alternative to traditional face to face encounters.

Research Topic: Access & Disparities in Care
Funding agencies: None
Grant support: None

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15. Reducing Delirium in the Postoperative Setting

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1. Minneapolis VA Health Care System

Abstract: BACKGROUND: Delirium in the hospital setting has been long associated with increased length of stay, increased complications, and overall poorer patient outcomes. There are many predisposing factors that lead to delirium, some inherent, such as increased age and dementia, and others which are modifiable, such as opioid analgesics and other medications. METHOD: We attempted to elucidate a best approach to pain management for patients in the postoperative setting of orthopedic surgical hip fracture repair with hopes of augmenting length of stay and incidents of delirium by decreasing modifiable pharmaceutical risk factors. Specific modifiable pharmaceutical risk factors initially shown to be of note within our medical institution included redundant analgesic medications and specific deleriogenic medications such as hypnotics, antihistamines, and sedatives. A uniform order set dictating the pharmaceutical regimen for postoperative pain control was created and implemented within our electronic medical record system for patients undergoing surgical hip fracture repair. This order set aimed to eliminate redundant and excessive medications associated with postoperative delirium. Following this, a small-scale study was undertaken using local data which took a retrospective look at a consecutive 20 patients' postoperative course for orthopedic surgical intervention for hip fracture and compared them to a prospective cohort of 20 consecutive patients after the implementation of the order sets. RESULT: The length of stay, incidence of documented delirium, and total analgesic type, number, and administration were documented. The comparisons of these results are pending at this time. CONCLUSION: Although this small scale project could be viewed as a success in regards to overall streamlining and standardizing the postoperative regimen of these patients, the overall effect of this implementation was unable to show a decrease in length-of-stay or incidence of delirium.

Research Topic: Health Systems
Funding agencies: None
Grant support: None

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16. Communicating about healthcare inequality: The role of providers' prior beliefs on their receptivity to different narrative frames

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2. University of Minnesota
3. ENRM Bedford VA Medical Center
4. Boston University
5. Jesse Brown VA Medical Center
6. University of Illinois at Chicago
7. Georgia State University
8. HEROIC, Ralph H. Johnson VA Medical Center
9. Medical University of South Carolina
10. Portland VA Health Care System
11. Oregon Health & Science University

Abstract: Research Objective: To explore the role of preexisting beliefs about the causes of healthcare inequality on providers' responses to persuasive narratives that differ in their framing of the issue, in order to inform the development of communication strategies to engage providers in disparity-reduction initiatives. Study Design: Individual semi-structured interviews were conducted with 53 providers from three healthcare facilities, who read and discussed two narratives about race in healthcare, which varied in the extent to which they emphasized the provider contribution to disparities. Based on a prior survey, providers were stratified by their beliefs that factors external to the patient, contributed to healthcare inequality (low external versus high external). Raters coded all transcripts for indicators of acceptance or rejection of the narratives (blinded to providers' classification). Principal Findings: Preexisting beliefs about the causes of healthcare inequality were related to responses to narrative type. The dimension that distinguished responses between low external and high external providers was whether the issue of race was or was not successfully resolved by the end of the narrative. Low external providers resonated most strongly with narratives in which issues of race were successfully resolved by a provider who engaged in a patient-centered communication approach, identifying with and expressing admiration for the narrator and manifesting positive emotions. Low external providers showed strong resistance to narratives in which problems related to race and racism were not successfully resolved. By contrast, high external providers resonated with both types of narratives. High externals were also more likely to engage in extensive reflection about their own experiences and mistakes they made caring for non-white patients, to recount stories of discrimination that they experienced or witnessed, to acknowledge the importance of race, and to criticize providers in the narratives for not doing enough to address issues of race. Conclusion: Providers' preexisting beliefs about healthcare inequality were associated with responses to narratives involving race in healthcare. This study provides a foundation for developing communication strategies and framing educational initiatives to engage providers in efforts to reduce healthcare inequality.

Research Topic: Special Populations
Funding agencies: HSR&D
Grant support: VA HR&D IIR #11-328-2

17. Acquisition of a Seahorse XFe96 Extracellular Flux Analyzer System via the Shared Equipment Evaluation Program (ShEEP)

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1. Minneapolis VA Health Care System
2. University of Minnesota Department of Food Science and Nutrition
3. University of Minnesota Obesity Center

Abstract: Background: The Minneapolis VA Health Care System has recently acquired the Seahorse XFe96 Analyzer System (Seahorse Bioscience, MA USA) through the Shared Equipment Evaluation Program (ShEEP) under the Research Equipment Management (Office of Research and Development BX003083). This is the only instrument that can simultaneously measure cellular respiration and glycolysis in physiologically relevant cellular models, through non-invasive measurements that provide real time kinetic results. Currently, we are the only Midwest VA research programs to acquire this device. The equipment is housed within the Minneapolis VA Health Care System Research Services laboratory space and is available for use under the direction of Dr. Tammy A. Butterick. The use of this equipment compliments an existing inventory of multiuser based instruments with the end goal of increasing the efficiency of translational VA research. Minneapolis VA Health Care System researchers currently using the Seahorse XFe96 Analyzer System span multiple research disciplines and represent both basic and translational research in areas such as aging, cardiovascular, cancer, neuroscience, stem cell therapies and obesity. Relevance to VA Health Care and Research Mission: The ability for Minneapolis VA Health Care System to continue to remain one of the largest and most active research programs in the VAHCS depends on the ability of its investigators to gain access to the newest generation of high-sensitivity and high-resolution instruments. The acquisition of the Seahorse Flux Analyzer has accelerated and enhanced the rate at which researchers from multiple disciples acquire, analyze, display, and understand data. The long-term goal of research conducted using this device aims at benefiting the unique health care needs of US Veterans. This not only benefits the progress of VAHCS research in general but health care for all Americans.

Research Topic: Other Chronic Diseases
Funding agencies: BLR&D
Grant support: Department of Veterans Affairs ORD 1 ISI BX003083 and BLRD 1 IK2 BX001686

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18. Brain Function in Gulf War Illness (GWI) and Associated Mental Health Comorbidities

Christova Savayan, Peka[1]; James, Lisa[1]; Lewis, Scott[1]; Carpenter, Adam[1]; Miller, Ryan[1]; Engdahl, Brian[1]; Georgopoulos, Apostolos[1]

1. Brain Sciences Center, Minneapolis VA Health Care System

Abstract: Gulf War Illness (GWI) is a disease of unknown etiology that has afflicted veterans of the 1990-91 Gulf War. Among symptoms affecting at least 6 domains (fatigue, pain, neurocognitive/mood, skin, gastrointestinal, respiratory), the most prominent and most incapacitating has been the one manifesting as Neurological, Cognitive and Mood (NCM) disorder. The existence of brain abnormalities in GWI has been hotly debated during the past twenty-odd years with a current lack of consensus as to their presence, kind, significance and impact. Here we show, for the first time, that subcortical volume is substantially and significantly reduced in GWI, as compared to healthy GW veterans. We calculated the volume of 87 brain areas (35 cortical in left and right hemispheres, 13 left and right subcortical, and the brainstem) in 24 control GW veterans and 19 veterans suffering from GWI, as determined using criteria of the Center for Disease Control and Kansas City. Participants underwent a high-resolution structural Magnetic Resonance Imaging (sMRI) using the 3T MR scanner at this VA. For each participant, a high resolution T1-weighted anatomical image Turbo Field Echo (T1w TFE SENSE) was obtained (168 sagittal slices, TR= 8.1932 ms, TE = 3.7520 ms, Acquisition matrix 256 x 256, Flip angle 8 deg, voxel size 0.9375 x 0.9375 x 1 mm). The T2-weighted anatomical image (T2w VISTA HR SENSE) was also obtained (180 slices, TR= 2500 ms, TE = 363.072 ms, Acquisition matrix 256 x 256, voxel size =0.7813 x 0.7813 x 1 mm). A 704-core High Performance Computing system (CentOS 6.5 Linux, Rocks 6.1.1) with Matlab R2012 (64 bit), Human Connectome Project (HCP, humanconnectome.org) pipeline with FreeSurfer (FS http://surfer.nmr.mgh.harvard.edu) HCP version (freesurfer-hpc) were used for processing the data to extract the volumes above. We found a substantial reduction in the volume of the left (by 11%, P = 0.002) and right (by 8%, P = 0.042) subcortical areas, and brainstem (by 12%, P = 0.35) (adjusted for age and gender, analysis of covariance). The highest reduction was found in the volume of the left cerebellar cortex (by 14%). In contrast, mean cortical volumes of the left and right hemisphere did not differ significantly between the two groups (P = 0.621 and P = 0.982, respectively). These findings document, for the first time, a major brain abnormality in GWI veterans centered on subcortical brain areas, and the cerebellum in particular.

Research Topic: Gulf War Veterans Illness
Funding agencies: CSR&D
Grant support: None

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19. Efficacy of Simulation and Debriefing to improve Nursing Confidence in Assessment of Opioid Withdrawal

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1. St. Cloud VA Health Care System

Abstract: The Objectives of this trial will test the following hypotheses: 1. Simulation as an educational adjunct increases staff confidence in utilization of an assessment tool, 2. Nurses perceive increased ability to provide adequate symptom management practices by utilization of the Clinical Opiate Withdrawal Scale (COWS) assessment tool, 3. Significantly less inter-rater variations in groups utilizing debriefing as part of the simulation than groups without debriefing, and 4. Staff who receives simulation and debriefing training will have significantly less inter-rater variation on COWS scores at post-treatment and follow-up than the other groups. The Research Plan and Methods outline that this study will be a randomized controlled trial. The study will consist of three groups (N = 90) of nursing staff. One group of nursing staff (n = 30) will be provided a verbal scenario of a patient undergoing opiate withdrawal, followed by simulation training and instruction with debriefing. A second group (n = 30) will only be provided the verbal scenario of a patient undergoing opiate withdrawal, followed by simulation without debriefing. The third group (n = 30) will only be given the verbal scenario condition. The COWS and a questionnaire will be administered pre- and post-treatment, as well as a 30-day follow-up. Each class will consist of no more than 30-minute sessions. The group will be directed by a nurse educator trained in the use of simulation and the COWS. There is significant Clinical Relevance of this study as there is currently very little in the nursing research that specifically addresses nurses' confidence and attitudes measured in relation to training methods. Although early qualitative studies presented positive results, there is still insufficient evidence. It is understood that nurses' self-confidence is an important outcome that needs to be evaluated and studied in relation to the use of an opioid withdrawal assessment tool. The use and effectiveness of simulation can potentially go a long way in nursing education and training, as this is an area of nursing that has historically lacked simulation scenarios and technologies. The Findings, Results and Conclusion of this study are currently pending. The study is currently accruing subjects and actively being conducted.

Research Topic: Substance Abuse
Funding agencies: None
Grant support: None

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20. VA Traumatic Brain Injury (TBI) Model System of Research: 2016 Update

Crocker, Jillian[1]; Finn, Jacob[1]; Lamberty, Gregory[1]

1. Psychology, Minneapolis VA Health Care System

Abstract: The Traumatic Brain Injury Model System (TBIMS) program was created in 1987 by the National Institute on Disability and Rehabilitation Research (NIDRR). It is a prospective, 20-year longitudinal, multi-center study which examines TBI recovery and outcomes following coordinated acute medical care and inpatient rehabilitation. The civilian TBIMS has enrolled over 13,000 people with TBI at 16 hospitals, making it the largest longitudinal TBI database in the United States. In 2008, the Department of Veterans Affairs Polytrauma Rehabilitation Centers (PRCs) joined TBIMS and have enrolled over 700 Veterans nationwide. The Minneapolis VA is one of the five PRCs currently enrolling Veterans admitted to an inpatient rehabilitation program as a result of a TBI. Data collection continues, and projects are being proposed and analyzed using the existing PRC data, as well as collaborations with the civilian TBIMS. The purpose of the current project is to update the Minneapolis VA researchers, providers, and interested stakeholders in the progress of the PRC TBIMS efforts, both in Minneapolis and nationally. In particular, the PRC TBIMS recently expanded to include an additional funded project titled 'Improved Understanding of Medical and Psychological Needs in Veterans and Service Members with Chronic TBI' (I-MaP), which follows co-morbid health conditions and needs of Veterans and their family members and caregivers. Because acute and long-term effects of TBI continue to be relevant to Veteran populations, the PRC TBIMS will continue to grow and become a valuable tool to contribute to rehabilitation interventions and practice guidelines in VA PRCs.

Research Topic: Acute & Traumatic Injury
Funding agencies: DOD; MVMREF
Grant support: None

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21. Veterans' perceptions about prostate cancer screening benefits, harms, and intention to screen: a mixed methods study to inform a patient education tool

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1. Minneapolis VA Health Care System
2. University of Minnesota Medical School
3. University of Minnesota School of Public Health

Abstract: Background: The US Preventive Services Task Force (USPSTF) and the VA recommend against screening average risk men for prostate cancer with the Prostate Specific Antigen (PSA) blood test. The probability of preventing prostate cancer death with PSA testing is small, while the chance of causing harm is moderate to high. The USPSTF concluded that the potential benefits of screening do not outweigh the likely harms. Screening rates remain high nonetheless. VA researchers developed an educational pamphlet to inform Veterans about PSA testing guidelines. We present the results of a pre/post survey with focus group participants who reviewed this pamphlet. Our objective was to quantify changes in perceptions of potential benefits and harms of PSA testing and to evaluate the impact on intention to screen. Methods: We held six focus groups of 5-9 participants each at the Minneapolis VA in 2013 and 2015. Two groups each included white men ages 50-69, white men ages 70-85, and black men ages 50-85. Participants completed a pre-discussion survey with 6 questions about perceived benefits and harms of PSA testing. During the focus groups, a trained facilitator led the participants in a review and discussion of the educational pamphlet. Participants then completed a similar post-discussion 10-question survey that included a query about intent to screen. Results: Forty-four focus group participants returned at least partial survey responses. Prior to discussion, 77% of participants reported a moderate to high chance that the PSA test helps men avoid prostate cancer death and 55% reported a small chance of harms from the PSA test. After discussion, 56% described the chance of avoiding death as small and 77% reported a moderate to high risk of harms. After reviewing the pamphlet, 49% of participants were willing to forego PSA testing if recommended against by their provider. White men ages 70-85 were most likely to desire continued screening (60%). Compared with men who would forgo testing, those who reported continued intention to screen quantified benefits and harms similarly, but were more likely to conclude that benefits outweigh harms (56% vs. 10%). Conclusions: An educational pamphlet improved knowledge of benefits and harms of prostate cancer screening among white and black Veterans who reviewed the pamphlet during a focus group. After reviewing the pamphlet, nearly half of the participants were willing to forgo screening.

Research Topic: Cancer
Funding agencies: HSR&D
Grant support: - LIP HVC: 15-1: PI Danan; Patient and PROvider Training & Education about prostate Cancer Testing (PROTECT) A High Value Care Initiative: Extension Project with African American Veterans - HSR&D LIP: PI: Partin; PROvider Training to Eliminate overuse of prostate Cancer Testing (PROTECT): Refinement of the patient education portion of the training

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22. Diffusional kurtosis imaging correlates of head injury history among healthy military members

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1. Minneapolis VA Health Care System
2. University of Minnesota
3. Defense Veterans Brain Injury Center

Abstract: Mild traumatic brain injury (mTBI), or concussion, is common among military service members. A growing body of evidence using diffusion tensor imaging (DTI) suggests that mTBI is associated with disruptions in white matter integrity (WMI); however, there is emerging evidence that diffusional kurtosis imaging (DKI) may provide additional sensitivity to mTBI-related white matter pathology. Due to a lack of pre-injury MRI data, it is unknown to what extent observed WMI disruptions represent vulnerability factors, direct injury-related pathology, or indirect pathways (e.g., post-traumatic reactions). We have collected DKI data from over 100 Minnesota Army National Guard service members shortly before basic military training. Initial data indicate no relationship between DKI metrics and reported mTBI history prior to training, though expected relationships with age were observed. Associations with additional baseline measures will be presented. Preliminary longitudinal analyses of DKI data will also be presented.

Research Topic: Acute & Traumatic Injury
Funding agencies: RR&D
Grant support: IK2 RX000709

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23. Influence of Negative Emotionality on Retrospective Self-Reports of Military Experiences

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1. Minneapolis VA Health Care System
2. University of Minnesota
3. Defense Veterans Brain Injury Center

Abstract: Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are both common, and often comorbid, among military personnel. Diagnosis and treatment of these conditions in military populations is highly reliant on self-reported information. Of particular concern is the possibility that the personality traits influence the reporting of factual information used in the diagnosis of PTSD and mTBI, potentially introducing a source of artificial comorbidity. We have assessed personality (Multidimensional Personality Questionnaire; MPQ), PTSD symptomatology (PTSD Checklist – Civilian; PCL-C), and self-reported stress (Perceived Stress Scale; PSS) in over 100 healthy young Minnesota National Guard service members prior to beginning several months of intensive military training. Upon their return home, we have collected factual (e.g., training conditions) and subjective information about training experiences from 50 of these Soldiers. Negative Emotionality (NEM) subscales of Alienation and Aggression, measured prior to training, were positively related to reported levels of Military Social Stress during BCT, suggesting a predisposition to the perception of this type of stress.

Research Topic: Acute & Traumatic Injury
Funding agencies: RR&D
Grant support: IK2RX000709

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24. Polygenic Predictors of Psychosis and Schizotypal Personality Phenotypes in Members of Families Affected by Severe and Persistent Psychopathology

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1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Dimensions of psychosis and schizotypal personality can be used to characterize people affected by severe psychopathology as well as their first-degree biological relatives. It is unclear how phenotypic dimensions pertinent to severe psychopathology are related to recently identified polygenic predictors of disorders such as schizophrenia, schizoaffective disorder, and bipolar affective disorder. To investigate how genetic variation predicts variation in psychosis and schizotypal personality phenotypes we carried out whole genome analyses of probands, first-degree biological relatives of probands, and unrelated healthy control participants in a family study of severe and persistent psychopathology. We examined a set of phenotypes derived from the Schizotypal Personality Questionnaire (SPQ), Brief Psychiatric Rating Scale (BPRS), and the Chapman Scales. Polygenic risk scores (PGRS) were calculated based on 73 of the 108 schizophrenia-associated genetic loci identified by the Psychiatric Genetics Consortium (Nature, 2014) analyzed in a manner consistent with the International Schizophrenia Consortium (Purcell et al., 2009). Relative to first-degree relatives and controls, PGRS was significantly higher in the entire proband sample and also specifically schizophrenia patients. There was no difference in PGRS between patients with schizophrenia, bipolar disorder, and schizoaffective disorder, nor was there a difference between relatives and controls. PGRS did not significantly differentiate groups on specific dimensions of psychosis or schizotypal personality. Together, these findings suggest that genetic liability may differentiate genetic risk when comparing probands with relatives and controls, but that the specific genetic factors contained within the PGRS did not correlate with risk-related dimensional phenotypes. Future research should expand the characterization of genetic risk and dimensional phenotypes to better understand the mechanisms by which polygenic factors predict the onset of severe and persistent psychopathology.

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: 5 I01 CX000227 Quantitative Modeling of Visual Perception Endophenotypes in Schizophrenia

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25. MMPI-Based Boldness and Disinhibition Predict Distinct Trajectories of PTSD Symptomology Following Combat Exposure in National Guard Soldiers

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1. Minneapolis VA Health Care System

Abstract: Little is known about dispositional factors that may confer risk or resilience to the development of mental health problems including post-traumatic stress disorder (PTSD) following combat exposure (CE). Two traits likely to play opposing roles in the development of PTSD are disinhibition (i.e., the general liability underlying impulse-control disorders; hypothesized to be a risk factor for PTSD) and boldness (i.e., dispositional fearlessness; hypothesized to be a protective factor). The current study examined the prospective prediction of pre-deployment boldness and disinhibition measured using item-based scales from the MMPI-2-RF (modeled from Sellbom et al., 2015) in a longitudinal sample of National Guard Soldiers (N = 522) to a latent measure of combat exposure, as well as three latent trajectory classes of PTSD identified by Kramer and colleagues (in prep). Chronic and Vulnerable-Risk PTSD trajectory groups had significantly higher CE than the Resilient class (OR = 2.80 and 2.14, respectively). Pre-deployment boldness and disinhibition both positively predicted CE (β = .11 and .26, respectively), and displayed a significant interaction (β = -.12), such that those soldiers concurrently low on both boldness and disinhibition had the lowest levels of CE. Critically, MMPI- RF based boldness and disinhibition distinguished PTSD trajectory over and above CE. The Chronic and Vulnerable-Risk PTSD trajectories had significantly higher disinhibition and lower boldness than the Resilient trajectory, whereas the Chronic and Vulnerable-Risk trajectories were distinguished by boldness (Vulnerable > Chronic), but not disinhibition. The clinical implications for considering disinhibition and boldness as dispositional risk and resilience factors will be discussed.

Research Topic: Mental Illness
Funding agencies: DOD
Grant support: This research was supported by grants from Minnesota Medical Foundation (Grant #3662-9227-06) and Department of Defense Congressionally Directed Medical Research Program (CDMRP; W81XWH-07-2-003). This material is the result of work supported with resources and the use of facilities at the Minneapolis VA Health Care System, Minneapolis, MN.

