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CONTRACTING ORGANIZATION:

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14. ABSTRACT

We proposed to assess dementia severity by telephone in veterans of operations "Enduring Freedom" and "Iraqi Freedom" (OEF /OIF) with Traumatic Brain Injury (TBI) using a latent dementia-specific phenotype constructed via a unique confirmatory bifactor model in a Structural Equation Model (SEM) framework (i.e., "δ" for dementia). Logistical issues prevented us from recruiting our entire sample. Regardless, our approach proved successful. Two δ composites administered by lay interviewers over the telephone accurately diagnosed cases of "Mild Cognitive Impairment (MCI)" in OEF /OIF veterans and were strongly associated with dementia severity as independently rated by an experienced clinician. Other analyses suggest that one of these composites is associated with self-reported TBI exposure. Future analyses with data in hand may relate our composite to serum protein and imaging biomarkers. One manuscript has been published from these data. A second is in review and we anticipate at least three more in 2020.

15. SUBJECT TERMS

Cognition; δ; Functional Status; *g*; MCI; TBI

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1. Introduction

"δ" (for "dementia") is a dementia-specific phenotype constructed via a unique confirmatory bifactor model in a Structural Equation Model (SEM) framework. Because it is derived from Spearman's general intelligence factor "*g*", δ can be constructed from any cognitive battery. So many are possible that we refer to each instance as a "homolog". In genetics, a homolog is a gene descended from an ancestral gene in the same species and that retains the original's function.

A δ homolog can be "reified" as a composite "d-score" and applied to individuals as an omnibus dementia severity metric i.e., a continuously distributed, transdiagnostic measure of dementia severity. All δ homologs validated to date (≧14) are strongly associated with dementia severity as measured by the Clinical Dementia Rating Scale "Sum of Boxes" (CDR-SB) and achieve high Receiver Operating Characteristic Curve (AUC /ROC) for dementia's discrimination from normal controls (NC).

Because they can be developed in any cognitive battery, δ homologs can be engineered to meet any agenda. We proposed to assess dementia severity by telephone in veterans of operations "Enduring Freedom" and "Iraqi Freedom" (OEF /OIF) with Traumatic Brain Injuries (TBI), and to associate their cognitive performance with serum protein and imaging biomarkers.

2. Keywords

Cognition; δ; Functional Status; *g*; MCI; TBI

3. Accomplishments

What were the major goals and objectives of the project?

This proposal had three Aims:

Aim 1: Construct and validate a latent dementia phenotype (i.e., dTEL) from existing Texas Alzheimer's Research and Care Consortium (TARCC) psychometric data that can be applied to veteran TBI cases by telephone.

Aim 2: Prospectively validate dTEL-derived diagnoses of "NC", "Mild Cognitive Impairment (MCI)" and "Alzheimer's Disease (AD)" in veteran TBI cases against blind "gold-standard" consensus expert clinical diagnoses and against serum protein biomarkers previously associated with clinical "AD".

Aim 3: Test dTEL's association with neuroimaging biomarkers, including: T2 structural imaging, resting state connectivity, Diffusion Tensor Imaging (DTI) and Arterial Spin Labeling (ASL).

What was accomplished under these goals?

Aim 1 is completed. A manuscript has been published by the *Journal of Neuropsychiatry and Clinical Neurosciences* (Royall & Palmer, 2018). It validates the dTEL homolog in data collected by TARCC. dTEL's model had excellent fit. It correlated strongly with CDR-SB) ($r = 0.78$, $p<0.001$). The dTEL composite's AUC for the discrimination between NC v AD cases was 0.97 (95% CI: 0.964-0.975).

Aim 2 is partially completed. 79 OEF /OIF veterans were recruited from a proposed sample of 100. 63 completed psychometric assessments. 50 subjects were imaged. Only one participant was diagnosed with dementia. These OEF /OIF veterans had a high prevalence of self-reported TBI (86%) including TBI with loss of consciousness (LOC) (60%). Educational attainment was relatively high (15.7 ± 5.8 years). Mean Geriatric Depression Scale (GDS) scores were in the clinically depressed range (14.4 ± 6.3).