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26. Identification of a fatty acid binding protein-UCP2 axis regulating microglial mediated neuroinflammation

Duffy, Cayla[1,2]; Yuan, Ce[1-3]; Xu, Hongliang[4]; Nixon, Joshua[1,2]; Bernlohr, David[4]; Butterick, Tammy[1,2,5]

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2. Department of Food Science and Nutrition, University of Minnesota
3. Biomedical Informatics and Computational Biology Program, University of Minnesota
4. Department of Biochemistry, Molecular Biology, and Biophysics, University of Minnesota
5. Minnesota Obesity Center

Abstract: Hypothalamic inflammation contributes to metabolic dysregulation and the onset of obesity. Dietary saturated fats activate microglia via an NFκB mediated pathway to release pro-inflammatory cytokines, resulting in dysfunction or death of surrounding neurons. Fatty acid binding proteins (FABP) are lipid chaperones regulating metabolic and inflammatory pathways in response to fatty acids. Although inhibiting FABP4 in peripheral macrophages results in reduced obesity-induced inflammation via a UCP2-redox based mechanism, the expression of FABP4 and a potential FABP4-UCP2 axis in microglia cells is largely uncharacterized. We hypothesized that microglial cells express FABP4 and that inhibition would up regulate UCP2 and attenuate lipopolysaccharide (LPS)-induced pro-inflammatory response. Embryonic murine brain tissue and immortalized murine microglial cells (designated BV2) were evaluated for the presence of FABP4 by qRT-PCR. To assess the role of FABP4 in microglial inflammation, BV2 cells were pretreated in the presence or absence of a pan-FABP inhibitor (HTS01037; 30 μM) for 3h, and then treated with or without LPS (100 ng/ml) for 12h. Microglial cells were collected for qRT-PCR analysis of gene expression. Gene expression analysis reveals that embryonic mouse brain and BV2 cells express FABP4. Exposure of the FABP inhibitor HTS01037 in the presence or absence of LPS increased expression of UCP2 ($p<0.0001$ vs. control and LPS only) and arginase ($p<0.05$ vs. control and $p<0.001$ vs. LPS only). Moreover, cells exposed to HTS01037 exhibited attenuated expression of inducible nitric oxide synthase compared to LPS alone ($p<0.0001$) indicating reduced NFκB signaling. To our knowledge, this is the first report demonstrating an FABP-UCP2 axis with the potential to modulate the microglial inflammatory response. Relevance to Veterans Health: Obesity disproportionally affects US Veterans. Veterans represent a large and unique population in that those individuals were at one point extremely physically active yet veterans dependent on VA health care services are more likely to become obese despite high levels of activity in prior military service. Continual effort that is focused on treatment and prevention of obesity through understanding hypothalamic neural mechanisms would be of significant benefit to all American Veterans.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: BLR&D; NIH; UMN
Grant support: BLR&D IK2 BX001686 (to TAB), R01 DK053189 (to DAB), University of Minnesota Healthy Foods, Healthy Lives Institute (to CMD)

27. Visual preference for images of primate faces in non-human primates

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2. University of Minnesota Department of Biomedical Engineering
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4. Brain Science Center, Minneapolis VA Health Care System

Abstract: Autism is a devastating neurological disorder of unknown cause, unclear pathogenesis and without an effective treatment. Approximately 1 in 88 American children are on the autism spectrum, and it's estimated that 1 in 54 boys and 1 in 252 girls are diagnosed annually in the US, which is a 10-17% annual growth over the past decade. Although there are many animal models of this disorder, particularly in rodents, the relevance of these models to a human disease that is defined by abnormal social interaction is debatable. Non-human primates have a deeply developed sense of social cognition, and ethological studies have noted that these social interests can even be stronger than interest in information critical to survival. In an effort to characterize natural social behaviors in non-human primates that might be altered in a monkey model of autism, we studied preferences for different classes of visual images. Image content included: (i) neutral inanimate objects, (ii) familiar food, (iii) and faces (human and monkey). We trained two monkeys on a task in which they choose between two simultaneously presented images via a saccade: First they were required to hold their gaze on a central fixation point for 500-700 ms after which they were presented two images (target on). After maintaining fixation on the center point for another 500-700 ms (delay), the center fixation point disappeared (go signal) and the subject made a saccade to one of the images, holding on the image target for 300 ms to receive the reward. The eye movements were monitored continuously and the subjects were rewarded regardless of which image they chose. When presented with two neutral inanimate images, the monkeys showed no preference ($p<0.0001$, binomial distribution fit). When images of a face were paired with a neutral object or a familiar food, the monkeys preferred the face in more than 80% of trials ($p<0.0001$, binomial distribution fit). There were no differences in preferences for familiar or unfamiliar faces. In addition to their preference, the animals had shorter performance times toward faces ($p<0.01$, Wilcoxon rank sum). Our data suggest that the preference of non-human primates for faces is driven by considerations of social cognition that are so prominent in all primates. We believe that this natural tendency to prefer images of other primates could be used as an assay to probe for autistic behavior in monkey models of autism.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: None
Grant support: None

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28. Establishing the Feasibility of a Sensor-Based Sock Management System

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Abstract: Lower limb amputations are a significant health problem for veterans leading to morbidity, mortality, and loss of function. The residual limb of an amputee fluctuates in volume based on activity levels, weight gain/loss, and muscle atrophy. These changes make it difficult for amputees to maintain proper socket fit throughout the day. Amputees use residual limb socks to help restore socket fit. These socks are worn or taken off depending on how the residual limb volume is changing. For inexperienced amputees and those who suffer from neuropathy or cognitive impairments, knowing when to add or remove socks is a big challenge. Not maintaining the correct number of socks leads to an improper socket fit that will cause pain, discomfort, and breakdown of the residual limb tissue. The goal of this project was to explore the feasibility of a sock management system. We explored different locations within a socket where a force sensor can be placed to discriminate between different socket fits. Testing was done on a model to simulate an under-socked, an over-socked, and a correct fit condition. These conditions were tested under simulated standing. We found that the best locations for a force sensor would be at the patellar tendon bar and at the distal end of the socket. These locations provide the best repeatability, accuracy, and sensitivity to changes in different socket fits. A future sensor-based system would help amputees know when to add or remove socks based on the changes in their residual limb volume throughout the day. Through this project, we established the feasibility of such a system and identified the ideal locations for force sensors. Future work will involve testing on veterans with lower limb amputations in dynamic conditions.

Research Topic: Acute & Traumatic Injury
Funding agencies: RR&D; UMN; MVMREF
Grant support: University of Minnesota Undergraduate Research Opportunities Program (UROP)

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29. Brain Function in Gulf War Illness (GWI) and Associated Mental Health Comorbidities

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Abstract: Background: Objective indicators of Gulf War Illness (GWI) have not been identified. Prior research has demonstrated that synchronous neural interactions (SNI) derived from magnetoencephalography (MEG) provide a unique brain-based objective indicator of various psychiatric and neurological disorders. Here we examined whether SNI discriminates among veterans with GWI, GWI plus co-occurring mental health problems (GWI+MH), and healthy controls. We also compared subjective reports of GWI symptom characteristics across groups. Methods: All participants completed diagnostic interviews to establish the presence of GWI and assess mental health status. They also underwent a MEG scan to assess brain synchronicity. SNI distributions among control, GWI and GWI+MH groups were compared overall and for each hemisphere. Findings: GWI symptom severity differed significantly across groups (Control < GWI < GWI+MH). SNI distributions of the GWI group also differed significantly from the other groups in a systematic hemispheric pattern, such that the presence of GWI involved predominantly the left hemisphere, and presence of mental health disorders involved, in addition, the right hemisphere. Interpretation: Taken together, both objective (neural) and subjective (reports/interviews) indices suggest that GWI is distinct from healthy controls and varies in severity in a continuum that leads, at the higher end, to a diagnosable mental disorder.

Research Topic: Gulf War Veterans Illness
Funding agencies: CSR&D
Grant support: None

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30. Initial Results of a Lung Cancer Screening Demonstration Project: a Local Program Evaluation

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Abstract: Rationale: Screening for lung cancer is complex, with little information about implementation feasibility. Objective: We report initial results from the Minneapolis Veterans Affairs lung cancer screening program, one of eight medical centers participating in a national Veterans Health Affairs Demonstration Project. Feasibility outcomes include collection of initial tobacco pack year information, patient screening uptake in response to different screening invitation approaches, and the results of screening computed tomography including incidental findings. Methods: An electronic health record algorithmic search identified patients meeting preliminary eligibility for screening and activated a tobacco pack-year prompt at primary care appointments. Patients eligible for screening were randomized to either Direct Invitation or Usual Care at a 2:1 ratio. Direct Invitation patients received a shared decision-making booklet and invitation letter, reminder letter, and a phone call to discuss lung cancer screening; calls were discontinued during the evaluation due to feasibility constraints. Usual Care patients could be referred for screening by their primary care provider, but were not proactively invited. Lung nodules were tracked by templated radiology reports and clinic progress notes that interfaced with a tracking database. Incidental findings were recorded by pre-specified categories. Significant findings were identified by radiology recommendation and clinical review of the electronic health record. Measurements and Main Results: From 1/2/2014-8/15/2014, there were 6,133 patients with pack-year information; 1,388 were randomized to Direct Invitation (n=926) or Usual Care (n=462). Screening scans were completed by 20% of the Direct Invitation patients, and 0.6% of Usual Care patients. Within the Direct Invitation group, scans were completed by 22% of the patients assigned to mailings plus attempted phone calls (n=766). Of the 190 patients who completed a scan, 59% had a lung nodule that required follow-up: 12 patients required diagnostic evaluation and 3 had lung malignancies. There were 180 incidental findings in 117 patients; 21% were significant. Conclusions: Local screening implementation as part of a national demonstration was feasible. Elements of successful screening implementation include accurate identification of eligible patients, invitation approaches that utilize available resources, and standardized methods for tracking nodule results.

Research Topic: Cancer
Funding agencies: None
Grant support: The Lung Cancer Screening pilot program was funded by a grant from the VA National Center for Health Promotion and Disease Prevention

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31. Design of an Ergonomic Wheelchair Drive System for Improved Shoulder Biomechanics

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Abstract: There are a reported 1.5 million manual wheelchair users in the United States. Current wheelchair propulsion is achieved via hand rims which are connected directly to large drive wheels. Wheelchair drive wheels must be far enough behind the user's center of mass to prevent the chair from tipping backward. However, shoulder muscle stress and metabolic cost are minimized when the hand rim is located in front of the shoulders. Thus, current manual wheelchair designs do not allow optimal hand rim positioning for shoulder health and function, potentially leading to chronic overuse injury and pain. Additionally, the wheelchair user's hands make frequent incidental contact with the wheels themselves, leaving the hands dirty. In a hospital environment this could also facilitate the transmission of hospital-acquired infections. The drive wheel placement also interferes with lateral transfers, requiring the wheelchair user to transfer either diagonally or over the wheel. Researchers at the Minneapolis VA Health Care System have developed a proof-of-concept wheelchair demonstrating the separation of drive wheel and hand rim through the use of a chain drive. This novel design allows the hand rim to be optimally positioned, reducing shoulder extension during propulsion and eliminating hand contact with the drive wheels. A quick release mechanism allows the hand rims to be easily removed to permit unobstructed lateral transfers. Additionally, the chain drive system allows for gear ratio modification, which could help reduce shoulder pain. Manipulation of the gear ratio could reduce the force needed for propulsion, thus supporting users who have reduced arm or shoulder function but who wish to remain in a manual wheelchair.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: RR&D; MVMREF
Grant support: This project is supported by the Mike Utley Foundation.

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32. Association of Albuminuria with Risk of Incident Clinical Fracture and Rate of Hip Bone Loss: the Osteoporotic Fractures in Men (MrOS) Study

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Abstract: Prior studies suggest a positive association between albuminuria and risk of nonvertebral fractures in women and not men, but included relatively few fracture events in men. We used data from the MrOS Study, a large, prospective cohort of community-dwelling men aged >=65 years, to evaluate the association of albuminuria with subsequent fractures and hip bone loss. From urine collected at the 12/03-3/05 visit, we calculated the albumin/creatinine ratio (ACR) (Roche Modular P chemistry analyzer). Subsequent clinical fractures were ascertained from triannual questionnaires and centrally adjudicated by blinded review of radiographic reports. Total hip BMD was measured by DXA at the 12/03-3/05 and 3/07-3/09 visits (mean interval 3.5 +/- 0.5 SD years). Risk of incident clinical fracture and major osteoporotic fracture (MOF) (hip, clinical spine, wrist, or humerus) were estimated using multivariate-adjusted Cox proportional hazards models, and annualized rate of change in total hip BMD was assessed using ANCOVA, both across ACR quintiles and in men with versus without microalbuminuria (ACR >=30 mg/g vs. <30 mg/g). Of 2982 men with calculable ACR, 9.4% had microalbuminuria. During a mean of 8.7 +/- 3.4 SD years of follow-up, 20.0% and 9.6% of men had incident clinical fractures and incident MOF, respectively. In multivariate-adjusted models (adjusted for age, clinic site, race, past fracture since age 50, any fall in the past year, difficulty with activities of daily living, loop diuretic use, osteoporosis drug use, antidepressant drug use, Geriatric Depression Scale score >6, grip strength, and cystatin-based estimated GFR), small increases in risk of incident clinical fracture and incident MOF associated with ACR were not statistically significant, neither across ACR quintiles (p for trend 0.75 and 0.29, respectively) nor in men with versus without microalbuminuria (HR, 1.28 [95%CI, 0.90-1.81] for incident clinical fracture; HR, 1.31 [95%CI, 0.82-2.09] for incident MOF). There was a borderline positive, multivariate-adjusted association between annualized rate of total hip bone loss and albuminuria modeled in ACR quintiles (p=0.09) but not with albuminuria modeled as ACR >=30 mg/g versus <30 mg/g (0.54% vs. 0.41%, p=0.15). In these older men, possible small increases in risk of incident clinical fracture, incident MOF, and annualized rate of hip bone loss associated with albuminuria were not statistically significant.

Research Topic: Degenerative Diseases of Bones and Joints
Funding agencies: NIH
Grant support: NIA, NIAMS, NCATS, and NIH grants U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128.

33. Satisfaction with Life after Traumatic Brain Injury: A VA TBI Model Systems Study

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Abstract: Research Objectives: To identify predictors of satisfaction with life in veterans at one year following traumatic brain injury (TBI). Design: The current study utilized a longitudinal design to identify predictors of satisfaction with life at one year following TBI. Predictors included demographics (e.g., age, education, marital status), pre-injury variables (e.g., mental health history, employment status), and military service variables (e.g., injury during deployment, active duty vs. guard or reserve status at time of injury) collected upon enrollment and one year post-injury follow-up. Setting: The VA TBI Model Systems project includes five Veterans Affairs (VA) Polytrauma Rehabilitation Centers (PRCs). Participants: Participants included veterans enrolled in the VA TBI Model Systems longitudinal study who completed the Satisfaction with Life Scale at Year 1 follow-up. The project includes participants who have sustained a TBI ranging in severity from mild to severe. The sample is largely male (96%) and Caucasian (72%), with a median age of 27 upon study enrollment (interquartile range: 23-43). Interventions: Not Applicable. Main Outcome Measure: Satisfaction with Life Scale (SWLS; Diener et al., 1985). Results: Multivariate regression analyses revealed that age, marital status, pre-injury employment status, pre-injury mental health history, and active duty status at the time of injury were all significant predictors of satisfaction with life at Year 1 follow-up. Conclusions: Results of the current study suggest that satisfaction with life in veterans with TBI is mediated by several factors that might inform rehabilitation interventions and discharge recommendations. Pre-injury variables (e.g., employment) and active duty status (a unique aspect of the veteran population) influence life satisfaction at one year post-injury. Limitations and future clinical implications will be discussed.

Research Topic: Acute & Traumatic Injury
Funding agencies: DOD
Grant support: This research was sponsored by VHA Central Office VA TBI Model Systems Program of Research, Subcontract from General Dynamics Health Solutions (W91YTZ-13-C-0015) from the Defense and Veterans Brain Injury Center, US Army Medical Research and Material Command (USAMRMC), US Department of Veterans Affairs grants (1 I50 HX001233-01, W81XWH-13-2-0095) and US Department of Defense Congressionally Directed Medical Research Programs

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34. Deep Transcranial Magnetic Stimulation for Medication Refractory Depression in Mild Traumatic Brain Injury

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Abstract: Major Depressive Disorder (MDD) is a complex problem with approximately 14.8 million American adults affected with an estimated cost of $70 billion per year. Traumatic brain injury (TBI) is also a common problem with 1.5 million new injuries in the United States each year and an estimated cost of $17 billion. Importantly, these two disorders are often comorbid with depression present in as many as 50% of mild TBI (mTBI) cases. Unfortunately, those with mTBI who develop psychiatric complications have been shown to have overall poorer outcomes. Patients with mTBI and depression will typically get management consistent with their non-mTBI depressed counterparts but with varying degrees of success. In the general population, approximately 80% of people treated for depression will respond to medications (NIH, 1998) but in mTBI success rates appear to be much lower and with increased levels of side effects. Sadly, many mTBI depressed patients are left with severe medication refractory disease (MRD). Deep transcranial magnetic stimulation (dTMS) has been shown to be effective (and is FDA labeled) for the management of severe MRD. TMS is a non-surgical brain stimulation technique that uses magnetic fields to alter brain activity. Studies show 58% of patients get at least a 50% reduction in symptoms and 37% get completely into remission. While TMS has shown tremendous promise in MRD in general, it has yet to be specifically evaluated in mTBI. This study will examine the effect of TMS on MRD in those with and without mTBI. Stimulation will be completed using a Brainsway Deep Transcranial Magnetic Stimulation Device. It is FDA approved for use in non-psychotic MRD and is labeled for a full course of 20 once per day stimulation sessions (5 days per week for 4 weeks). Each session is 20 minutes in length. The first stimulation session requires motor response mapping (MAP) and the first stimulation session of each week involves motor threshold determination (MT). Participant's level of depression will be assessed at the beginning and end of the stimulation course as well as at 1, 3, and 6 months post intervention. If shown to be effective in mTBI, TMS would provide a new avenue of intervention for a very common and debilitating disorder that is frequently comorbid with mTBI. Further, the results of this study could help identify specific symptoms of both depression and mTBI that would make subjects particularly well-suited to TMS as an intervention.

Research Topic: Mental Illness
Funding agencies: DOD
Grant support: None

35. High Prevalence of Hypomagnesemia and its Relation to BMI, Type 2 Diabetes, and Clinical Disease Measures in a VA Outpatient Rheumatology Clinic Population

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Abstract: Background/Purpose: It has been estimated that nearly half the US population consumes less than the daily requirement of magnesium. There are very few studies of the prevalence of hypomagnesemia in the general population, and no studies in a Rheumatology outpatient clinic population. The purpose of this study was to determine the prevalence of hypomagnesemia in a VA Rheumatology outpatient clinic population, and explore its relationship to BMI, Type II diabetes, clinical disease measures, and potential contributing factors, including PPI use. Methods: Serum magnesium (Mg), ESR and CRP were measured, and BMI was recorded in 100 consecutive new referrals to the Minneapolis VA Health Care System Rheumatology clinic and 100 consecutive established inflammatory arthritis patients. Data regarding Type 2 diabetes, rheumatoid arthritis (RA), renal function, alcohol, PPI, diuretic and vitamin use was collected. In new patients, self-reported pain scores (VAS) were recorded. DAS28 scores were calculated in the subset of patients with newly diagnosed rheumatoid arthritis. Chi-square and multivariable logistic regression analysis were used for statistical analysis. Results: 76 of 200 patients (38%) had low serum magnesium levels (< 1.8 mg /dl). Magnesium levels in the overall group tended to be low with an overall mean of 1.8 mg/dl ±0.25. Mean Pain scores were slightly higher in the low magnesium group. Mean DAS28 scores were slightly higher in the RA patients with low Mg vs normal Mg (5.7±1.5 vs 3.9±1.9). The unadjusted effect of PPI use on prevalence of hypomagnesemia was small (OR 1.67, p=0.09). The concomitant use of diuretics did not significantly alter the risk. There was no significant association between reported alcohol or supplement use and hypomagnesemia. There was a weak association of BMI and hypomagnesemia (OR 1.05, p=0.04). The strongest association was with T2DM, which was an independent risk factor for hypomagnesemia (OR 3.77, p=0.001). Conclusions: We found an alarmingly high prevalence of hypomagnesemia in a cohort of VA Rheumatology clinic patients. BMI and PPI use were weakly associated with hypomagnesemia. Hypomagnesemia may be associated with higher disease activity in rheumatoid arthritis. We found a strong association between T2 DM and hypomagnesemia. This study supports the need for future investigation of the prevalence and causes of hypomagnesemia in rheumatic disease, and its role in disease activity.

Research Topic: Autoimmune, Allergic & Hematopoietic Disorders
Funding agencies: None
Grant support: None

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36. Differential Effects of Mild TBI Severity and PTSD Symptomatology on Cognitive Performance in Veterans

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Abstract: Cognitive assessment of veterans with a history of mild traumatic brain injury (mTBI) can be complicated by comorbid psychiatric conditions. Differentiating between cognitive deficits associated with mTBI and those attributable to a comorbid disorder, such as PTSD, is challenging. This study examined the relationship between cognitive performance, mTBI severity/recurrence, and PTSD symptoms in veterans. Participants (n=36, Mean age=49.8 yrs) were administered the CogState battery of tasks, including a one-back working memory task (One-Back task) and a continuous recognition visual learning task (One Card Learning Task). mTBI symptoms, including a composite score of mTBI severity/recurrence, were assessed using the Minnesota Blast Exposure Screening Tool (MN-BEST). PTSD symptoms were assessed using the PTSD Checklist - Civilian Version (PCL-C). Correlation and multiple regression analyses were used to examine the relationship between performance on the cognitive tasks, MN-BEST non-blast mTBI severity scores, PCL-C total scores, and age. For the One-Back task, reaction time was significantly positively correlated with mTBI severity score (r=.49, p=.001), PCL-C total score (r=.31, p=.03), and age (r=.31, p=.03); those with higher scores on these variables had longer reaction times. In the reaction time multiple regression model, only mTBI severity score had a significant regression weight (standardized β=.477, p=.003), while neither PCL-C total score nor age significantly contributed to the model. For the One-Card Learning task, reaction time was significantly positively correlated only with mTBI severity score (r=.39, p=.01), not with PCL-C total score nor age; those with higher mTBI severity scores had longer reaction times. Accuracy on the One-Card Learning task was significantly negatively correlated only with PCL-C total score (r=-.44, p=.008), not with mTBI severity nor age. Results suggest that mTBI severity/recurrence was uniquely associated with reaction time, but not accuracy, during tasks measuring working memory and visual learning. PTSD symptomatology, however, was singularly (negatively) associated with accuracy on the learning task, controlling for effects of mTBI severity and age. These results (i) suggest unique relationships between mTBI, PTSD, and different aspects of cognitive performance, and (ii) demonstrate the importance of considering the effects of both mTBI history and current clinical symptoms on cognitive functioning.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: DOD
Grant support: This study is supported by the Defense and Veterans Brain Injury Center.

37. Blast-Related Mild TBI Severity and Current PTSD Symptomatology are Differentially Associated with Regional Homogeneity in Parietal Cortex

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Abstract: Blast-related mild traumatic brain injury (mTBI), commonly reported in veterans of Operations Enduring and Iraqi Freedom (OEF/OIF), has been associated with (a) post-deployment rates of PTSD, and (b) long-distance resting state brain functional connectivity (FC) dysfunction. Little is known, however, about short-range spontaneous brain activity, or Regional Homogeneity (ReHo), in these veterans. While FC represents functional integration via temporal similarities of distant brain regions, ReHo represents the clustering of neighboring neuronal ensembles, reflecting regional functional specificity. This study used ReHo analysis to help identify regional resting state functional connectivity associated with blast mTBI severity and current PTSD symptomatology. Six-minute eyes-closed resting-state fMRI data was collected from 127 OEF/OIF veterans (Mean age: 32.7 yrs). Blast-related mTBI symptoms were assessed using the Minnesota Blast Exposure Screening Tool (MN-BEST). Whole-brain ReHo maps representing local connectivity were calculated for each subject. Scores from the MN-BEST representing blast mTBI severity/recurrence were regressed (linear regression analyses) with the ReHo maps. Resulting F-statistic maps were used to identify brain regions in which individual ReHo variability was related to individual severity of blast mTBI. Clusters in these regions that survived correction for multiple comparison were identified. Correlations between ReHo in these cluster(s) and scores on the Clinician Administered PTSD Scale (CAPS) were then performed across those participants with available CAPS data (n=84). Results showed that severity of blast mTBI was negatively correlated with ReHo in Inferior Parietal Lobule/Supramarginal Gyrus (IPL/SMG) in right hemisphere (Spearman's rho=-.185, p=.037). Subsequently, higher ReHo in right IPL/SMG was significantly correlated with higher current CAPS criterion B (r=.273 , p=.012), criterion D (r=.251 , p=.021), and Total scores (r=.254 , p=.020). The severity of veterans' blast-related mTBI was associated with lower ReHo magnitude in right parietal cortex. In turn, increased ReHo in this area was associated with greater PTSD symptomatology. This parietal region is involved in the retrieval of unpleasant experiences and conscious recollection of previously experienced events, important aspects of PTSD. These results highlight the detrimental relationship between blast-related brain injury and neural dysfunction underlying PTSD.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: RR&D; DOD; MVMREF
Grant support: CDMRP W81XWH-08-2-0038, MVMREF, and VA RR&D 1 I01 RX000622.

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38. Reducing impulsivity and risk-taking behavior using transcranial direct current stimulation (tDCS)

Gilmore, Casey[1,2]; Carson, Molly[1,2]; Gentz, Carolyn[1,2]; Dickmann, Patricia[1,3]; Lamberty, Greg[1,3]; Armstrong, Michael[1]; Lim, Kelvin[1-3]

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Abstract: Impulsivity is a multidimensional construct that includes a lack of premeditation, sensation-seeking, and impaired cognitive control. Impulsivity is observed in a variety of psychiatric disorders, and manifests as aggression, poor decision-making, and excessive risk-taking. Previous studies involving healthy subjects have applied transcranial direct current stimulation (tDCS) over dorsolateral prefrontal cortex (DLPFC) - an area involved with cognitive control functions - inducing a significant decrease on performance measures of risk-taking (e.g. Balloon Analog Risk Task (BART); Risk Task). This study explores the effects of tDCS on risk-taking across a broad range of subjects who exhibit clinically-relevant impulsivity. Subjects complete two tDCS sessions per day for five days with additional one and two month follow-up sessions. Subjects complete questionnaires of impulsivity (e.g. Barratt Impulsiveness Scale; BIS), and pre- and post-intervention behavioral measures of risk-taking (e.g. Delay Discounting Task, Risk Task). Subjects are randomly assigned to receive either active or sham tDCS during performance of the BART at each of the ten sessions. At the follow-up sessions, subjects complete the questionnaires and risk-taking tasks only. Preliminary results on 6 subjects, 3 receiving active tDCS and 3 receiving sham, suggest that active tDCS can effectively reduce 1) risk-taking propensity as measured by performance on the BART, and 2) impulsivity as measured by change in BIS scores from baseline to post-treatment. Averaged across BART sessions, the active tDCS group had a significantly lower adjusted number of balloon pumps (an indication of less risky behavior) than did the sham group. Subjects' impulsiveness, as measured by total score on the BIS, decreased an average of 16% in the active tDCS group while only decreasing 4% in the sham group when comparing the first and last days of tDCS treatment. This study provides preliminary evidence that tDCS may effectively reduce impulsive and risk-taking behavior in subjects who exhibit clinically-relevant impulsivity, extending previous research that has only included healthy subjects. This study aims to measure the magnitude of change on a number of outcome tasks from pre- to post-intervention, and the stability of these effects over time. Further, this study could have potential application as a non-invasive clinical intervention for treating patients with decreased cognitive control.

Research Topic: Mental Illness
Funding agencies: DOD
Grant support: This study is supported by the Defense and Veterans Brain Injury Center.

39. Successful treatment of Paroxysmal Ataxia and Dysarthria in MS with Levitracetam

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Abstract: Paroxysmal ataxia and dysarthria (PAD) is a disease manifestation in a subset of Multiple Sclerosis patients. PAD involves transient dysfunction in control, coordination and initiation of speech and/or limb movements. Attacks are typically brief (5-10 seconds) but usually occur multiple times per day. We report a female patient with PAD Brain MRI showed a lesion in the posterior aspect of the midbrain as well as in the right posterior internal capsule abutting the red nucleus. Prior case reports have described successful treatment of PAD with anticonvulsants such as carbamazepine, oxcarbazepine, and lamotrigine (all of which are considered to work by sodium-channel blockage). We wondered whether Levetiracetam , which has fewer risk associated and does not generally require blood test monitoring, would be an effective treatment. The PAD episodes reduced in frequency (but did not abate completely) at a dose of 500 mg bid, and stopped entirely when the dose was increased to 750 mg bid. Levetiracetam is generally well-tolerated, has straightforward pharmacokinetics, and does not require a titration period. We suggest that Levetiracetam be considered for management of PAD, and perhaps for other paroxysmal MS symptoms as well.

Research Topic: Other Chronic Diseases
Funding agencies: NIH; UMN
Grant support: PNI Training Program (NIH T32 DA007097)

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40. Improving Ambulatory Education through Block Scheduling

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Abstract: Ambulatory education in residency training has long been structured as ½ day per week continuity clinic experience. Programs have been tasked with redesigning ambulatory training to improve the quality of ambulatory education, resident satisfaction, and reduce the conflict between inpatient and outpatient duties. Beginning July 2015, the University of Minnesota Internal Medicine Residency Program implemented block scheduling with a full day of continuity clinic each week on non-inpatient blocks. This project is aimed at assessing if moving to a 4+4 block schedule model from the traditional clinic model improves ambulatory care training including time spent in clinic, value placed on ambulatory education and comfort level in clinic. We gathered administrative clinical and resident survey data with the traditional format for continuity clinic and have begun to collect the same data with 1 year of block scheduling coming to a close. In the 14-15 academic year, with a traditional continuity clinic model, 37% of resident clinics were cancelled. 92% of residents felt the program valued inpatient general medicine 'A Lot' compared to 27% of residents for continuity clinic. When asked about preparedness for a type of practice, residents ranked themselves at 85/100 for hospital medicine and 61/100 for ambulatory medicine. Finally, when ranking their likelihood of pursuing a career 18% of residents reported likely or very likely for primary care, 42% for hospitalist medicine, and 62% for specialty medicine. Thus far during the 15-16 academic year, 7% of clinics were cancelled, compared to 37% the year prior and residents spent 46 half days in clinic compared to 33 the year prior. The University of Minnesota used a traditional model for continuity clinic for many years, which led to 1/3 of continuity clinics being cancelled, as well as a perception that the program valued inpatient medicine more than ambulatory medicine. Residents in the program have felt less prepared in ambulatory medicine, and self-reported that they are less likely to pursue a career in primary care. With block scheduling the residents are now spending more time in continuity clinic which we theorize will lead to a change in perception of program values as well as resident preparedness and likelihood to pursue primary care.

Research Topic: Health Systems
Funding agencies: None
Grant support: None

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41. The Latest Occult 'Hypoallergenic' Allergen: Ethylhexylglycerin

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Abstract: Ethylhexylglycerin is an emollient and emulsifier that is increasingly used in personal care products. We report a healthy 34-year-old female with a history of childhood eczema and severe hand dermatitis. Previous patch testing in 2010 revealed positive reactions to neomycin, bacitracin, formaldehyde-related preservatives, methyldibromo glutaronitrile, decyl glucoside, benzalkonium chloride, and ethyleneurea melamine formaldehyde. Her dermatitis improved significantly with avoidance, but then flared again with additional affected body sites (face, neck, trunk, elbows, legs). Additional testing in 2015 included NACDG standard series, corticosteroids, cosmetics, preservatives, vehicle, perfumes/flavors, plants/ woods, rubber, textiles, and 24 personal items. Newly identified positive reactions included ethylhexylglycerin, group B steroids (budesonide, amcinonide), cocamidopropopyl betaine, shellac, and limonene. She also reacted to several personal products, including a baby lotion containing ethylhexylglycerin. Ethylhexylglycerin sensitivity has been reported sporadically in Europe. This is the third reported case in North America. The NACDG added it to their screening series in 2013. We present this case to raise awareness of potential reactions to this relatively newly-identified allergen which is increasingly utilized in North American products.

Research Topic: Autoimmune, Allergic & Hematopoietic Disorders
Funding agencies: None
Grant support: None

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42. Delineating the Paths from Antisocial Behavior to PTSD

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1. Minneapolis VA Health Care System

Abstract: Antisocial behavior is associated with greater risk for PTSD. Studies suggest that this may be due to increased levels of combat exposure and decreased social support among veterans with antisocial behavior. Antisocial behavior is best conceptualized as two related dimensions, aggressiveness and disconstraint, and it is unclear how the two dimensions relate to PTSD and whether they show differential associations either with PTSD or with the two potential mediators of combat exposure and social support. The present study tested an integrated model of the associations between the two dimensions of antisocial behavior (aggressiveness and disconstraint) and post-deployment PTSD severity. Based on the existing literature, we considered combat exposure and social support as potential mediators. Our sample included 522 National Guard soldiers who were assessed before and after a combat deployment, with the assessment of aggressiveness and disconstraint occurring pre-deployment and the assessment of combat exposure, social support, and PTSD severity taking place post-deployment. Results show that increased combat exposure partly mediates the association between pre-deployment disconstraint and PTSD, whereas reduced social support mediates the relationship between pre-deployment aggressiveness and PTSD. In addition, direct paths remained from both disconstraint and aggressiveness to PTSD, with aggressiveness predicting greater PTSD severity and disconstraint predicting reduced PTSD severity. The results of this study clarify the etiology of PTSD symptoms in soldiers with antisocial traits and have important implications for intervention. In particular, prevention efforts could be tailored to the specific vulnerabilities of service members high on either aggressiveness or disconstraint.

Research Topic: Mental Illness
Funding agencies: HSR&D; DOD; UMN
Grant support: This work was supported by the Minnesota Medical Foundation (grant number 3662_9227-06), the Department of Defense Congressionally Directed Medical Research Program (grant number W81XWH-07-2-0033), the Department of Veterans Affairs Health Services Research and Development (grant number RRP 08-385), and the University of Minnesota Press.

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43. A Proactive Smoking Cessation Intervention For Low-Income Smokers: The Role Of Smoking-Related Stigma

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1. Center for Chronic Disease Outcomes Research
2. North American Quitline Consortium
3. University of Minnesota School of Public Health, Division of Health Policy and Management

Abstract: Background: Smoking de-normalization has led to increased smoking-related stigma. The stigmatization of smoking has been paralleled by a reduction in smoking prevalence, although rates of smoking in low-income populations remain high. Methods: Data are from an RCT evaluating the effect of a proactive cessation intervention on abstinence. 2406 smokers enrolled in MHCP were randomized to outreach (n=1200) or usual care (n=1206). The intervention used mailings, telephone calls, and free NRT and telephone counseling. Groups with lower (n=1227) and higher stigma (n=1093) were formed. Intervention, stigma, and an interaction term predicted abstinence at follow-up. Results: Low stigma smokers had more peer smokers and were less motivated to quit. In the low stigma group, the abstinence OR for outreach vs usual care was 1.94. Conclusions: The intervention was more effective for low stigma smokers, suggesting proactive interventions are a promising strategy for these hard-to-reach smokers.

Research Topic: Access & Disparities in Care
Funding agencies: HSR&D; NIH
Grant support: This study was funded by the National Cancer Institute (1R01CA141527-01), National Institutes of Health.

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44. Transport Characteristics of Lymphatic Endothelial Cells

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1. Minneapolis VA Health Care System

Abstract: Lymphatic capillaries are responsible for fluid and solute uptake from the tissues. In the context of central nervous system (CNS), substantial evidence exists that lymphatics contribute to the cerebrospinal fluid (CSF) drainage in addition to arachnoid tissue. However, data on the barrier characteristics of lymphatic endothelium remains very scarce. Using in vitro cell models, we explored transport of lymphatics including cell monolayer permeability before and after endothelial junction disruption. Rat Arachnoid and Lymphatic Cells were immortalized by LgTAg vector. 12-well Transwell plates were used to examine permeability, transport and TEER. Our findings show that multiple transport mechanisms may contribute to CSF drainage and clearance via the lymphatic pathway. The research in this project and understanding what drives transport is integral to furthering the care of people with traumatic brain injury and those suffering hydrocephalus.

Research Topic: Acute & Traumatic Injury
Funding agencies: BLR&D
Grant support: VA Merit Review Grant #1I01BX001657-01

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45. Spiritual Distress and Dyadic Adjustment in Couples Managing PTSD

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2. Minnesota Veterans Medical Research & Education Foundation
3. Center for Chronic Disease Outcomes Research
4. University of Minnesota (Fairview)

Abstract: Within the Department of Defense, Chaplaincy interventions are often the first efforts to help couples managing the relationship sequelae of PTSD. While these types of interventions are in broad use, there is very little data on either their effectiveness or even the more foundational relationships between spirituality and dyadic adjustment in couples managing PTSD. This study used mailed surveys to assess spiritual distress and relationship outcomes among Veterans who had initiated treatment for PTSD and partners of such Veterans. Fifty-eight Veterans and 59 partners returned surveys. Results indicated that: 1. Among veteran trauma survivors, spiritual distress was correlated with higher levels of depressive symptoms, PTSD symptoms, and negative communication. In this group, spiritual distress was correlated with lower levels of relationship satisfaction. 2. Among veteran trauma survivors, after controlling for PTSD and depressive symptoms, spiritual distress was associated with higher levels of negative communication and lower levels of relationship satisfaction. The effect sizes in both of these cases were large; 23% of the variance in negative communication and 15% of the variance in relationship satisfaction. 3. Among veterans' partners, after symptoms of depression were controlled, spiritual distress did not predict either negative communication or relationship satisfaction.

Research Topic: Mental Illness
Funding agencies: None
Grant support: Sidran Trauma Institute, James B. Linsmayer Foundation

46. Exploration of Dietary Habits Associated with Healthy Brain Functioning Across the Lifespan

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1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: The Healthy Brain Project (HBP) is a unique study at the Brain Sciences Center that integrates neuroimaging, genetics, cognitive, and lifestyle data in order to identify characteristics associated with healthy brain aging. Participants are cognitively healthy adults and are primarily women veterans, who range in age from 30 to 100+ years of age. Participants return annually, permitting our research team to discover associations between study variables cross-sectionally and to validate them longitudinally, thus enabling potential forecasting of future cognitive status. In collaboration with the Hospital's Nutrition and Food Service, we have recently extended this rich data set to include detailed nutritional information, since nutritional status can have a major effect on brain functioning. In addition, collecting such data from a healthy population could allow for more detailed identification of dietary habits associated with healthy brain function across the lifespan. In our study, participants are asked to prepare food journals by recording food and beverage intake for three days, two weekdays and one weekend day. The items are then entered into Nutritionist Pro Version 6 software for further analysis. Using this software, we are able to quantify 115 macro and micro-nutrients, including amino acids, trace minerals, and lipids. We have received an excellent response and have collected, up to now, detailed nutritional data from 100 participants. Preliminary analyses have revealed large variety in participants' intake of several nutrients, which allows for a rigorous, ongoing, exploration of associations with neural functioning, as assessed by magnetoencephalography in our Center.

Research Topic: Dementia & Neuronal Degeneration
Funding agencies: UMN
Grant support: None

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47. The Older Driver with Cognitive Impairment: Perceptions of Driving Ability and Results of a Behind the Wheel Test

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1. GRECC, Minneapolis VA Health Care System
2. MIRECC, Houston VA Health Care System

Abstract: Older adult drivers with cognitive impairment pose a potential safety risk to themselves and others. Providers are often uncertain about when to request a formal evaluation of driving ability, leaving subjective reports of concerns by the patient or family as common initiators of objective driving evaluation referral. This observational study evaluated the correspondence of patient and caregiver report of driving concerns relative to objective behind-the-wheel (BTW) testing. Data were analyzed from occupational therapy driving evaluations of older adult U.S. Veterans referred from cognitive disorder specialty clinics between 2005 and 2015 (n = 151). Driving ability was evaluated with a pre-testing interview of the patient and a knowledgeable caregiver, followed by objective BTW testing. Patients referred had a mean age of 77.6 (SD = 8.1) years, were 97% male, and 98% white. Results demonstrated that most patients are evaluated for driving concerns far too late, with only 3% of the sample being evaluated as independent to drive without restrictions, and 38% recommended to retire from driving. Although both patients and caregivers denied specific driving concerns (e.g., obey signs and lights) relative to objective testing, caregiver concerns were greater than their respective patient's concerns ($p < 0.001$) and were associated with objective road test outcome ($p = 0.001$).

Research Topic: Dementia & Neuronal Degeneration
Funding agencies: None
Grant support: This work was partially funded by the VA Health Care System VISN 23 Strategic Initiative Plus.

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48. MRI assessment of cardiac function in a swine model of hibernating myocardium three months following bypass surgery

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2. Cardiology, Minneapolis VA Health Care System

Abstract: OBJECTIVE: Clinical studies suggest functional recovery of hibernating myocardium (HM) may be delayed following coronary artery bypass graft (CABG) surgery. Cardiac magnetic resonance imaging (CMR) has been proven effective in identifying HM in clinical studies. Our animal model of HM has shown partial but incomplete functional recovery one month following CABG using echocardiography. Our current study uses CMR to more accurately characterize myocardial viability and recovery at one and three months following CABG. METHODS: Swine (N=12) underwent left anterior descending artery (LAD) 1.5cm constrictor placement to create a territory of HM over 12 weeks. CMR performed at 12 weeks confirmed hibernation without infarction (N=12). Off-pump left internal mammary artery (LIMA) to the LAD was performed in 9 animals. 3 animals were sacrificed as HM controls. CMR was repeated in all revascularized animals at one month (N=4) and three months (N=5) prior to termination. CMR was performed at baseline and with dobutamine infusion (5 and 10 ug/kg/min). RESULTS: 12 weeks post constrictor placement, CMR confirmed viability in LAD region of all animals. In HM, wall thickening is notably reduced at baseline but with contractile reserve present during dobutamine infusion. Following revascularization, CMR confirmed LAD stenosis proximally and patent LIMA graft (N=9). Regional function shows partial recovery one month post-bypass, and trends towards normal levels by three months. CONCLUSION: CMR confirms HM is present in swine model by 12 weeks. With revascularization, CMR demonstrates trend toward recovery in a single vessel territory and longitudinal assessment of functional improvement up to three months.

Research Topic: Heart Disease
Funding agencies: BLR&D
Grant support: VA Merit Review #I01 BX000760

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49. Brain Correlates of Human Leukocyte Antigen Protection in Gulf War Illness

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1. Brain Sciences Center, Minneapolis VA Health Care System
2. University of Minnesota

Abstract: We recently reported that six alleles of Class 2 genes (DPB*01:01, DPB1*06:01, DQB1*0202, DRB1*01:01, DRB1*08:11, DRB1*13:02) from the Human Leukocyte Antigen (HLA) confer protection on Gulf War veterans from Gulf War Illness (GWI) [1]. The most substantial and statistically significant protection was conferred to the Neurological/Cognitive/Mood (NCM) domain of GWI symptomatology, such that the severity of NCM symptoms decreased as a linear function of the number of copies of those alleles ($r = -0.455$, $P < 0.001$, $N = 82$ veterans). We tested the hypothesis that this protection is exerted by modulating neural communication patterns, as assessed by brain's synchronous neural interactions (SNI). SNIs are zero-lag, pairwise crosscorrelations obtained from prewhitened, 60-sec resting-state magnetoencephalographic (MEG) recordings @1kHz from 248 axial gradiometers [1]. SNIs have proved powerful in successfully discriminating various brain diseases [2], including posttraumatic stress disorder (PTSD) [3,4], and in identifying neural correlates of resilience to trauma [5], of posttraumatic growth [6], and of measures of psychopathology [7]. We recorded MEG activity in 82 GW veterans (66 with GWI and 16 control) and tested our hypothesis above by regressing NCM symptom severity against the interaction term (product: HLAxSNI) of Number of allele copies X SNI, while including the SNI itself, age and gender as covariates. We found a highly statistically significant effect of the HLAxSNI term ($P < 10.10$) on NCM. The SNIs affected by this interaction involved mostly the posterior parieto-occipital cortex and the left cerebellum. These findings demonstrate, for the first time, the presence of genetics/neural interactions and identify their localization in the brain. 1. Georgopoulos AP, et al. (2015) Reduced Human Leukocyte Antigen (HLA) Protection in Gulf War Illness (GWI). EBioMedicine 3: 79-85; 2. Georgopoulos AP, et al. (2007) J Neural Eng 4: 349-355; 3. Georgopoulos AP, et al. (2010) J Neural Eng 7: 016011; 4. Engdahl B, et al. (2010) J Neural Eng 7: 066005; 5. James LM, et al. (2012) JAMA Psychiatry 70: 410-418; 6 Anders SL, et al. (2015) Exp Brain Res 233: 2013-2010; 7. James LM, et al. (2015) Exp Brain Res 233 : 3543-3552

Research Topic: Gulf War Veterans Illness
Funding agencies: None
Grant support: Service-directed research grant 3105 from the US Department of Veterans Affairs

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50. Operation Iraqi Freedom and Operation Enduring Freedom Veterans' Perceptions of Their VA Healthcare Experience

Jensen, Agnes[1]; Bangerter, Ann[1]; Widome, Rachel[2]; Fu, Steven[1]

1. Minneapolis VA Health Care System, Center for Chronic Disease Outcomes Research
2. Division of Epidemiology and Community Health, University of Minnesota School of Public Health

Abstract: Background: The objectives of this project were to describe perceptions of VA healthcare from men and women who served during the post 9/11-era. Methods: This study used data from the Northstar New Generation Survey, a cross-sectional survey of veterans who served during the conflicts in Iraq and Afghanistan. The outcomes of interest were perceptions of care across four domains: convenience, friendliness, quality of care and meeting of veterans' healthcare needs. This analysis assessed the associations between characteristics such as demographics, service utilization, diagnoses or self-reported health and perceptions of VA experience for the entire sample (N=922), then separately for males (n=508) and females (n=414). Results/findings: While 90% of veterans reported that VA clinics are friendly, nearly 40% reported VA clinics were inconvenient to access. Nearly 25% of veterans surveyed reported that the VA does not meet their needs, but most (83%) agree the care they receive is excellent. Veterans without a primary care visit within the 30-month study period (24% of sample) were more likely to have negative perceptions across all four domains ($p<.05$ under multivariate analysis). Veterans who self-reported fair/poor health who were nearly 2.5 times more likely to disagree VA clinics are friendly, disagree the VA meets their healthcare needs, and disagree they usually receive excellent care at the VA. Female veterans with self-reported fair/poor health were nearly five times more likely to disagree they receive excellent care at the VA or that the VA meets their needs. Veterans with a diagnosis of either depression or anxiety had more positive perceptions of VA care when compared to those without a depression or anxiety diagnosis. Gender, minority race, service connected disability status, and work status were not associated with negative perceptions for any question under multivariate analyses. Veterans cite inconvenience, preference of other health care coverage and questions about eligibility as reasons for not using the VA. Conclusions: Self-reported fair/poor health and not using primary care services were associated with negative perceptions. Veterans with depression or anxiety had more positive perceptions of the VA. This study makes a unique contribution in that the voices of Iraq/Afghanistan era veterans, particularly women and those veterans not currently using the VA are heard.

Research Topic: Health Systems
Funding agencies: HSR&D
Grant support: VA Health Services Research and VA HSR&D Career Development Award CDA 09-012-2.

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51. Anti-oxidant Therapy and Postoperative Cardiac Events: ACE Trial

Johnson, Debra[1]; Herrmann, Rebekah[1]; Zakharova, Marina[1]; Mazzula, Franchesca[1]; Garcia, Santiago[1]; McFalls, Edward[1]

1. Minneapolis VA Health Care System

Abstract: Purpose: To determine whether receiving the antioxidant coenzyme Q10 prior to vascular surgery reduces inflammation levels (measured with biomarkers or blood samples) and troponins (a heart biomarker that indicates heart tissue damage). Background: Patients undergoing vascular surgery have an increased risk of developing cardiac events during or following their surgery. Recent studies have shown that these may be due to an inflammation process that happens following surgery. Additionally, several studies have shown that certain medications may interrupt the inflammation process, thereby decreasing the number of cardiac events. One medication may be an antioxidant called Coenzyme Q10. Hypothesis: Brief pretreatment of coenzyme Q10 before elective vascular surgery reduces peak cardiac biomarker elevations, as estimated by a troponin I level at 24 hours post-vascular surgery. Description of Study: 60 eligible vascular surgical patients; Randomization; Medication (Coenzyme Q10 400 mg or placebo) x 3 consecutive days prior to surgery; Pre-surgical Labs & ECG; Post surgical 24 & 48hr Labs (Troponin, BNP, C-Reactive Protein, ECG); Post surgical 30 day follow up phone call & medical record review. Eligibility: Advanced vascular disease; Candidate of major elective vascular operation; 18 years of age or older; Willing and able to give informed consent. Exclusion: Known allergic reactions to CoQ10; Enrolled in research study that would confound interpretation of endpoints; Urgent need for vascular operation that would preclude screening.
Research Topic: Heart Disease
Funding agencies: None
Grant support: None

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52. Blood Biomarkers of Chronic Inflammation in Gulf War Illness

Johnson, Gerhard[1]; Slater, Billie[1]; Leis, Linda[1]; Rector, Thomas[1]; Bach, Ronald[1]

1. Minneapolis VA Health Care System

Abstract: Background: Approximately 300,000 of the 697,000 U.S military personnel who served in the 1990-1991 Gulf War suffer from an unexplained chronic multi-system disorder known as Gulf War Illness (GWI). GWI is defined by symptoms in at least 2 of 3 categories – fatigue, mood-cognition, musculoskeletal pain – that are not attributable to other diseases. The etiology of GWI remains poorly defined, and the case definition is based solely on symptoms. Goals: To identify objective criteria for GWI diagnosis and to identify a potential therapeutic target for GWI treament. Methods: A surveillance study of 85 Gulf War veteran volunteers identified from the Department of Veterans Affairs Minnesota Gulf War registry was performed. Fifty-seven subjects had GWI as defined by CDC 10 criteria (Fukuda case definition), and 28 did not have symptomatic criteria for a diagnosis of GWI. Peripheral blood counts and immunoassays of 61 plasma proteins were performed. Statistical analyses were conducted using the Mann-Whitney rank sum test to compare biomarker distributions and stepwise logistic regression to formulate a diagnostic model. Results: Lymphocytes, monocytes, neutrophils, and platelets were higher in GWI subjects. Six inflammation-related plasma proteins (C-reactive protein, leptin, brain-derived neurotropic factor, matrix metalloproteinase-2, matrix metalloproteinase-9, and fatty acid binding protein 3) were significantly different in GWI subjects. A diagnostic model of three biomarkers„lymphocytes, monocytes, and C-reactive protein„had a predicted probability of 90% (CI 76-90%) for diagnosing GWI when the probability of having GWI was above 70%. Conclusions: Quantification of inflammation-related plasma proteins and cellular enumeration provide objective criteria for the diagnosis of GWI. This biomarker evidence supports the hypothesis that chronic inflammation is a significant part of the underlying pathobiology of GWI and is a potential therapeutic target. Relevance to Veterans' Health Care: Based on the results of this study we are now conducting a clinical trial here at the MVAHCS.

Research Topic: Gulf War Veterans Illness
Funding agencies: DOD
Grant support: DoD, Congressionally Directed Medical Research Program, Gulf War Illness Research Program, Research Award GW080080

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53. Screening for Cognitive Function in Veterans with Posttraumatic Stress Disorder

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2. University of Minnesota

Abstract: The Montreal Cognitive Assessment (MoCA) is a brief screening instrument that is widely used in clinical and research settings to evaluate for mild cognitive dysfunction. Diverse conditions including Parkinson's disease, Alzheimer's disease, traumatic brain injury, depression, schizophrenia, and substance use disorders have been associated with impaired performance on the MoCA. To date, no published studies have evaluated MoCA performance in individuals with posttraumatic stress disorder (PTSD). In the present study, 175 veterans with PTSD and 231 healthy control veterans completed the MoCA as part of a larger study on brain functioning and PTSD. Results indicated that both groups performed in the 'normal' range; nevertheless, the MoCA total score, after controlling for group differences in age, was significantly lower in veterans with PTSD relative to healthy control veterans ($p = .027$). Multivariate analyses demonstrated that impairments on the abstraction ($p = .017$) and delayed recall ($p= .034$) domains accounted for the lower total score in veterans with PTSD. Notably, group differences were not accounted for by depression. Although veterans with PTSD may not exhibit broad cognitive dysfunction, relative deficits may impart specific functional impairment.
Research Topic: Mental Illness
Funding agencies: None
Grant support: Service directed grant from US Department of Veterans Affairs

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54. The Effect of Electronic Ordersets on Emergency Room Efficiency

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1. University of Minnesota Medical School
2. Minneapolis VA Health Care System

Abstract: Purpose: Prolonged emergency department throughput times are associated with increased inpatient mortality, increased length of hospital stay and increased costs for admitted patients. Our aim was to reduce throughput time in the Minneapolis VA Emergency Department via the creation and implementation of electronic order sets, to be initiated by triage nurses and physician providers. Methods: Order sets were built for four chief complaints: shortness of breath, chest pain, hematuria, and flank pain. Using EDIS data, median throughput times were collected for our chosen chief complaints over two months, prior to implementation. The order sets went live in February 2016, and staff was educated over the course of the following weeks, via email from the ED director and using an educational hand-out. EDIS data was gathered for March and April of 2016, with the same analysis performed as for the pre-order set months. Median throughput time was our primary outcome for measurement. Results: We found no significant differences in the throughput times for any of our order sets. As we were unable to create a 'flag' for pulling charts in which the order sets were used, we found it difficult to assess the frequency with which they were being utilized. For example, we estimated that the 'Shortness of Breath' order set was initiated on 7 out of 85 patients presenting with a correlating chief complaint. Minnesota Board of Nursing Nurse Practice Act guides nurses' practice, and unfortunately prevented the RNs at triage from initiating diagnostic order sets, because they are only allowed to 'implement interventions that are delegated, ordered, or prescribed by a licensed health care provider.' This significantly impacted the efficacy of the project as much of the hypothesized reduction in throughput time was going to come from initial work-up. Conclusions: Useful conclusions from this project pertain to future directions for improvement, as our actual throughput data was inconclusive due to low usage of the order sets by providers and prevention of triage RNs from using the order sets. In order for this project to have its desired effect, the issue with the Minnesota Board of Nursing must be worked out to allow nurses to initiate order sets from triage. This would likely have a larger impact on throughput than any other change.

Research Topic: Health Systems
Funding agencies: None
Grant support: None

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55. Cyclin D1 regulates glucose metabolism during hepatocyte proliferation and in hepatocellular carcinoma (HCC)

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1. Minneapolis VA Health Care System
2. Minnesota Veterans Medical Research & Education Foundation
3. University of Kentucky

Abstract: Cyclin D1 is a cell cycle control protein that regulates progression through G1 phase and plays a pivotal role in hepatocyte proliferation and liver regeneration. It is also an important oncogene that is overexpressed in about half of human cancers, including hepatocellular carcinoma (HCC). The incidence of HCC is rapidly increasing in the Veterans population and the current treatment options are very limited. The risk factors that contribute to the development of HCC commonly occur in military Veterans including Hepatitis C, obesity, and fatty liver. Our previous work suggested that cyclin D1 regulates numerous aspects of metabolism in hepatocytes, but this link has not been well studied. Our current study focuses on understanding the relation between cyclin D1 and metabolism in HCC. Here, we showed that siRNA-mediated knockdown of cyclin D1 increased glucose uptake and decreased lactate production in the AML12 mouse hepatoctye cell line and human HCC cells, suggesting a shift towards the Krebs cycle from glycolysis. We cultured cyclin D1-depleted AML12 cells in the presence of U-13C-glucose, which confirmed increased glucose flux into Krebs cycle via the pyruvate carboxylase (PC) pathway. Further, knockdown of cyclin D1 perturbed Krebs cycle activity and enhanced ROS production. These results indicate that cyclin D1 regulates glucose metabolism by favoring glycolysis over the Krebs cycle to suppress oxidative stress. To our knowledge, these are the first studies to indicate that cyclin D1 promotes glycolysis metabolism, and thus may regulate a key aspect of tumor metabolism. Further study of the link between the cell cycle and tumor metabolism may provide insight into novel therapies for HCC, which may advance the care of Veterans with this malignancy.

Research Topic: Cancer
Funding agencies: NIH; MVMREF
Grant support: None

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56. Incidence of Unprovoked Venous Thromboembolic Events (VTE) in Patients with Chronic Lymphocytic Leukemia (CLL)

Katkish, Lauren A[1]; Rangaraju, Sravanti[1]; Rector, Thomas S[2]; Johnson, Gerhard J[3]; Klein, Mark A[3]; Gupta, Pankaj[3]

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2. Center for Chronic Disease Outcome Research, Minneapolis VA Health Care System
3. Hematology/Oncology Section, Minneapolis VA Health Care System

Abstract: Thrombogenicity of CLL is unclear. With IRB approval, we estimated the risk of unprovoked VTE in patients (pts) diagnosed with CLL (1997-2014) in the absence of known thrombogenic conditions. Records were reviewed for clinical and lab data and VTE (pulmonary embolism [PE] or deep vein thrombosis [DVT]) and confirmatory imaging reports examined. We followed 308 pts (99% males, mean age 70 yrs) from CLL diagnosis or when CLL follow-up at VA began to last contact/death (122/308 [39.6%] pts died during the observation period). Mean follow-up was 4.6 + 2.9 yrs; 90% pts were followed continuously at the VA. Exclusion criteria: preceding immobility, serious illness requiring hospitalization, hypercoagulable state, recent chemotherapy. Over 1408 pt-yrs follow-up, 9 unprovoked VTEs (6 DVT, 3 PE) occurred; est. incidence rate of VTE: 0.64 per 100 pt-yrs, 95% CI [0.33, 1.23]. All were males, ages 55-95 yrs at CLL diagnosis. Eight had symptoms prompting imaging; 1 PE was diagnosed incidentally on re-staging CT. All had bulky lymphadenopathy; none compressed the relevant veins. Small, stable monoclonal paraproteinemia was identified in 2/5 VTE pts tested. At development of VTE, 4, 1, 1, 3 pts had Rai stage I, II, III, IV CLL, respectively. While there were relatively few events, there was no clear relationship of VTE with advanced CLL stage. Recurrence of unprovoked VTE occurred in only 1/9 (11%) pts after intentionally stopping anticoagulation. In the general population in our region, overall incidence of VTE in 70-74 year old males is 0.65 per 100 pt-yrs (Arch Internal Med 1998;158:585-93). Since 17-47% of all VTEs were unprovoked in various population series, the incidence rate in our CLL pts (0.64; 95% CI: 0.33, 1.23) approximates the expected population incidence. If CLL was an independently thrombogenic condition, the development of unprovoked VTE would be skewed towards pts with advanced CLL stage and/or associated with frequent recurrence. Duration of anticoagulation varied, likely reflecting the previously unknown thrombogenicity of CLL. This is the first long-term study of unprovoked VTE in pts with CLL, with >1400 pt-yrs of follow-up. The low incidence of unprovoked VTEs observed in our study suggests that primary thromboprophylaxis may not be required in pts with CLL who do not have additional risk factors for thromboembolism. Risk of recurrence of unprovoked VTE in CLL appears to be relatively low.

Research Topic: Cancer
Funding agencies: None
Grant support: None

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57. Instrumental assessment of dyskinesia across dimensions of genetic liability and severe psychopathology

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2. Midwestern University
3. University of California San Diego

Abstract: Dyskinesia, which is linked to basal ganglia dysfunction, has been reported in first-episode psychosis and those at ultrahigh risk of developing psychosis (UHR). Instrumental assessment of dyskinesia yields high-resolution quantification of motor function, and digitized handwriting assessment has revealed abnormal handwriting kinematics in UHR. Aim 1 of this study examined whether dyskinetic movement is present in first-degree relatives, who carry unexpressed genetic liability for the development of schizophrenia. Given the presence of motor dysfunction across a range of psychological disorders as well as the proposal that certain motor abnormalities form a core non-mental symptom of psychosis specifically, Aim 2 examined dyskinesia across various symptom dimensions of severe psychopathology. Aim 3 explored the relationship between dyskinesia and working memory given putative shared circuitry. Fifty-two people with schizophrenia or schizoaffective disorder (SZ), 45 first-degree biological relatives of people with a psychotic disorder (REL), 17 people with bipolar affective disorder (BD) and 58 non-psychiatric controls (CN) completed a handwriting task on a computerized tablet. Participants wrote 'lleellee' in cursive in 1, 2 & 4 cm vertical boundary conditions. Dyskinesia was quantified by calculating average normalized jerk (ANJ), a measure of the changes in acceleration over the course of a pen stroke. There was a main effect of group (p=.036); SZ had higher ANJ than CN (p=.009) and REL (p=.019). ANJ for BP fell between SZ and REL. ANJ was significantly associated with SANS anhedonia in SZ (r=.298, p=.032), and with digit span scores in SZ (r=-.351, p=.038) and BP (r=-.589, p=.016). Correlations with chlorpromazine equivalent doses were not significant, though one correlation with course of illness was (r=.34, p=.014). Increased handwriting dysfluency in SZ is consistent with models of the disorder implicating hyperdopaminergia in the basal ganglia. The absence of dysfluency in REL is interesting in light of previous findings of dyskinesia in REL as measured by a force variability task, and highlights the utility of instrument-based assessments in teasing out the presentation of motor abnormalities in REL. Symptom and working memory correlates may indicate shared neural substrates between anhedonia and working memory deficits and dyskinesia.

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: VA Clinical Science Research & Development grant 1 I01 CX000227A (to Scott Sponheim).

58. Targeting Intracellular Pathways in Mesothelioma

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1. Minneapolis VA Health Care System

Abstract: Introduction: Mesothelioma is a highly fatal cancer with limited therapeutic options. Low expression of the endogenous CDK4 inhibitor p16INK4A has been demonstrated in up to 90% of mesothelioma tumors. Inhibition of CDK4 is associated with decreased levels of thymidylate synthase and cell cycle arrest. Pemetrexed forms the backbone of treatment in mesothelioma. A major mechanism of action of pemetrexed is via inhibition of thymidylate synthase (decreased levels of thymidylate synthase have been associated with increased response to pemetrexed). CDK4 has also been demonstrated to activate manganese superoxide dismutase, which can decrease superoxide levels in cells and may make them less susceptible to induction of apoptosis. Hypothesis: The CDK4 inhibitor palbociclib will sensitize mesothelioma cells to anti-cancer therapy. Results: Previously, we have demonstrated that palbociclib inhibits mesothelioma cell proliferation, inhibits retinoblastoma protein (Rb) phosphorylation, and results in cell cycle arrest. Mesothelioma cells in culture were treated with palbociclib and pemetrexed alone and in combination. At concentrations at 100 uM or greater, single agent palbociclib was associated with decreased cell proliferation versus single agent pemetrexed. The results are consistent with at least an additive effect on cell proliferation in H2373 and H2461 mesothelioma cells at 1 uM palbociclib plus 10 nM pemetrexed. In H2373 cells treatment with palbociclib at 10 uM results in complete inhibition of phosphorylation of site T826 in Rb, while treatment with 1 uM palbociclib results in partial inhibition of phosphorylation at the same site. Treatment with 100 nM pemetrexed plus 1 uM palbociclib resulted in complete inhibition of phosphorylation at T826. We also evaluated the effects of gentian violet on mesothelioma cells. Gentian violet is known to cause downregulation of thioredoxin-2, an antioxidant protein. After 72h incubation with gentian violet, decreased cell proliferation was observed for 3 separate cell lines (IC50 = 365, 870, and 920 nM, respectively). Also, gentian violet sensitized mesothelioma cells to palbociclib in a cell proliferation assay. Conclusion: Pemetrexed affects Rb phosphorylation and sensitizes mesothelioma cells to treatment with palbociclib. Gentian violet also sensitizes mesothelioma cells to palbociclib. Further investigation of this combination approach may demonstrate these combinations are useful for mesothelioma treatment.

Research Topic: Cancer
Funding agencies: DOD
Grant support: DOD Peer-Reviewed Cancer Research Program, CDA; Development of Novel p16INK4a Mimetics as Anticancer Therapy

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59. Recruitment outcomes and baseline characteristics of participants in the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) Trial

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1. Minneapolis VA Health Care System
2. University of Minnesota
3. Indianapolis VA Medical Center
4. Indiana University

Abstract: Background: Although long-term opioid therapy is commonly prescribed, no trials have reported long-term outcomes of opioid therapy for chronic pain. The SPACE trial is an ongoing pragmatic randomized controlled trial designed to compare benefits and harms of opioid versus non-opioid medication therapy over 12 months among Veterans with chronic back pain or hip/knee osteoarthritis pain. Objective: To describe SPACE trial recruitment outcomes and baseline participant characteristics. Methods: Eligibility criteria were chronic back or lower extremity osteoarthritis pain with moderate-severe intensity and interference with function; exclusion criteria included current long-term opioid therapy, regular benzodiazepine use, bipolar disorder or schizophrenia, severe untreated mental health disorder, active substance use disorder, and moderate-severe cognitive impairment. Primary care providers in the Minneapolis VA Health Care System were asked for permission to approach potentially eligible patients. Veterans from participating providers with a recent visit for back, hip, or knee pain were identified electronically. Potentially eligible Veterans were mailed an invitation letter, then contacted for a telephone-based eligibility interview. Those who met criteria and consented to participate completed a comprehensive in-person baseline study assessment. Approximately one week later, participants were scheduled for their first treatment visit and randomized to either opioid or non-opioid treatment arm. Pain, function, and adverse effects outcomes are assessed at 3, 6, 9, and 12 months. Results: The study team attempted to contact 5571 potentially eligible patients from 65 primary care teams. Of potentially eligible patients, 1213 (21.8%) were never reached for a telephone eligibility interview, 2341 (42.0%) were determined to be not eligible, 1752 (31.4%) declined to participate, and 265 (4.8%) enrolled. Of those who enrolled, 25 withdrew before randomization and 240 were randomized. Enrolled participants are 12% female with an age range of 21-80. The primary pain condition was back pain for 66% and hip/knee osteoarthritis for 34%. Conclusions: The SPACE trial will fill a critical research gap by comparing pain, function, and quality of life outcomes of treatment with opioid versus non-opioid medications for Veterans with chronic back or osteoarthritis pain.

Research Topic: Other Chronic Diseases
Funding agencies: HSR&D
Grant support: HSR&D 1 I01 HX 000671

60. Million Veteran Program (MVP): A Partnership with Veterans

Lederle, Frank[1]; Parks, Patricia[1]; Lucas, Susan[1]; Condon, Debra[1]; Meyeraan, Tacy[1]

1. Minneapolis VA Health Care System

Purpose: The goal is to improve Veterans' health through the collection and testing of blood samples and health information to learn which genes are linked to which health characteristics. MVP is a national, voluntary research program conducted by the Department of Veterans Affairs, Office of Research & Development, that collects genetic and health information to help find new ways of prevention, early detection, and treatment of illnesses. MVP will provide a better understanding of how genes affect health and illness, with the goal of improving health care for Veterans. Genomic analyses, including SNP genotyping, whole genome sequencing, and whole exome sequencing is being conducted on MVP samples. Nationally, 466,415 Veterans have enrolled at 50 VAs including 12,344 at the Minneapolis VA Health Care System. Methods: Participation involves: 1. Filling out surveys through the mail; 2. Completing a one-time, approximately 20 minute, study visit to provide a blood sample for the genetic testing; 3. Permitting authorized MVP staff to access information in your medical record on an ongoing basis; 4. Agreeing to future MVP contact. Next Steps - MVP Data Analysis: The first projects approved to utilize the MVP data are focused on issues that are relevant in our Veteran community. These studies will not only provide valuable research results, but are also helping to develop and streamline the data access procedures for future researchers. Current Studies (*Coordinated by VA Boston & VA CT Health Care Systems): +The Genetics of Functional Disability in Schizophrenia and Bipolar Illness*, Bronx VAMC; Miami VAMC +Genomic Study of Posttraumatic Stress Disorder*, San Diego VAMC; VA Connecticut Health Care System +Genomics of Gulf War Illness in Veterans*, VA NJ Health Care System; VA Cooperative Studies Epidemiology Center Durham +Genetic Vulnerability of Sustained Multi-substance Use in MVP, VA Connecticut Health Care System; Philadelphia VAMC +Cardiovascular Disease Risk Factors, Prevalent Cardiovascular Disease, and Genetics in the Million Veteran Program, Atlanta VAMC; Boston VA Health Care System +Pharmacogenomics of Risk Factors and Therapies Outcomes for Kidney Disease, VA Tennessee Health Care System +Genetics of Cardio-metabolic Disease in the VA Population, VA Palo Alto Health Care System; Philadelphia VAMC +Genetic Risk for AMD in Diverse Veteran Populations, Cleveland VAMC; VA Western NY Healthcare System

Research Topic: Personalized Medicine & Genomics
Funding agencies: CSR&D
Grant support: VA Cooperative Studies Program (VA CSP)

61. Network of Dedicated Enrollment Sites (NODES) Initiative

Lederle, Frank[1]; Condon, Debra[1]; Meyeraan, Tacy[1]; Kantorowicz, Alexandra[1]

1. Minneapolis VA Health Care System

Abstract: The Network of Dedicated Enrolled Sites (NODES) initiative is a pilot program that was developed from a response to support the VA Cooperative Studies program (VA CSP). The specific aims of the initiative include; enhancing study performance and enrollment rates; provide a more consistent and comprehensive approach to CSP study management, quality and regulatory compliance at the VA Medical Centers; obtain center-level perspectives in the design and execution of studies; and provide opportunities for research personnel interested in supporting the VA CSP research mission. A Director, Manager, Administrator, and Research Nurse support these efforts at each individual NODES location. The current NODES locations are: Dallas, Hines, Houston, Long Beach, Minneapolis, Palo Alto, Portland, Salt Lake City, and San Diego. NODES UPDATE: The following achievements reflect cumulative data of the NODES sites from October 2012–Present: 1. Established cross-coverage on all open CSP studies; 2. NODES staffing incorporated as part of local CSP study teams; 3. Created Mentorship Program for new local study coordinators; 4. Created procedures for recruiting at CBOCs; 5. Work stream meetings on improving study design & procedures; 6. Beta testing case report forms; 7. Enhanced recruitment through Mobile Recruiting Equipment; 8. Development of Research/HR Management Proposal; 9. Development of Partnership between NODES and Non-NODES facilities to assist in study teams with low recruitment; 10. Publication in JAMA; 11. Pending publication in Contemporary Clinical Trials; 12. Creation of NODES Executive Board

Research Topic: Health Systems
Funding agencies: CSR&D
Grant support: VA Cooperative Studies Program (VA CSP)

62. Non-invasive examination of cortical and subcortical neural oscillations in Parkinson's disease patients

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3. Department of Neuroscience, University of Minnesota

Abstract: There is no definitive method to diagnose Parkinson's disease (PD) and differentiate it from neurological disorders with similar symptoms (e.g., Lewy body disease, ...). The excessive amount of beta oscillations (15-30 Hz) in the basal ganglia is a clear indicator of Parkinson's disease, however only invasive techniques are available currently to record activity deep in the brain. Notwithstanding, it is theoretically possible to estimate the neural oscillatory activity of deep sources in the brain by using spatial filters (i.e., beamforming) on neural activity recorded outside of the head. For these reasons, we did a preliminary study to examine whether magnetoencephalography (MEG) could be used to estimate neural oscillatory activity from subcortical structures such as the basal ganglia. To this end, we recorded resting-state neuromagnetic signals from two PD male patients (72 and 87 years of age) in 'on' and 'off' medication states using a 248-channel whole-head MEG system. The 'on' and 'off' states were determined empirically from the natural fluctuation of drug treatment effect ('on' state: 1 h after the administration of dopamine-replacement drug; 'off' state: 1 h before the time scheduled for medication). Each patient performed 2x1 minute periods with eye fixation on a dot in the center of the visual field. Neural oscillatory activity was extracted for the basal ganglia, thalamus and precentral gyrus using a linear constrained minimum variance (LCMV) beamformer. Due to the moderate spatial resolution of MEG for deep brain structures, we did not divide the basal ganglia into its different nuclei. First we compared the power spectra across the three brain regions and found that the 'on' vs. 'off' state had distinctly different effects across regions, which indicates that each region plays a distinct role in the neural oscillatory characteristics of the cortico-basal ganglia pathways. Second we compared the beamformed oscillatory activity from the basal ganglia with published data obtained using invasive deep brain electrodes. We found that the beamformed activity was in agreement with the activity recorded invasively. These results suggest that beamforming MEG signals can be used to estimate the oscillatory characteristics of subcortical structures, such as the basal ganglia. If confirmed this would mean that beta oscillations in the basal ganglia, an hallmark of PD, can be estimated reliably using a non-invasive technique like MEG.

Research Topic: Dementia & Neuronal Degeneration
Funding agencies: CSR&D
Grant support: CX-0004-37

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63. Development of Biomarkers for the Diagnosis of Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a uniformly fatal disease involving progressive degeneration of motor neurons leading to relentless muscle wasting, limb and bulbar weakness and respiratory compromise. In addition to the well-characterized progressive motor neuron degeneration, approximately one third of patients develop symptoms of dementia, suggesting non-motor system neuronal involvement of the cerebral cortex. With the exception of the genetic forms confirmed by mutation analysis, there is no definitive biomarker specific for diagnosis involving sporadic cases of ALS. The overall goal of this research project is to identify biomarkers of ALS using magnetoencephalography (MEG) in order to determine factors that distinguish ALS from other disorders and to correlate the MEG data with clinical measures of ALS severity. We have 3 hypotheses: 1) MEG can be used to distinguish ALS from healthy control subjects even in early onset disease, 2) MEG can distinguish between ALS and diseases with a similar presentation, and 3) MEG can monitor disease progression. Our published studies demonstrate that anomalies in neural communication assessed by MEG differentiate various brain diseases from healthy brain functioning, providing evidence of candidate biomarkers. Neural communication patterns are assessed using synchronous neural interactions (SNIs) derived from changes in the brain's magnetic field that occur over less than 1millisecond. We recruited 4 male veteran subjects (ages 66-79) with ALS as diagnosed by the Neurology Neuromuscular Clinic. They were assessed with neurological and EMG exam, the Edinburgh Cognitive and Behavioral ALS Screen, and the Revised El Escorial Criteria by the neurologists subspecializing in neuromuscular disease. We found that the ALS and control subjects could be distinguished by the SNIs alone. The differences were observed within each hemisphere, between hemispheres, and across the whole brain. The areas of greatest difference were in the posterior frontal and anterior parietal cortices, right greater than left. There appears to be a further relationship between the SNIs and the degree of cognitive involvement. Based on these early results we predict MEG will be helpful in detecting CNS involvement in the early stages of ALS and prove beneficial in making an earlier definitive diagnosis of ALS and thus better serve the Veteran population.

Research Topic: Dementia & Neuronal Degeneration
Funding agencies: MVMREF
Grant support: None

64. What factors do patients consider most important in making lung cancer screening decisions? Findings from a demonstration project conducted in the Veterans Health Administration.

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3. Division of Pulmonology, Minneapolis VA Health Care System
4. Pulmonary and Critical Care, Wayne State University

Abstract: Background. Lung cancer is the leading cause of cancer morbidity and mortality in the United States. Although prevention is the most effective strategy for reducing the burden of lung cancer, lung cancer screening (LCS) improves early detection. Recent guidelines for low-dose computed tomography (LDCT) emphasize patient decision making, and highlight both the benefits and the harms of LCS. Objective: To identify factors patients consider important in making LDCT-based LCS decisions, and explore variations by patient characteristics and LDCT participation. Methods: Observational survey study of the Minneapolis VA LCS Demonstration Project in which LDCT-eligible Veterans (N=1388) were randomized to either Direct Invitation (mailed with decision aid, N=926) or Usual Care (provider referral, N=462). We surveyed participants 3 months after randomization (response rate 44%) and report the proportion of respondents rating 8 decision-making factors (lung cancer risk, fear of lung cancer, chance of incidental findings, convenience of LCS, chance of a false positive result, anxiety of waiting for the LCS results, knowledge of LCS, and health risks of LDCT itself) as important by condition, patient characteristics, and LDCT completion. Results: Overall, the most important factor was personal risk of lung cancer and the least important factor was LDCT health risks. Compared to Usual Care respondents, a larger proportion of the Direct Invitation respondents rated the chance of false positive results, LCS knowledge, LCS convenience, and anxiety as important. The importance of decision-making factors varied by smoking, health status, education level, and LDCT completion. Conclusion: Exposure to direct LCS invitation increased Veterans' attention to specific decision-making factors. The perceived importance of decision-making factors varied by respondent characteristics, and those completing LCS considered screening harms less important. These findings suggest decision tools influence perceptions about factors important to LDCT-based LCS decision making. Targeted materials for specific subgroups may be warranted.

Research Topic: Cancer
Funding agencies: HSR&D
Grant support: VHA Health Services Research & Development Locally Initiated Project, HSR&D Associated Health Postdoctoral Fellowship (Lillie), Research Career Scientist award RCS 10-185 (Partin).

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65. Involvement of nucleus accumbens and lateral hypothalamus in spontaneous physical activity variability

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3. Minneapolis VA Health Care System

Abstract: Rising obesity rates within the United States demand innovative therapies. Successful treatment will account for individual differences in susceptibility to obesity. One source of variance is the degree in which calories are burned through non-exercise activity thermogenesis (NEAT). In our current rat model, we investigated the biological mechanisms involved in NEAT-associated activity, known as spontaneous physical activity (SPA). Within a population of Sprague-Dawley rats, we have identified a difference in SPA that is stable across time. These rats are classified as either high activity (HA) or low activity (LA), with HA rats moving 1.5 times as much as LA rats throughout 4 days of 24-hour activity measurements. Orexin A is a neuropeptide previously shown to increase SPA and energy expenditure after injection into the rostral lateral hypothalamus (rLH). The nucleus accumbens (NAcSh) sends projections to the rLH and modifies neural activity of the rLH. We hypothesized that HA rats would be more responsive to orexin A, and that inhibition of the NAcSh would potentiate this effect. To test this, we injected rats with increasing doses of orexin A and measured physical activity for 2 h, with or without simulation and inhibition of the NAcSh. We found that both HA and LA rats exhibited increased SPA with increasing doses of orexin-A peptide (OxA) injected into the rostral lateral hypothalamus (rLH), but the magnitude of the HA response was greater ($p<0.05$). Simulation of the NAcSh by orexin A slightly reduced SPA in HA but not LA rats ($p<0.05$), whereas inhibition of NAcSh with muscimol (GABA agonist) potentiated the physical activity effect of OxA injection in rLH in both activity phenotypes ($p<0.05$). Finally, we looked at cfos expression following OxA injection in rLH, as an indicator of orexin cell activation. Within the caudal lateral hypothalamus (cLH), where the orexin cell bodies reside, we found a main effect of OxA treatment in both groups ($p<0.001$) but no differences in the proportion of orexin neurons activated between the two activity phenotypes ($p=0.303$). Together, these data demonstrate that differences in orexin responsivity may underlie variability in propensity toward physical activity, but many aspects of orexin circuitry underlying responsively appears equal between high and low activity phenotypes. Further study into the therapeutic potential of orexin may aid the development of more individualized obesity treatments.

Research Topic: Other Chronic Diseases
Funding agencies: RR&D; NIH
Grant support: NIH-R01-DK100281-01A1

66. Encoding, recollection and familiarity in schizophrenia, bipolar disorders, and first-degree relatives

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Abstract: The natural process of drawing connections between stimuli in the environment in order to efficiently form a memory is disrupted in severe and persistent mental illnesses like schizophrenia (SCZ) and bipolar disorder (BPD). Relatives of schizophrenia patients show attenuated disruptions in memory consistent with a cognitive deficit reflective of genetic liability. The Relational and Item-Specific Encoding (RISE) Task (Ragland et al., 2012) was designed for fine-tuned analysis of semantic processes contributing to deficits in encoding and recognition. RISE includes item-specific and relational encoding; performance and response confidence are measured for item-specific and associative recognition. In the current study patients with schizophrenia spectrum or bipolar disorders, first-degree biological relatives of patients, and healthy controls completed the RISE task. Results indicate that the encoding and recognition conditions affected group differences in recognition performance. Poor recognition of relationally encoded items was most evident in those with schizophrenia or genetic risk for the disorder, reflective of disrupted associative recognition. Recognition of item-specific encoded material was poor in both patient groups, reflective of disrupted source memory. Presenting the items as pairs (versus individually) during recognition did not improve performance of schizophrenia patients' recall, consistent with disrupted recollection processes. Confidence of responses was lower for people with schizophrenia regardless of how the item was encoded, further supporting recollection deficits in schizophrenia. Differences in how material is encoded and presented at recall are related to disorder specific patterns of memory deficits supported by recollection and familiarity processes in severe and persistent mental illness.

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: #ICX000227A

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67. Prevalence Rate of Personality Disorders in National Guard OIF Soldiers and Psychosocial Functioning at 2 years Post-Deployment

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2. Temple University
3. University of Minnesota

Abstract: The Department of Defense has faced allegations that military service members were wrongfully discharged with a pre-existing personality disorder (PD) diagnosis instead of a service-related posttraumatic stress disorder (PTSD) or traumatic brain injury diagnosis (Leroux, 2014). This allegation may be partially supported by evidence that the prevalence rate of PD in the United States is estimated at 10% (Lenzenberger et al, 2007), yet service members were discharged due to PD at rates between 1% (National Guard) and 29% (Navy)(Vietnam Veterans of America, 2012). However, there is limited research on the prevalence of PD in the military or the influence of PD traits on the psychosocial functioning of service members. The current study aimed to assess 1) prevalence rates of probable PD diagnoses among National Guard Soldiers deployed to Operation Iraqi Freedom (OIF) and 2) psychosocial functioning of National Guard OIF soldiers who screened positive for probable PD (PD+), compared to those who did not (PD-), upon return from deployment to OIF and two years later. Participants were 348 National Guard soldiers drawn from the Readiness and Resilience in National Guard Soldiers (RINGS) study, a longitudinal study of mental health after deployment to OIF. Soldiers completed self-report measures (Social Adjustment Scale, Navy Quality of Life Survey) at 2-3 months post-deployment and again two years later. At 6-12 months post-deployment, they were assessed for probable PD diagnoses using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders. Results indicate that 30.5% of National Guard OIF soldiers screened positive for at least one probable PD. PD+ soldiers also reported increased PTSD symptoms and depressive symptoms compared to PD- soldiers; analyses of psychosocial functioning controlled for the influence of post-deployment distress (PTSD symptoms). Upon return from OIF, PD+ soldiers reported greater impairment compared to PD- soldiers in areas of work, social and leisure activities, and friend/family relationships as well as decreased satisfaction with income and relationships with relatives. Groups did not differ on satisfaction with leisure activities and friend/family relationships. Two years later, PD+ soldiers reported increased impairment and decreased satisfaction across all domains compared to PD- soldiers. Findings support the utility of early identification and intervention for PD traits that may influence military performance.

Research Topic: Mental Illness
Funding agencies: DOD
Grant support: This research was supported by grants from Minnesota Medical Foundation (Grant #3662-9227-06) and Department of Defense Congressionally Directed Medical Research Program (CDMRP; W81XWH-07-2-003). This material is the result of work supported with resources and the use of facilities at the Minneapolis VAHCS, Minneapolis, MN.

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68. Lower Brain Glutathione Concentration in the Cognitively Normal Healthy Elderly People Human Brain than in Young Adults

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3. GRECC, Minneapolis VA Health Care System
4. School of Public Health, University of Minnesota
5. Department of Neuroscience, University of Minnesota

Abstract: Although numerous studies have measured low levels of glutathione (GSH) in the blood and cerebrospinal fluid of elderly adults, it was not previously possible to measure antioxidant concentrations in intact human tissue. The increased sensitivity of magnetic resonance technology has made it possible to noninvasively quantify the concentrations of GSH and ascorbate in the human brain. Ultra-high field magnetic resonance spectroscopy (MRS) was used to measure the concentrations of GSH and ascorbate in the occipital cortex (OCC) and posterior cingulate cortex (PCC) of seventeen young (7 males, 19 - 22 years old) and sixteen cognitively normal (Montreal Cognitive Assessment scores ≥ 25) elderly (9 males, 70 - 88 years old) adults. The concentration of GSH was found to be lower ($p = 0.02$) in the OCC of the elderly in a way that is not contingent upon the transverse relaxation rate (T2) for the first time. There was also a trend ($p=0.06$) for lower ascorbate. Absence of such age-associated differences in the PCC demonstrates that the brain ages differently depending on region. This assay had sufficient specificity to identify two elderly subjects with higher brain GSH concentrations in the PCC than most of the other participants. The short-echo-time MRS approach inherently retained numerous resonances, from which a profile of 15 neurochemicals was measured. Taken together, these outcomes link low age-associated neurotransmitter concentrations to mitochondrial dysfunction in the OCC whereas reactive gliosis is more apparent in the PCC. These findings fill part of the gap in understanding how the brain deteriorates throughout aging. The technology supplies a hitherto missing tool to measure steps along the pathway to preventing and treating cognitive decline, and therefore means to identify: which antioxidant is compromised, in which brain region it is compromised, in whom it is compromised, and whether intervention achieves normalization.

Research Topic: Aging
Funding agencies: NIH
Grant support: NIH R01: Noninvasive Antioxidant Quantification in the Human Brain under Oxidative Stress

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69. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches: ISCHEMIA

Maron, David[1]; Johnson, Debra[2]; Herrmann, Rebekah[2]; Ishani, Areef[2]; Bertog, Stefan[2]; Siddiqui, Rizwan[2]; Garcia, Santiago[2]; Hansen, Ronnell[2]; McFalls, Edward[2]

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2. Minneapolis VA Health Care System

Abstract: Objective: To compare an initial invasive strategy of catheterization and optimal revascularization (PCI or CABG) + optimal medical therapy (OMT) with a conservative strategy of OMT alone, with catheterization reserved for OMT failure. Significance: Ischemic heart disease is the leading cause of death and disability worldwide and affects 17,600,000 Americans, resulting in about 450,000 deaths in the United States annually. Globally, 7.2 million deaths are caused by ischemic heart disease each year. Medical therapy (medication and lifestyle changes) should always be used to treat ischemic heart disease. Many doctors routinely use an invasive approach in addition to medical therapy to treat ischemic heart disease; however, it is not known if this approach is better than medical therapy alone as the initial treatment of patients with stable ischemic heart disease. Trial Design: The study population will consist of 8,000 patients from over 400 international sites. Minneapolis VA Health Care System enrolling 20 participants. Patients with stable ischemic heart disease and at least moderate ischemia on stress test will be randomized to an invasive strategy of cardiac catheterization followed by revascularization with PCI or CABG in addition to optimal medical therapy, or a conservative strategy of optimal medical therapy alone with cardiac catheterization and revascularization reserved for patients who fail medical therapy. Key Inclusion Criteria: At least moderate ischemia by stress test modality (ECHO, CMR, NUC, ETT); Willing to comply with all aspects of the protocol, including adherence to medical therapy, follow-up visits, and assigned strategy. Key Exclusion Criteria: LVEF < 35%; History of unprotected left main stenosis >50%; Prior known coronary anatomy unsuitable for either PCI or CABG; History of noncompliance with medical therapy; Acute coronary syndrome < 2 months; PCI < 12 months; Canadian Cardiovascular Society Class III angina of recent onset; Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina; Prior CABG (if preformed >12 months ago with anatomy amenable to PCI or repeat CABG); Stroke < 6 months or intracranial hemorrhage; NYHA class III-IV heart failure or hospitalization for exacerbation of CHF < 6 months.

Research Topic: Heart Disease
Funding agencies: NIH
Grant support: ISCHEMIA is sponsored by a grant from the U.S. National Heart, Lung, and Blood Institute of the National Institutes of Health.

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70. Trauma-Relevant Distractors during Working Memory: Impact of Posttraumatic Stress Symptoms

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1. University of Minnesota
2. Minneapolis VA Health Care System

Abstract: Altered attention is a common feature of many anxiety and stress-related disorders. Investigations have documented that these conditions are associated with prolonged and inefficient engagement with threat information. It is less well understood how these attentional biases may contribute to the cognitive difficulties of patients with elevated anxiety. We report results from 128 post-deployment military veterans who completed a modified n-back task. Memory stimuli were superimposed on task-irrelevant background images that contained either neutral or combat stimuli in order to probe the distracting influence of threat information. Accuracy and reaction time were impaired across all participants with greater cognitive (2- vs. 0-back) and affective (combat vs. neutral) load, but no effects of a diagnosis of posttraumatic stress disorder (PTSD) were observed. However, symptom severity scores were related to task performance. Dysphoria symptoms were associated with reduced accuracy. Intrusive thoughts, avoidance, and dysphoria symptoms were associated with altered reaction times, particularly during the background display of combat images. In summary, symptoms of PTSD appear to play a role in working memory efficiency with dysphoria possibly compromising accuracy. A lack of effects for the DSM-IV-TR PTSD diagnosis highlights the importance of dimensional characterization of symptoms when studying this heterogeneous disorder.

Research Topic: Mental Illness
Funding agencies: RR&D
Grant support: Rehabilitation R&D Program (I01RX000622)

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71. Antimicrobial Susceptibility Testing of Urine Isolates from Veterans to Guide Empiric Therapy

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2. Minneapolis VA Health Care System

Abstract: Background: Urinary Tract Infection (UTI) is common among patients at Veterans Affairs Medical Centers (VAMCs), many of whom are elderly men with underlying medical or urological problems. Most UTI treatment guidelines address uncomplicated UTI in women and presume knowledge of local uropathogen susceptibility patterns, which often are unknown or are inferred from E. coli. To inform selection of empiric therapy for UTI at our VAMC, we compiled susceptibility data for one year's urine isolates. Methods: Susceptibility results (from a bioMerieux VITEK® instrument) were compiled for the 2,109 significant urine isolates in the Minneapolis VA Health Care System clinical microbiology laboratory from June 1, 2013 to May 31, 2014. For "drug-bug" combinations that were not tested directly we imputed results based on local or published data, and/or expert opinion (40% of 52,725 data points). Cumulative % susceptible was then calculated for 25 relevant agents, both overall and stratified by Gram stain group. Given the uncertainty, susceptibility of Enterococcus spp. (ENTC) to trimethoprim/sulfamethoxazole (SXT) was analyzed as both 0% and 100%. Results: Of 2,109 urine isolates, 561 were Gram-positive and 1,548 Gram-negative. E. coli predominated (32%), followed by ENTC (18%), Klebsiella (15%), Staphylococcus (9%), and Pseudomonas (8%). The most active oral agents (as % susceptible) were SXT (79%, if ENTC susceptible; 60%, if resistant), fluoroquinolones (FQs, 68%), and nitrofurantoin (NF, 64%). The most active intravenous agents were imipenem (93%), piperacillin/tazobactam (91%), aminoglycosides (77-81%), cefepime (74%), ertapenem (69%), and 3rd-gen. cephalosporins (65-69%). Antibiotic rank order by % susceptible differed greatly for Gram-positives vs. -negatives, and for E. coli vs. other Gram-negatives (not shown). Conclusion: Among urine isolates from veterans, no oral agent provided ≥ 80% overall susceptibility; SXT either led or trailed FQs and NF, depending on its presumed activity against ENTC; and FQs and NF were closely matched. E. coli was a minor contributor and represented poorly the total population. Data such as these could improve selection of empirical UTI therapy for veterans, as could urine Gram stains.

Research Topic: Infectious Diseases
Funding agencies: NIH; UMN
Grant support: NIH T32 training grant

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72. The alteration of sensorimotor rhythms by hypothalamic orexin-A reflects motor preparedness

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3. Department of Medicine, University of Minnesota
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Abstract: Orexin-A is a hypothalamic neuropetide implicated in the regulation of wakefulness, appetite, reward processing, muscle tone, and other physiological processes. The broad range of systems affected stems from the widespread projections of orexin-producing neurons toward multiple brain regions, including the basal ganglia and the thalamus which are involved in sensorimotor processes. Here we tested the hypothesis that orexin-A changes the patterns of sensorimotor oscillatory activity to reflect an increased preparedness of the sensorimotor system for motor action. To this end we recorded the sensorimotor oscillatory activity of freely-moving rats (N=8) after injection of orexin-A (OXA) or artificial cerebrospinal fluid (CSF) in the ventrolateral preoptic area of the hypothalamus. Neural activity was recorded during 60 minutes using epidural electrocorticography (ECoG). The electromyographic (EMG) activity of neck muscles was recorded as well. For each 10 s segments, (a) we scored the vigilance state (Awake, Paradoxical Sleep, Slow-Wave Sleep) on the basis of ECoG and EMG signals; (b) we computed the fast Fourier transform (FFT) of the ECoG signal; and (c) we computed the integrated EMG. We found that, as expected, the proportion of time spent in each vigilance state was dependent on the injection condition. Specifically, OXA increased significantly the proportion of Awake state, and decreased the proportion of sleep states. In addition, we found significant differences in the power spectra of ECoG between the OXA and CSF conditions. In particular, in the Awake state the power was significantly decreased in the OXA vs CSF conditions in the theta (5-7 Hz), alpha (8-12 Hz) and beta bands (15-20 Hz), whereas it was significantly increased in the delta (<2.5 Hz) and gamma (>35 Hz) bands. These changes are markers of increased sensorimotor excitability. Consistently, we found that OXA induced greater muscle activity. Finally, we found that the magnitude of the change of power spectrum due to OXA was positively correlated with the proportion of Awake state. These results indicate that orexin-A modulates sensorimotor neural oscillations. Specifically, OXA induces a reduction of sensorimotor alpha/beta oscillations and an increase of gamma oscillations which suggest that the sensorimotor system is in a higher state of motor preparedness.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: CSR&D; RR&D; NIH
Grant support: CX-0004-37; F7212W; R01 DK100281

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73. VA CSP 588 Randomized Endo Vein Graft Prospective (REGROUP) Trial

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Abstract: CABG is the most common major surgical procedure in the U.S. and the VAMC Health System, and typically requires vein from the leg to be used to bypass around critically blocked coronary arteries. There are two methods commonly used to harvest the saphenous vein from the leg, open vein harvest (OVH) and endoscopic vein harvest (EVH). OVH removes the vein by making multiple small incisions on the leg or a single long incision on the leg. EVH uses a scope and two small incisions to remove the vein from the leg. While EVH has become the preferred method for harvest the vein because it provides a minimally invasive approach; more recent investigations indicate potential for reduced long-term bypass graft patency and worse clinical outcomes with EVH. In order to offer the safest and most durable revascularization strategy for veterans requiring CABG surgery, it is imperative to provide definitive evidence on the long-term clinical outcomes of EVH in order to minimize harvest site morbidity while preserving long-term clinical outcomes.

Research Topic: Heart Disease
Funding agencies: HSR&D
Grant support: VA Cooperative Studies Program (VA CSP)

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74. Direct input into CPRS vs dictation for operative reports at the Minneapolis VA.

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2. Minneapolis VA Health Care System

Abstract: Introduction: Electronic health records (EHR) were pioneered by the VA in the 1970's with Vista, modified in 1997 to CPRS. A limitation of CPRS was an inability for surgeons to directly enter operative reports into patients' medical records. Surgeons have been required to use the traditional multi-step approach involving dictation, transcription and proofreading and signing. We resolved this issue by collaborating with HIMS to develop a system using electronic templates to enter operative reports directly into the EHR. Study Purpose: Determine whether direct input of operative reports into the EHR by the surgeon using templates 1) Causes faster availability of the full operative report in CPRS, 2) Results in a more complete and accurate documentation of the operation, 3) Saves time for the surgeon, 4) Reduces costs. Methods: Performed review of 50 operative reports generated by 5 general surgeons at the Minneapolis VA. Results: 32 reports were dictated, 18 were generated using templates and directly entered into CPRS. For dictated reports, the median delay between the end of the operation and the entry of the signed report into CPRS was 12 hours 8 minutes. In contrast, the median time for the electronic template modality was 1 hour 26 minutes. Surgeons spent a median of 10 minutes 42 seconds (SD+/- 4 minutes 41 seconds) dictating each operative report. Based on the 40 hour work week, 250 annual procedures, and an estimated compensation (including benefits) of $430,000 potential savings were determined to be $9,202/physician/year. As a measure of accuracy and completeness, each operative report was reviewed for seven specific parameters of operative notes required by JACHO. Both modalities of documentation were 100% compliant with respect to the name of the procedure, pre/post op diagnoses, surgeons' names, and operative findings. However, templated notes were 100% compliant with respect to specimens removed vs 78% for the dictated notes. Estimated blood loss was documented in 83% of the templated notes and in 91% of the dictated notes. Sponge needle and instrument count accuracy was documented in 83% of the templated notes and in 72% of the dictated notes. Implementation of the electronic templates expedited the addition of more accurate and complete operative reports to the patients' EHR. Uniform adoption of these electronic templates throughout the entire VHA system has the potential to expedite the process of care and reduce costs.

Research Topic: Health Systems
Funding agencies: None
Grant support: None

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75. A Randomized Controlled Trial of a CPR Decision Support Video for Patients Admitted to the General Medicine Service.

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2. North Memorial Medical Center
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Abstract: Background: Patient preferences regarding cardiopulmonary resuscitation (CPR) are important, especially during hospitalization when a patient's health is changing. Yet many patients are not adequately informed or involved in the decision-making process. Objectives: We examined the effect of an informational video about CPR on hospitalized patients' code status choices. Design: This was a prospective, randomized trial conducted at the Veteran's Administration Hospital in Minneapolis, MN. Participants: One hundred and nineteen patients, hospitalized on the general medicine service, and at least 65 years old were enrolled. The majority were men (97%) with a mean age of 75. Intervention: A six minute video described code status choices; full code (CPR and intubation if required), Do not resuscitate (DNR), and Do not resuscitate/Do not intubate (DNR/DNI). Participants were randomized to watch the video (N=59) or usual care (N=60). Main Measures: The primary outcome was participants' code status preferences. Secondary outcomes included a questionnaire designed to evaluate participants' trust in their healthcare team and knowledge and perceptions about CPR. Results: Participants who viewed the video were less likely to choose full code (37%) compared to participants in the usual care group (71%) and more likely to choose DNR/DNI (56% in the video group vs 17% in the control group) ($p<0.00001$). We did not see a difference in trust in their healthcare team or knowledge and perceptions about CPR as assessed by our questionnaire. Conclusions: Hospitalized patients who watched a video about CPR and code status choices, were less likely to choose full code and more likely to choose DNR/DNI.

Research Topic: Health Systems
Funding agencies: None
Grant support: None

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76. Characterizing partner sleep functioning over the course of military deployment

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1. Minneapolis VA Health Care System

Abstract: Despite studies indicating negative influences of deployment on military spouses' health, the research on disruptions to sleep is preliminary and cross-sectional, precluding examination of the course of sleep change over time and prospective predictors of these changes. This study investigates trajectories of change in partner sleep over the course of deployment in a cohort of at-home partners. Data were drawn from the Readiness and Resilience in National Guard Soldiers (RINGS-2) project, a prospective, longitudinal study of National Guard Brigade Combat Team soldiers deployed to Iraq/Kuwait (2011-2012) and their partners. Spouses or cohabitating partners (N = 686) of soldiers completed assessments of risk/protective factors within 3-6 months of their partners' deployment to Iraq, 3 months and 8 months into the deployment, and 3-6 months following the soldiers' return. Results of latent class growth analyses (LCGA) reveal quadratic change in partners' sleep over the deployment cycle, with four distinct trajectories: good, stable sleep (61%), elevated sleep complaints over the deployment (22%), initially elevated sleep complaints that improve (10%), and chronic sleep problems (7%) groups. Predictors of these classes will be discussed. Understanding the course of sleep complaints among at-home partners during deployment may be useful for prevention and targeted intervention.

Research Topic: Mental Illness
Funding agencies: HSR&D; UMN
Grant support: Funding from VA Health Service Research & Development (SDR-10-398) and the University of Minnesota Press.

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77. Extent of Intestinal Colonization with E. coli ST131 and Fluoroquinolone (FQ)-resistant E. coli (FQREC) among Veterans and their Household Contacts

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Abstract: Background: E. coli ST131, currently the leading cause of human FQREC infections globally, is especially prominent among U.S. veterans. The distribution of ST131 and other FQREC as intestinal colonizers among veterans and their household (HH) contacts is undefined. Methods: Randomly selected Minneapolis VA Health Care System outpatients and inpatients, and any available HH members (humans and pets), were recruited as fecal donors for cross-sectional surveillance of colonization with ST131 and other FQREC. Fecal samples were screened for E. coli and FQREC by selective cultures, and for ST131 by PCR analysis of isolated colonies and population DNA. Results: The 457 subjects to date included 185 veterans (117 outpatients, 68 inpatients) and 272 HH members (142 humans, 130 animals), and represented 98 multi-subject HHs (370 total subjects) and 87 "veteran-only" HHs. Overall, 31 subjects carried ST131 (22 FQ-resistant [FQ-R], 9 FQ-susceptible [FQ-S]) and 40 carried FQREC (22 ST131, 18 non-ST131). Colonization prevalence declined by host group (inpatients > outpatients > household members > animals) for ST131 overall, FQ-R ST131, and FQREC, but not FQ-S ST131. ST131 accounted for ≥ 50% of FQREC within each host group except animals (no ST131). Within the multiple-subject HHs, colonization with ST131 or FQREC clustered by HH, being more likely if another HH member was so colonized than if not (for FQREC, 10/27 [37%] vs. 17/353 [5%]: $P < 0.001$; for ST131, 8/23 [35%] vs. 16/370 [4%]: $P < 0.001$). Conclusion: Among veterans (especially inpatients) and their HH contacts, colonization with FQ-R ST131 is relatively frequent, and equals or exceeds the frequency of colonization with other FQREC. Within-HH strain sharing is likely. These phenomena may underlie the high burden of ST131 disease among veterans, and may be amenable to preventive interventions.

Research Topic: Infectious Diseases
Funding agencies: MVMREF
Grant support: VA Merit Review grant # 1 I01 CX000920-01A1

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78. Persistent Serious Mental Illness among Former Applicants for VA PTSD Disability Benefits and Long-Term Outcomes: Symptoms, Functioning, and Employment

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Abstract: Millions of US Veterans have returned from military service with posttraumatic stress disorder (PTSD), for which a substantial fraction receive Department of Veterans Affairs (VA) disability benefits. Although PTSD is treatable, comorbid serious mental illness could complicate these Veterans' recovery. Using VA administrative data, we examined the burden of persistent serious mental illness in a nationally representative cohort of 1,068 men and 1,512 women who applied for VA PTSD disability benefits between 1994 and 1998 and served during or after the Vietnam Conflict. Self-reported outcomes are restricted to the 714 men and 1,014 women who returned surveys at each of 3 collection points. More than 30% of men and almost half of women had persistent serious mental illness; of these, 91.4% of men and 87.1% of women also had persistent PTSD. Those with persistent serious mental illness consistently reported severer PTSD symptoms and poorer functioning than other participants (all p's < .001), and their employment rate never exceeded 30%. Interactions between persistent serious mental illness and PTSD were significant only for employment (p = .002). Persistent serious mental illness in this population was nearly 15 times higher than in the US general population. Implications of these findings are discussed.

Research Topic: Mental Illness
Funding agencies: HSR&D
Grant support: VA HSR&D #IIR-09-359

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79. Responsiveness, Stability, and Validity Of patient-reported Outcomes in Aphasia

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Abstract: Aphasia affects approximately 80,000 people annually in the United States. Veterans Affairs outpatient clinics treat approximately 2,000 new cases each year. Since the risk of acquiring aphasia increases with age, the incidence is expected to increase in the near future as the average age of the American population increases. The same trends that led to the establishment of the Patient-Centered Outcomes Research Initiative under the Affordable Care Act of 2010 have increased interest in patient-reported outcome (PRO) measures in clinical aphasiology. Preliminary results from Hula et al. (2015) on the reliability and validity of the Aphasia Communication Outcome Measure found positive correlation with other measures of communicative functioning and high covariance-based reliability. These results will be discussed in addition to the methodology to assess the sensitivity of the ACOM to change over time and the stability of the measurement model of the ACOM. As reported by Hula et al. (2015), the measurement model of the ACOM was supported by high estimates of covariance-based reliability and positive correlations with other standardized measures of communicative functioning in an initial field trial. Given this positive support, further research is warranted to assess the stability of the ACOM with change over time and its application to patients who are no longer engaged in active speech-language therapy. This aim is currently being addressed through the recruitment of 300 participants with aphasia at VA hospitals in Pittsburgh, Tennessee Valley and Minneapolis. Participants with aphasia will complete two testing sessions with a 1-4 week hiatus during which they refrain any communication-related therapy. During each testing session, the participant will complete the ACOM in addition to standardized measures of communication, nonverbal intelligence, psychological well-being, and a motor speech exam. These data will provide test-retest reliability of score estimates from participants not receiving treatment, correlations among items on the ACOM, and PRO measures of communication, cognition, and physical functioning. With these data we hope to address the responsiveness of the ACOM to treatment-related change, the validity of the ACOM as a clinical tool, and the efficacy of the underlying constructs of the ACOM as a measure of patient-reported communicative functioning.

Research Topic: Other Chronic Diseases
Funding agencies: RR&D
Grant support: VA RR&D

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80. Use of Statistical Text Mining (STM) to Adjust Colonoscopy Follow-up Rates for Patients with Positive Fecal Occult Blood Test (FOBT+) Results

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1. Minneapolis VA Health Care System

Abstract: Objectives: We used STM to search unstructured text from clinical notes for valid reasons for not receiving a colonoscopy (i.e., colonoscopy refusal (CR) or private sector colonoscopy (PSC)) in the VHA within 6 months post FOBT+. This information was used to adjust colonoscopy follow-up rate estimates. Methods: We identified 74,014 patients with FOBT+ between August 2009 and March 2011. We extracted > 85,000 clinical documents on the 41.4% of FOBT appropriate patients not receiving a colonoscopy within 6 months post FOBT+. We performed annotation using eHOST software on 828 notes from 250 randomly selected patients. Annotators highlighted key words (i.e., terms) in the notes and classified notes as associated with CR, PSC, or neither. We used annotated terms in STM to develop logistic regression based classification algorithms to separately predict CR and PCS using split-half development (DS) and validation (VS) subsets from all annotated notes. We used the developed models to construct predicted probabilities of CR and PSC for the non-annotated notes. These predicted probabilities were used in sensitivity analyses reclassifying predicted refusals and PSC from having no follow-up to having appropriate follow-up. Results: Annotators demonstrated very good agreement classifying notes indicating CR (kappa = .898) and PSC (kappa = .834). Model agreement of our CR classification algorithm was 98% for DS and 80% for VS; our PSC algorithm yielded 87% for DS and 75% for VS. Applying the scored logistic regression model to all FOBT+ cases in the sample, we estimated that 8.8% refused colonoscopy while 10.1% received a colonoscopy in the private sector. The sensitivity analysis treating identified CR or PSC as being adequately followed up increased overall colonoscopy follow-up estimates at 6 months from 49% to over 67%. Conclusions: We successfully employed STM techniques to estimate CR and PSC in our population of FOBT+ patients. Impact: Receipt of care outside the VA or intention to treat is often only documented in clinical notes. STM provides a useful technique to glean structured information from unstructured text. With the advent of the Veterans Choice Act receipt of care outside the VA will most likely increase.

Research Topic: Health Systems
Funding agencies: HSR&D
Grant support: Department of Veterans Affairs Health Services Research & Development Service, grant # IIR 08-334

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81. Automating Symptom Management Monitoring in an RCT Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) Trial

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1. Minneapolis VA Health Care System

Abstract: Objective: To automate symptom monitoring for study patients using results from interactive voice response (IVR) telephone surveys to generate clinical CPRS progress notes. Methods: SPACE is a pragmatic randomized clinical trial (RCT) comparing the effectiveness of two medication prescribing strategies delivered within a care management model for chronic musculoskeletal pain (opioid-intensive versus opioid-avoidant) over 12 months. The clinical pharmacist care manager (CPCM) implements the intervention by developing an analgesic treatment plan (according to assigned treatment arm), monitoring response, and adjusting medications based on that response. Information is shared with primary care providers via CPRS. CPCM clinical visits are supplemented by interval reassessment of pain, adverse effects, mood, and medication adherence through automated symptom monitoring, via a 16-item IVR survey scheduled between study clinic visits, after medications changes, and at time points customized by the CPCM. IVR survey results are posted back to CPRS as progress notes. To automate the creation of progress notes, the study programmer built a custom application using AudioCare (a VA-purchased commercial product). AudioCare systems are currently connected to local VistA systems and used clinically to conduct appointment reminder calls and automate prescription renewals. The custom application allows study staff to import IVR results into a database, generate text, and create a CPRS progress note, which is reviewed and signed by the CPCM. Results: Of the first 200 participants, 93% received IVR calls. Participants averaged 5 calls each. Of more than 1,000 calls, > 70% were answered; of which 86% resulted in a generated CPRS progress note. Participants averaged 4 progress notes (mean=3.6, SD 2.0, range 1-10). Calls took approximately 5 minutes to complete (mean=4.78, SD 0.83, range 3.2-8.9). Nearly, one quarter of participants (22.1%) requested a change to their medication during their IVR phone survey. Conclusion: The Audio-Care IVR system was successfully used to automate symptom monitoring between study visits and to generate CPRS progress note documentation. Impact: Automated IVR technology is an efficient tool to facilitate collection and CPRS documentation of patient-reported measures in a manner that is highly acceptable to patients allowing the CPCM to better anticipate the pain management needs of the patients.

Research Topic: Health Systems
Funding agencies: HSR&D
Grant support: Department of Veterans Affairs Health Services Research & Development Service, grant # IIR 11-125

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82. Cyclin D1 Regulates Adipose Triglyceride Lipase to Influence Hepatic Lipid Droplet Metabolism and Cell Proliferation

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2. Minnesota Veterans Medical Research & Education Foundation
3. Minneapolis VA Health Care System

Abstract: Non-alcoholic fatty liver disease (NAFLD) has a rising prevalence in the veteran community. In its advanced stages NAFLD can lead to non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma. Cyclin D1 (D1) is a cell cycle protein that regulates G1/S transition, the rate-limiting step in cell division. D1 is highly expressed in liver cancer and its overexpression (OE) leads to lipid droplet (LD) accumulation in hepatocytes. Liver-specific knockdown of adipose triglyceride lipase (ATGL), the rate-limiting enzyme in triglyceride (TG) catabolism, promotes LD accumulation. In order to characterize a potential link between D1 and ATGL we employed studies in primary hepatocytes, mouse immortalized AML12 cells, and in vivo mouse systems. As expected, in the absence of mitotic stimuli, D1 OE was sufficient to drive DNA synthesis in primary hepatocytes. However, these effects are abrogated with ATGL activity. Knockdown of D1 in the presence of mitogens inhibited DNA synthesis and increased ATGL mRNA expression, but knockdown or chemical inhibition of ATGL recovered DNA synthesis. Moreover, cell cycle analysis using flow cytometry confirmed that D1 knockdown increased accumulation of cells in the G0/G1 phase and reduced cells in the S and G2/M phase; these results were reversed with ATGL knockdown or chemical inhibition. In whole animal mouse studies, there is an increase in hepatocyte cell death when animals are subjected to partial hepatectomy along with OE of ATGL by adenoviral vectors when compared partial hepatectomy alone. Taken together, these data illustrates for the first time that cyclin D1 regulates ATGL to alter hepatic LD metabolism and proliferative capacity in primary hepatocytes and AML12 cells.

Research Topic: Cancer
Funding agencies: NIH
Grant support: This study was supported by an NIH/NIDDK Grant (DK054921) to Jeffrey Albrecht, an NIH/NIDDK Grant (DK093604) awarded to Douglas Mashek, and the Minnesota Obesity Center (DK050456).

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83. Ensuring Post-Discharge Appointment Scheduling with the Pre-Discharge Process: A Pilot Study

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1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Background & Aim: At the MVAHCS (Minneapolis VA Health Care System), the process of scheduling the primary care clinic (PCC) follow-up appointments is generally initiated by a phone call after the hospital discharge. However, our preliminary data showed that this process fails to schedule 22% of the ordered appointments. Our aim is to create a process that generates the PCC follow-up appointments prior to patients leaving the hospital and evaluate its outcomes. Methods: We initiated a pilot project to generate the PCC follow-up appointments prior to hospital discharge in a 19-bed general medical ward (3F ward). The process includes a new order for scheduling the follow-up appointment and training of an inpatient medical support assistant to facilitate the process. The decision to use this novel system by discharging providers was voluntary. Results: Of 48 patients who were discharged with the PCC follow-up appointments order during 30-day period, 12 (25%) patients were enrolled in the pilot group and had the PCC appointments scheduled prior to leaving the hospital. This pilot group had more PCC appointments scheduled (n=12, 100%) than the conventional group (n=19, 53%, P=0.004). However, the two groups had comparable adherence rates to their follow-up appointments (n=6 [50%] vs n=17 [47%], respectively, P=0.87). The most common reason for non-adherence to the follow-up appointments was PCC cancellation after the appointments were deemed unnecessary by the PCC team (n=4, 33%) in the pilot group and failure to make a post-discharge telephone call (n=13, 36%) in the conventional group. Conclusions: By generating the outpatient follow-up appointments before patients leaving the hospital, we are able to guarantee that the follow-up appointments are made. Although our pilot project did not show the difference in the adherence rate to follow-up appointment, this process can be an important step to ensure that the necessary follow-up appointments are scheduled.
Research Topic: Health Systems
Funding agencies: None
Grant support: None

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84. Mindfulness Based Stress Reduction for Post-traumatic Stress Disorder among Veterans: A Randomized Clinical Trial

Polusny, Melissa[1,2]; Erbes, Christopher[1,2]; Thuras, Paul 2,3; Moran, Amy[3]; Lamberty, Greg[2,3]; Collins, Rose[3]; Rodman, John[3]; Lim, Kelvin[2,3]

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3. Minneapolis VA Health Care System

Abstract: Background: Existing evidence-based treatments for post-traumatic stress disorder (PTSD) have high rates of dropout and non-response among Veterans. Mindfulness-based interventions show promise as a novel treatment for PTSD. Objective: To compare Mindfulness Based Stress Reduction (MBSR) with Present Centered Group Therapy (PCGT) for treatment of PTSD. Design, Setting, and Participants: Randomized controlled trial of 116 veterans with PTSD recruited at the Minneapolis VA Health Care System. Outcomes were assessed before, during, and after treatment, and at 2-months follow-up. Interventions: Participants were randomly assigned to receive MBSR (n=58), consisting of 9 sessions (8 weekly 2.5 hour group sessions and a day-long retreat) focused on teaching patients to attend to the present moment in a non-judgmental and accepting manner, or PCGT (n=58), an active control condition consisting of 9 weekly 1.5 hour group sessions focused on current life problems, both delivered according to standard protocols. Outcomes and Measures: Primary outcome, change in PTSD symptom severity over time, was assessed using the PTSD Checklist (range, 17-85; higher scores indicate greater severity) at Baseline, Weeks 3, 6, 9, and 17. Secondary outcomes included the presence or absence of PTSD diagnosis and symptom severity assessed by independent evaluators using the Clinician Administered PTSD Scale (CAPS). Additional secondary outcomes included depressive symptom severity, quality of life, and mindfulness skills. Results: During treatment, participants receiving MBSR demonstrated significantly greater improvement in self-reported PTSD symptom severity ($p < .002$) and mindfulness skills ($p < .001$). MBSR was more effective than PCGT through the 2-month follow-up for: self-reported PTSD severity ($p < .001$), interview-rated PTSD severity ($p < .004$), mindfulness skills ($p < .001$), and quality of life ($p < .004$). While MBSR participants were more likely to show clinically significant improvement in self-reported PTSD symptom severity (48.9% vs. 28.1%; , $p = .029$) at the 2-month follow-up, no difference in loss of PTSD diagnosis was observed (53.3% vs. 47.3%, $p = .55$). Conclusion: Among veterans with PTSD, MBSR, compared with PCGT, resulted in a greater decrease in PTSD symptom severity.

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: This research was supported by VA grant 5 I01 CX000683 to Dr. Lim.

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85. Does Applying the San Francisco Syncope Rule at the Minneapolis VAHCS Emergency Department Increase Patient Throughput Time and Reduce Unnecessary Hospital Admissions for Syncope?

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2. Minneapolis VA Health Care System

Abstract: Background: Syncope is a common complaint among patients presenting to emergency departments, representing 1-2% of all emergency department visits and 6% of hospital admissions. The San Francisco Syncope Rule (SFSR) has been shown to identify syncope patients at 'high-risk' for complications if they meet one of following criteria: history of congestive heart failure, hematocrit <30%, EKG abnormalities, shortness of breath, or systolic BP <90 at triage. We aimed to implement a standardized syncope order set in order decrease patient throughput time and time to disposition decision in the ED while decreasing unnecessary hospital admissions for syncope. Methods: The SFSR was retrospectively applied to 30 patients seen in the emergency department presenting with syncope to determine risk stratification (high vs. low). Chart review was extended for 30 days post-ED evaluation to assess for the serious complications. We implemented a syncope order set incorporating the SFSR and analyzed SFSR risk stratification as well as ED throughput time and time to disposition decision for one month following implementation of the order set. Group differences were compared using paired student t-tests and chi square tests. Results: Percentage of high-risk patients admitted decreased from 93% to 80% ($p<0.05$) following the implementation of the SFRS order set. The percentage of inappropriately admitted low-risk patients increased from 22% to 37% ($p<0.05$) after implementing the order set. There were no differences in the number of adverse events reported within 30 days of ED visit before or after implementation of the order set. Throughput time and time to disposition did not significantly decrease after order set implementation (196 minutes to 182, $p=0.28$) (123 to 115 minutes, $p=0.61$). Conclusions: Implementation of the SFSR order set does not significantly reduce time spent in the ED for complaints of syncope, however, it does appear to increase the number of low risk patients admitted to the hospital. It is likely that many factors that influence admission decision for patients with syncope that the SFSR does not address. Overall, the SFSR order set may help to standardize care in patients with syncope, but should be used as an adjunct to, and not replacement of clinical decision making.

Research Topic: Health Systems
Funding agencies: None
Grant support: None

86. Adherence to Guideline Recommended Management of Newly Diagnosed Adrenal Incidentaloma at the Minneapolis VA Health Care System

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Abstract: Introduction: American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons (AACE/ AAES) recommended all patients with adrenal incidentaloma (AI) should undergo clinical, biochemical and radiographical evaluation for hypercortisolism, pheochromocytoma, aldosteronism (if hypertensive) and malignancy. Objective: The purpose of this retrospective study was to evaluate guideline recommended management of newly discovered AI at the Minneapolis VA Health Care System (Minneapolis VA Health Care System). Method: An electronic search of abdominal CT and MRI reports from 2010- 2014 was conducted in August 2014 to find cases of newly diagnosed AI. Data were collected by reviewing the identified medical records. Cases with active cancer were excluded. Results: A total of 22,684 CT and MRI of abdomen were done. AIs were identified in 426 images, of which 113 were new and 83 patients had no active cancer. Their average age was 66 ± 11 yrs and 2 were female. Hypertension was found in 57 (69%) and only 2 were not treated with medications. AIs were found in the left (66%), right (28%), and bilateral (6%) adrenal glands; median size was 1.6 cm (interquartile range 1.0 to 2.2 cm). Only 3 cases met the guideline criterion of 4 cm or greater for resection; 2 were resected and 1 was not. Conn's disease was diagnosed in 1 patient and resection was done later. Of 80 cases that didn't undergo surgical resection, all were followed for at least 1 year (mean of 2.7±1.1 years). Adrenal dedicated imaging was done in 8 (9.6%) cases. At least one of the recommended biochemical assessments was performed in 13 (15.7%) cases. Recommended tests for subclinical Cushing syndrome were done in 2 (2.4%) cases and for pheochromocytoma in 7 (8.4%) cases. Of the 57 patients who had hypertension, 3 (5.3%) had appropriate test for hyperaldosteronism. Of the 26 patients who do not have hypertension, 3 (11.5%) had hyperaldosteronism evaluation. None received all recommended tests. Of 13 AIs that were evaluated, 1 patient was diagnosed with Conn's disease. Otherwise, the biochemical evaluations were negative. Conclusion: A very small percentage of newly discovered AI cases at the Minneapolis VA Health Care System underwent guideline recommended evaluations. The utility of the recommended tests and patient outcomes warrant further study.

Research Topic: Other Chronic Diseases
Funding agencies: None
Grant support: None

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87. Use of PE and CPT in VHA Specialty Outpatient PTSD Programs

Sayer, Nina[1]; Rosen, Craig[2]; Nugent, Sean[1]; Orazem, Robert[1]; Kehle-Forbes, Shannon[1]; Chard, Kathleen[3]; Bernardy, Nancy[4]; Schnurr, Paula[4]; Mohr, David[5]

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2. National Center for PTSD, VA Palo Alto Health Care System
3. Cincinnati VA Medical Center
4. National Center for PTSD, White River Junction VA Medical Center
5. Boston VAHCS

Abstract: Objectives: To provide preliminary data across specialty outpatient PTSD programs (SOPPs) on: (a) use of Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE), the two evidence-based psychotherapies for PTSD VHA has rolled out; and (b) regional variation in use of CPT and PE. Methods: The Evidence-Based Psychotherapy CREATE study, PERSIST, required identification of outpatient PTSD teams that vary in use of PE and CPT. This study is based on the chart note data collected to quantify use of PE and CPT for the parent study. We extracted 1,002,721 psychotherapy chart notes for Veterans with PTSD who received individual or group psychotherapy in a SOPP over an 18 month period (4/ 2011-10/2012). We used SAS software for statistical text mining to identify use or discussion of PE and/or CPT. Data were aggregated up to the parent facility within VISN and nested into four US census regions: Northeast, Midwest, South, West. Results: 110,491 unique patients received group or individual psychotherapy for PTSD in a SOPP. Almost 20% of these Veterans received or discussed PE and/or CPT. The overall rate of CPT was twice the overall rate of PE (15% vs 7%). This pattern held across VISNs. There was a four-fold difference in PE and/or CPT use in SOPPS across VISNs (7% to 29%). PE and/or CPT use within SOPPs was even more variable across facilities, ranging from < 1% to 50%. The rate of PE and/or CPT was lower in the SOPPs in the Northeast (13%) compared with those in other US regions, which were largely comparable (20%-22%) and did not differ by facility urban/rural status. Number of SOPP providers who completed VHA training in PE and/or CPT was related to rate of use of these evidence-based psychotherapies. Implications: Findings indicate considerable variability across facilities and VISNs in use of PE and CPT across SOPPs. Reasons for variation and less widespread use of PE warrant further study. Impacts: In-depth study of high performing SOPPs may identify practices to reduce unwanted variation and augment use of PE and CPT.

Research Topic: Access & Disparities in Care
Funding agencies: HSR&D
Grant support: VA HSR&D CRE 12-021

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88. Comparative Efficacy Research in Veterans with PTSD (CERV-PTSD)

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1. White River Junction VA Medical Center
2. Cincinnati VA Medical Center
3. VA Palo Alto Health Care System
4. Minneapolis VA Health Care System

Abstract: Comparative Effectiveness Research in Veterans with PTSD (CERV-PTSD) is designed to compare efficacy of prolonged exposure (PE) and cognitive processing therapy (CPT). CERV-PTSD is the first direct comparison of these treatments. Seventeen VA hospitals will aim to randomize 900 Veterans. A screening process will determine eligibility. Once eligible, participants will be randomized to PE or CPT. Research visits will occur during and after treatment. Compensation for research visits is given. Recruitment has begun at the Minneapolis VA Health Care System. Eligible participants must have PTSD due to a military event, receive PTSD treatment in the study alone, and be on a stable regimen of medications for at least 1 month. Exclusionary conditions apply. Referrals are being accepted. Interested providers or Veterans can contact Jillian Wright-Martin Site Coordinator at 612-467-2184 for more information.

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: VA Cooperative Studies Program (VA CSP)

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89. Ecologically valid assessment of cognition and everyday function in older adults at risk for dementia: A new approach using pervasive computing and sensing technologies

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2. University of Minnesota
3. Oregon Health & Science University
4. Oregon Center for Aging & Technology
5. University of Michigan

Abstract: Background: Identifying pre-symptomatic changes in healthy older adults that signal future cognitive decline and transition to MCI and AD is an important goal for early detection, intervention, and design of clinical trials. Subtle changes in routine daily activities 'everyday cognition' may be a signal of future cognitive decline, yet are difficult to assess with traditional clinical measures. An alternate approach is to use pervasive computing and sensing technologies embedded in the home environment to monitor subtle changes in cognition and function (e.g., computer use, medication management, driving). Methods: Participants were 59 cognitively normal (CN) older adults (mean age = 86.2 years; 88% female) and 24 older adults with MCI (mean age=87.9; 75% female) enrolled in a longitudinal study of aging. Weekly data was used to derive summary measures of everyday cognition in the domain of home computer use; specifically, weekly on-line reporting to a short health questionnaire. Longitudinal generalized linear mixed effects models were generated with three online questionnaire response (OQR) variables: completion time, in seconds; start time in the day, in clock time; and staff assistance needed as unique outcomes, adjusted for covariates. We hypothesized that OQR variables would discriminate between groups over 1 year. Results: MCI and CN groups did not differ in the time of day they submitted their questionnaires initially; however, over time MCI participants began to submit their questionnaires progressively later in the day and needed greater assistance from staff ($p<0.05$). In an analysis of MCI subtypes, amnestic MCI participants took more time to complete their questionnaires than CN ($p=0.03$). Over time nonamnestic MCI participants began submitting their questionnaires progressively later in the day than CN ($p=0.02$). OQR variables were associated with conventional neuropsychological tests (p's <.01-.05). Conclusions: Real-world cognitive assessment utilizing technology is a promising approach for detecting the earliest changes associated with future cognitive decline in older adults at risk for dementia.

Research Topic: Aging
Funding agencies: NIH
Grant support: This work was supported by the National Institutes of Health grants AG024978, AG024059, and AG023477, P30AG008017, and AG042191. This work was also supported by an Alzheimer's Association New Investigator Research grant NIRG-15-362233.

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90. Diagnosis and Management of Chronic Obstructive Pulmonary Disease Care in Rural versus Urban Veterans Affairs Clinics

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Abstract: Rationale: Chronic obstructive pulmonary disease (COPD) is a common chronic illness that causes significant morbidity and is the third leading cause of death in Americans. Prior studies, though limited, have suggested that patients in rural settings receive disparate care for their COPD. Over half of the veterans in the Minneapolis Veterans Affairs Health Care System (Minneapolis VA Health Care System) receive primary care in rural clinics where they have limited access to diagnostic testing and pulmonary consultation. We aimed to determine if the quality of care for patients in rural and urban clinics within the Minneapolis VA Health Care System is disparate with regards to COPD diagnostic testing and management. Methods: Urban clinics were defined as within 40 miles of the Minneapolis VA Health Care System. Patients with a prior diagnostic code for COPD who were seen in Minneapolis VA Health Care System primary care clinics during March 2015 were identified. Proportional numbers of patients were randomly selected from each clinic. Patient demographics, spirometry, pneumococcal and influenza immunization status, short and long acting inhaler prescriptions were extracted from the healthcare record. Results: A total of 400 rural and 401 urban patients were compared. Rural and urban groups had similar demographics and mean FEV1. Fewer rural patients had prior spirometry (51% vs 82%, $p<0.01$). There were no differences in the number of patients who received influenza (79% vs 81%, $p=0.32$) or pneumococcal (88% vs 91%, $p=0.2$) immunizations, or prescription rates for short (66% vs 68%, $p=0.44$) and long acting inhalers (61% vs 59%, $p=0.69$). Conclusions: Within the Minneapolis VA Health Care System there were no differences in quality of care measurements between urban and rural clinics with regards to medical management of patients with COPD. Fewer rural patients had prior spirometry; however on-site spirometry in rural clinics only recently became available, which could explain why more urban patients had spirometry. The high rates of immunizations were similar between rural and urban groups, and are far above previously reported data in patients with COPD. Further studies of rural and urban care for patients with COPD are needed in other VA and non-VA systems, particularly to determine whether disparities, if found, are associated with important clinical outcomes including ER visits, hospitalizations and mortality.

Research Topic: Rural Health
Funding agencies: None
Grant support: None

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91. The Sub-Hemolytic Effect of Left Ventricular Assist Devices: Reduced Erythrocyte Survival as a Novel Biomarker of Device Thrombosis

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3. Minneapolis Heart Institute

Abstract: Background: Continuous-flow left ventricular assist devices (CF-LVAD) have transformed care for end-stage heart failure. Device thrombosis is a feared complication with challenging diagnosis. We investigated the sub-hemolytic injurious effect of CF-LVAD on circulating erythrocytes, in-vivo, using erythrocyte lifespan. Erythrocyte lifespan is a well-validated marker that employs endogenous breath carbon monoxide excretion as a quantitative indicator of erythrocyte turnover. Patients and Methods: Sixty non-smoking subjects were prospectively enrolled. Twenty-five subjects had a CF-LVAD without thrombosis (mean age 60.5±15.3 years, 76% male), 10 subjects had a CF-LVAD with thrombosis (67.3±5.1 years, 90% male), and 25 subjects were normal controls (57.2±14.1 years, 92% male). Results: The mean end-tidal breath carbon monoxide level was significantly higher in CF-LVAD subjects with (5.69±2.54 ppm) compared to those without (2.88±0.70 ppm) device thrombosis ($p<0.0001$). The levels in these 2 cohorts were significantly higher compared to normal controls (2.25±0.59 ppm, $p<0.0001$, and $p=0.001$, respectively). The calculated mean erythrocyte lifespan was significantly shorter in CF-LVAD subjects with (29.7±14.9 days) compared to those without (65.0±17.3 days) device thrombosis ($p<0.0001$). The lifespans in these 2 cohorts were significantly shorter compared to normal controls (96.0±24.9 days, both $p<0.0001$). Receiver operator curve demonstrated high sensitivity-specificity for use of erythrocyte lifespan to detect device thrombosis (area under the curve = 0.94). Conclusion: The inherent mechanical function of CF-LVAD induced significant sub-hemolysis in-vivo, which was more pronounced in the presence of device thrombosis. Further studies are needed to elucidate the utility of erythrocyte lifespan for the detection of subtle pre-clinical device thrombosis, as well as to assess its temporal relationship to thrombus formation.

Research Topic: Heart Disease
Funding agencies: None
Grant support: None

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92. Collaborative roles for CK2α and NF-κB p65 expression in pathogenesis of prostate cancer

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Abstract: Background: Protein kinase CK2 (universally accepted acronym for the former name casein kinase II or 2) plays a critical role in cell growth, proliferation and suppression of cell death. CK2 has been found to be overexpressed in all cancers studied so far and has been suggested as a prognostic biomarker. Further, it is recognized that CK2 cooperates with other cellular factors to promote oncogenesis. Since CK2 is also elevated in benign prostatic hyperplasia (BPH), its utility as a biomarker in prostate cancer (PCa) would be enhanced by identification of additional factors that serve to distinguish CK2 elevation in PCa compared to benign prostate growth. The present study was therefore designed to identify additional factors that may be used to distinguish CK2 biomarker activity in cancer vs benign prostate specimens. To that end, we have tested the hypothesis that combined expression of CK2α with nuclear factor kappa B (NF-κB) p65 might provide a distinction between PCa versus BPH. Methods: Immunohistochemical analysis was carried out to determine the expression level and localization pattern of CK2α and NF-κB p65 in PCa and BPH tissue specimens. Ki-67 staining was also scored. Results. Nuclear expression of CK2α and NF-κB p65 are significantly associated with the pathological characteristics of PCa, including Gleason score, age, and percentage of prostatic tissue involved. Combined expression of both CK2α and NF-κB p65 in the nucleus showed statistical correlation with the cancer phenotype (p=0.01), but not with BPH (p=0.1). Conclusions: The present findings provide proof of concept that combined analysis of CK2α and NF-κB p65 as markers in prostate specimens relates to the oncogenic status of the cells. Our results suggest that co-immunohistochemical analysis of CK2α and NF-κB p65 may be useful as a discriminatory marker in benign versus malignant prostate disease. [FQ was supported by Higher Education Commission of Pakistan Scholarship. Immunohistochemical analysis of prostate specimens was carried out by FQ at NUST under appropriate IRB approval].

Research Topic: Cancer
Funding agencies: BLR&D; NIH
Grant support: I01BX001731; R01CA150182

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93. Neuromagnetic study of brain mechanisms associated with motor preparation

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Abstract: Understanding brain activity associated with the preparation of a motor response is fundamental in the development of brain-controlled prosthetics. In this perspective it is important to investigate motor preparation in conditions of ambiguity about the response to prepare. Indeed, in many real-world activities, such as sports, driving, or video games , one often is prepared to respond in advance even though the response that will be needed is not known precisely. For these reasons, we studied neural oscillatory activity occurring during motor preparation in different conditions of reliability about the response to prepare. We recorded neuromagnetic signals using a 248-channel whole-head magnetoencephalography system while healthy participants (N=12) performed a targeted hand movement task. The task started with a baseline center-hold period which was followed by a visual cue. The cue identified with 50%, 75%, or 100% reliability the location where the upcoming target would appear. After a 1.0-1.5 s randomly variable delay a target appeared either at the location of the cue or at a different location on the screen. Participants responded by quickly moving a joystick-controlled cursor towards the target. The latency of response decreased with increased cue reliability, and it increased when the target appeared at a different location than the cue (incongruent trials). These results indicate that, as expected, the time-consuming mechanisms of motor preparation were altered by task conditions. In addition, we found task-related changes of neural oscillations across several frequency bands. However, only the power of beta-band oscillations (15-29 Hz) was linearly correlated with cue reliability: the greater the cue reliability, the more beta power decreased during motor preparation. The source of covariation of beta oscillations with reliability was localized in the sensorimotor region controlling the responding hand. Furthermore, we found that in incongruent trials there was a phasic increase in the power of theta (4-7 Hz) oscillations over sensorimotor and parietal regions. In conclusion, the results indicate that the power of beta oscillations in the sensorimotor cortex indicates the level of uncertainty regarding motor preparation; and that theta power indicates when the response prepared needs to be changed. This finding advances our understanding of brain oscillations and contributes to the design of neuroprosthetics.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: CSR&D
Grant support: CX-0004-37

94. Mindfulness Skills Mediate Improvements in PTSD Symptoms and QOL

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1. Minneapolis VA Health Care System
2. University of Iowa
3. University of Minnesota

Abstract: Background: A growing body of research documents the efficacy of mindfulness-based interventions for the treatment of PTSD, with accompanying benefits in quality of life (QOL). However, few studies have examined the potential mechanisms through which such treatments may reduce PTSD symptoms and improve QOL. In analyses of data from a controlled trial (Polusny, Erbes, Thuras, Moran, Lamberty, Collins, Rodman & Lim, 2015), we examined whether changes in mindfulness skills may mediate improvements in PTSD symptoms and QOL. Methods: Our sample was composed of 116 veterans with PTSD (primarily White; mean age: 58.5 years, SD = 9.8; 84% male) who participated in mindfulness-based stress reduction (MBSR) or present-centered group therapy. Subjects completed measures of mindfulness skills (FFMQ; mechanism) and PTSD symptoms (PCL; outcome) before, during, and after treatment and at 2-month follow-up, and a measure of QOL (WHOQOL; outcome) before and after treatment and at 2-month follow-up. Nonparametric mediation models tested the indirect effects of the intervention on PTSD symptom severity and QOL through change in mindfulness skills. Mediation was tested using the INDIRECT macro for SPSS (Hayes, 2009), which uses bootstrapped confidence intervals to estimate indirect effects in mediational models. Results: Improvements in mindfulness skills (baseline–17 weeks) mediated improvements in both PTSD symptoms (PCL; β = 2.59 (SE = 0.98), p = 0.008, CI: 0.976, 4.94) and QOL (β =-3.06 (SE = 1.19), p = 0.010, CI: -5.91, -1.31). In multiple mediation models, the FFMQ effects appeared to be driven by the 'non-reacting' mindfulness factor (PCL: β = 1.59 (SE = 0.77), p = 0.038, CI: 0.34, 3.59); WHOQOL: (β = -1.67 (SE = 0.91), p =0.067, CI: -3.97, -.032). Discussion: Among veterans with PTSD enrolled in a group MBSR treatment, increased mindfulness skills (particularly non-reactivity) were mechanisms of improvement in both PTSD symptoms and QOL. MBSR appeared to contribute to improved clinical and functional outcomes by fostering increased mindfulness (particularly non-reactivity to stimuli), which likely improved veterans' abilities to self-manage distressing situations and symptoms.

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: VA Grant 5 I01 CX000683 to Dr. Lim

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95. Disinhibition and Threat Sensitivity as Dispositional Liabilities for Suicidal Behavior: A Longitudinal Study of Deployed National Guard Soldiers

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2. Florida State University

Abstract: Suicidal behavior is a significant mental health concern for veterans returning from combat deployment. However, little is known about dispositional (or trait) liabilities for suicidal behavior in veterans. The current study evaluated the predictive relationship of two such liabilities – disinhibition (DIS) and threat sensitivity (THT) – in a sample (N=513) of National Guard troops assessed for these traits and suicidality before and after an extended combat deployment to Iraq. DIS is hypothesized to reflect deficits in inhibitory control (or executive function) capacity whereas THT is reflective of individual differences in engagement of the brain's defensive motivation systems. DIS and THT were operationalized using items from the Minnesota Multiphasic Personality Inventory – 2 – Restructures Format (MMPI-2-RF) and suicidal behaviors were assessed using the MMPI-2-RF suicidality scale and the Beck Depression Inventory-II suicidal ideation item. Consistent with previous findings in civilian clinical and community samples, we found DIS and THT to separately and interactively predict suicidal behaviors in cross-sectional analyses such that individuals at greatest risk were those with elevations on each trait. DIS and THT assessed pre-deployment predicted post-deployment suicidality (controlling for pre-deployment suicidality) at trend levels for main effects only. The current study further indicates DIS and THT are risk factors for suicidal behavior by demonstrating their associations within a combat veteran sample. Findings will be discussed in terms of DIS and THT as neurobehavioral constructs, consistent with the National Institute of Mental Health's Research Domain Criteria initiative (RDoC).

Research Topic: Mental Illness
Funding agencies: DOD
Grant support: DOD CDMRP W81XWH-07-2-003; Minnesota Medical Foundation grant number 3662-9227-06

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96. Impact of TrkB antagonism on food intake in sedentary and exercised rats

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Abstract: Introduction: We found running wheel (RW) exercise to reduce food intake, associated with increased BDNF in hypothalamic paraventricular nucleus (PVN), where we previously reported BDNF to reduce feeding. Studies suggest that using ANA12 as antagonist of BDNF receptor TrkB abrogates BDNF-induced feeding reduction. With ANA12, we tested a hypothesis that BDNF mediates exercise-induced feeding reduction. Methods: 1) Acute ANA12 injection: Male 7-mo old rats were cannulated in PVN and assigned to: sedentary (Sed)_Vehicle (Veh), Sed_ANA (10 .g/0.5 .l/side), RW_Veh, or RW_ANA. Daily injections were made 1 hour before dark, for 8 days. 2) Feasibility of chronic ANA12 infusion: Male 8-month old rats were divided into RW_Veh and RW_ANA, and cannulated in the PVN with connection to a Alzet minipump implanted in the back and filled with vehicle or ANA12 (25 .g/day, 28-d). Rats had RW access since day 7 post surgery. Daily body weight, food intake and running distance were analyzed with 2-way ANOVA. Results: 1) Acute injection: There were main effects (activity, drug, or interaction) on daily and cumulative feeding and body weight change. Differences in food intake ($P<0.05$) were found low in RW_Veh vs. Sed_Veh, high in Sed_ANA vs. Sed_Veh, and low in RW_ANA vs. Sed_ANA. Differences in total body weight change ($P<0.05$) were found low in RW_Veh vs. Sed_Veh, and low in RW_ANA vs. Sed_ANA. However, no such differences were found between RW_ANA and RW_Veh. 2) Feasibility of chronic infusion: There were no significant differences between RW_Veh and RW_ANA. We then merged the two groups as one for regression analysis. Cumulated 28-d food intake was negatively associated with cumulated 28-d running distance, and cumulated body weight was associated positively with cumulated food intake, and negatively with running distance; and daily food intake was associated with daily running distance negatively and daily body weight change positively. Compared to themselves, rats during RW ate significantly less vs. prior to, or post-closing RW access. Conclusions: 1) Exercise reduced feeding and body weight; 2) acute ANA12 in sedentary increased more feeding than sedentary control, suggesting inhibition of endogenous PVN TrkB; 3) ANA12 did not block exercise-reduced feeding, suggesting exercise-induced anorexia can be mediated by neural signaling in sites other than PVN; and 4) the amount of feeding during exercise may be determined by 'dose' (running distance) of exercise.

Research Topic: Diabetes & Major Complications
Funding agencies: BLR&D; NIH
Grant support: Brain Derived Neurotrophic Factor involvement in exercise modulation of appetite (VA), Brain-Derived Neurotrophic Factor Induced Weight Loss: Neural Mechanisms (NIH)

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97. Lithium For Suicidal Behavior In Mood Disorders (The Li+ Study: CSP 590)

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1. Minneapolis VA Health Care System

Abstract: Purpose: Randomized clinical trial specifically conducted to test lithium's efficacy in preventing suicides. Of primary interest is whether lithium leads to increases in the time to the first repeated episode of suicidal behavior, including suicide attempts, interrupted attempts, hospitalizations specifically to prevent suicide, and deaths from suicide. Additionally, this study will allow us to explore whether Lithium decreases the total number of suicidal behaviors, and whether it has comparable effects on impulsive and non-impulsive behaviors. Experimental treatment in this study supplements usual care for major depression or bipolar disorder, as well as VA's standard, enhanced management for patients at high risk. Methods: Participation involves: 1. Meeting with study staff regularly with follow-up lasting 12 months; 2. Adherence to medication regimen according to study protocol; 3. Willingness to have blood draws/vital signs taken regularly to maximize safety of medication; 4. Completing different questionnaires asking about psychiatric symptoms, medications, general well-being, and quality of life.

Research Topic: Mental Illness
Funding agencies: HSR&D
Grant support: VA Funded; Office of Research and Development

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98. Quality of Gout Care Assessment

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Abstract: Purpose: We reviewed the appropriateness of colchicine prescribing as an assessment of gout care quality at the Minneapolis VA Health Care System. Review of the Literature: American College of Rheumatology has specified Guidelines for use of colchicine for acute and chronic gout management. Methodology: In Nov 2011 421 patients had prescriptions for colchicine in the pharmacy database. Colchicine prescriptions were reviewed for appropriateness defined as 1) chart documentation for the diagnosis of definite, probable or possible gout; 2) appropriate dose (for 3 acute flares/month or daily prophylaxis) and dose reduction for kidney or liver disease 3) concomitant urate lowering treatment if ≥ 2-3 flares per year or tophi; 4) monitoring of potential adverse effects. A structured check list was developed for chart review. Results: 421 patients in the pharmacy database had active prescriptions for colchicine, however at chart review 32 did not have a colchicine prescription or were not taking colchicine and 17 were deceased, leaving 371 patients for review. The average age was 70.4yr, 191 had 1-2 comorbidities, 115 had 3-4 comorbidities and 27 had none. Diagnoses were: 94 (25%) definite gout , 74 (20%) probable gout; 60 (16%) possible gout, 121 NO evidence for gout (33%), 17 pseudogout (4.5%) and 3 other dx (<1%). Purpose of colchicine: 276 for prophylaxis, 105 for acute gout flares. There was minimal evidence that patients were monitored for adverse effects. Implications for Nurse Practitioners: Appropriateness of colchicine prescribing is an indicator of quality of gout care. We found that colchicine prescribing was NOT appropriate in 1/3 of patients because there was no evidence for the diagnosis of gout in the medical record. Co-managed care may have resulted in incomplete documentation. Advanced age and multiple medical co-morbidities make risk of adverse drug reactions and interactions a concern. Based on these findings we have established a Gout Management Clinic with a nurse practitioner and a pharmacist to evaluate / establish the accuracy of the gout diagnosis and implement urate lowering treatment to achieve a target urate level of <6-7 to minimize episodes of acute gout and reduce tophi. Once appropriate treatment has controlled disease the patient is returned to the referring provider with recommendations for safe monitoring of therapy. Ongoing quality of gout treatment by referring providers and in the gout clinic is being assessed.

Research Topic: Other Chronic Diseases
Funding agencies: None
Grant support: none

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99. Minneapolis VA Evidence-based Synthesis Program (ESP)

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Abstract: Objective: Provide timely and accurate synthesis of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers as they work to improve the health and healthcare of Veterans. Methods: Each of the four ESP sites prepares three or more systematic reviews each year. Topic nominations come from VA Central Office, VISNs, or individuals in the field (e.g. National Program Directors, Chief Consultants, leaders of VA Task Forces). The reviews are developed using standard methods for development of key questions and scope, identification of included evidence, data extraction, data synthesis, and evaluation of risk of bias and strength of evidence. A Technical Expert Panel (TEP) is identified for each topic to guide topic development and assist in refining the key questions and scope of the review. Draft reports undergo peer review by content experts and policy partners. Final reports are posted on VA HSR&D website and disseminated widely throughout the VA. Management Briefs and Cyberseminars are key dissemination strategies. Results: For 2015, the Minneapolis VA ESP developed systematic reviews on The Effectiveness and Harms of Pharmacist-led Chronic Disease Management Compared to Usual Care, Benefits and Harms of the Mediterranean Diet Compared to Other Diets, and Prevalence and Epidemiology of Combat Blast Injuries from the Military Cohort 2001-2014. Topics for 2016 are: The Effectiveness, Harms, and Cost of Alternative Care Models for the Treatment of Obstructive Sleep Apnea, Life Expectancy Calculators, and a Women's Health Update. Conclusions: The Minneapolis VA ESP prepares evidence syntheses on important clinical practice topics relevant to Veterans. These reports help develop clinical policies informed by evidence, lead to the implementation of effective services to improve patient outcomes and to, and guide the direction for future research to address gaps in clinical knowledge. Key Words: Systematic reviews, evidence-based, Veterans

Research Topic: Health Systems
Funding agencies: HSR&D
Grant support: Department of Veterans Affairs, Minneapolis VAHCS, Office of Research and Development, Quality Enhancement Research Initiative (QUERI)

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100. Identifying Gaps in Primary Care for Veterans with Dementia: A Qualitative Study

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Abstract: Dementia is a common, costly condition that results in negative consequences and poor quality of life for older primary care patients and their families. Due to its insidious onset and challenging behavioral symptoms, dementia is difficult to detect and manage in primary care (PC). Failure to address dementia in primary care can result in poor adherence to treatments for co-morbid illnesses, higher healthcare utilization, and decreased quality of life for the patients and families. Despite the guidance given by national expert consensus guidelines and VA expert panel recommendations, rates of detection for dementia in PC remain low. Recent innovations in VA (Patient Aligned Care Teams, PACT, and Primary Care-Mental Health Integration, PC-MHI) will result in an environment that is conducive to caring for these patients. PC-MHI providers are likely to see Veterans with dementia due to the well documented association between depression and cognitive impairment in older adults in addition to the common behavioral and psychological symptoms of dementia. PC-MHI programs, which place mental health providers into the PACT team, bring expertise to manage the challenging behavioral aspects of dementia. However, adoption of program improvements is dependent on the care environment into which they are implemented. Key stakeholders can provide essential information to address this issue. The purpose of the current study was to elicit key stakeholder perceptions of PC for veterans in order to 1) Describe common barriers to achieving high quality primary care for veterans with dementia and their family caregivers and 2) Explain how two VA health care system initiatives (PACT and PC-MHI) may help improve primary care for veterans with dementia and their families. Semi-structured and individual interviews were conducted to key stakeholders at two VA sites. All interviews were digitally recorded and professionally transcribed. Transcripts of the interviews were analyzed following a directed qualitative content analysis. Preliminary findings identified system complexity and resource limitations as notable barriers. Different stakeholder groups identify unique barriers, though with some notable overlap. Time constraints and negative emotional reactions to diagnosis were identified as barriers by all stakeholder groups. These results, as well as implications and future directions, will be discussed further.

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101. Microglial immune response to low concentrations of silver nanoparticles: A novel in vitro model of brain health

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Abstract: The brain is the central regulator for integration and control of response to environmental cues. Data from human and animal studies suggest that air pollution impact on brain regions controlling central energy balance may contribute to the propensity for obesity. We hypothesize that nanoparticle components of air pollution may underlie these effects. Worldwide increases in the intended and unintended production of nanoparticles have raised concerns regarding the potential neurological impact and downstream effects on brain health. Recent studies show that combustion generated nanoparticles (CGNP), such as those produced by internal combustion engines or aircraft engines, can directly and adversely affect brain health through induction of neuroinflammation, a deleterious immune response in brain tissue. To test this association, we have developed a novel in vitro biological sensor model of low-dose nanoparticle exposure using microglia, the resident immune cells of the brain, for testing neuronal inflammatory response to NPs, using 20 nm single metal silver nanoparticles (AgNP) as a surrogate for CGNPs. Here we demonstrate that low concentrations of AgNPs promote low-grade microglial activation as measured by increased metabolic activity, increased pro-inflammatory cytokine release (tumor necrosis factor-α; TNF-α), and upregulated pro-inflammatory gene expression (interleukin-1 β and inducible nitric oxide synthase). We also demonstrate increased production of reactive oxygen species (ROS) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) p65 activation in microglia after AgNP stimulation. Finally, we show that microglial secretions following low-dose AgNP negatively impact neuronal health, as conditioned media from AgNP-stimulated microglia significantly reduced cell survival of hypothalamic neurons in vitro. To our knowledge, this data shows for the first time the activation of NF-κB in microglia exposed to low dose of AgNP. Further, we show that low dose AgNP elicits an immune response similar to that others have shown for high dose exposure to AgNP.

Research Topic: Central Nervous System Injuries & Associated Disorders
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