Despite failing to recruit our entire proposed sample, we successfully reconstructed dTEL *de novo* in this non-demented subset of OEF /OIF veterans and a second manuscript is in review in *Neuropsychology* (Royall et al., in review). The *de novo* dTEL homolog was compared to a second composite obtained by applying TARCC's dTEL factor weights to veteran data. Both models fit the data well. The *de novo* composite's AUC for

independently diagnosed cases of MCI vs. NC was 0.80 (95% CI: 0.69 - 0.92). The TARCC composite's AUC was 0.88 (95% CI: 0.78 - 0.99). This was superior to the *de novo* composite and to all of both composites' indicators. Both composites correlated significantly with dementia severity as rated by the CDR-SB (*de novo* composite r = -0.84, p<0.001; TARCC composite r = -0.45, p<0.001).

A third manuscript is in preparation. That analysis successfully relates the TARCC dTEL composite to self-reported TBI exposure in OEF /OIF veterans, and both to dementia severity as measured by CDR-SB.

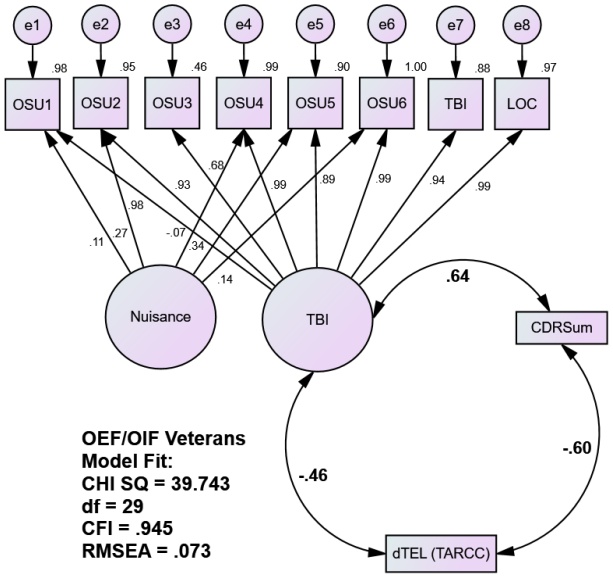

Figure 1: dTEL is Significantly associated with Self-rated TBI Exposure in Non-Demented OEF /OIF Veterans (Royall et al., unpublished)

In this Structural Equation Model (SEM), squares represent observed measures while circles represent latent constructs. The latent construct "TBI" represents self-rated and clinician confirmed TBI exposure. It correlates strongly with dementia severity as rated by the CDR-SB and moderately with the dTEL composite (TARCC loadings). dTEL is also strongly associated with CDR-SB. Model fit is good.
OSU = Oklahoma State University TBI (OSU-TBI) Identification Method items.
TBI = clinician confirmed TBI exposure
LOC = clinician confirmed loss of consciousness

We obtained blood samples from the participants. Serum protein biomarker analysis has been completed, and is now available to be related to dTEL, which will fulfill Aim 2. At least one additional manuscript is anticipated in 2020.

Aim 3 is partially completed. T2 structural image processing is complete. DTI and ASL image processing is nearing completion. Resting State connectivity image processing will be completed in January, 2020. Once these imaging biomarkers are available, they can be related to the dTEL homolog we have recently constructed, fulfilling Aim 3. At least one final manuscript is anticipated in 2020.

What opportunities for training or profession al development did the project provide?

Nothing to report.

How were the results disseminated to communities of interest?

One peer reviewed publication has been published (Royall & Palmer, 2018). A second is in review (Royall et al., in review). Dr. Royall presented at U.S. Army Medical Research and Development Command (USAMRDC) Congressionally Directed Medical Research Programs (CDMRP) Peer Reviewed Alzheimer's Research Program (PRARP) Fiscal Year 2016 (FY16) and 2019 (FY19) In-Progress Review Meetings at Ft. Detrick, MD.

What do you plan to do during the next reporting period to accomplish the goals and objectives?

Nothing to report.

4. Impact

What was the impact on the development of the principle discipline(s) of the project?

This project has provided proof of concept for the application of latent δ homologs in the assessment of TBI. Two dTEL homologs, administered to OEF /OIF veterans over the phone and by lay administrators, were strongly associated with dementia severity as independently assessed by expert clinicians, and significantly impacted by TBI. Future analyses will relate these composites to serum protein and imaging biomarkers using data in hand.

Because these analyses were derived from an incomplete sample noticeably lacking in dementia cases, these composites cannot be recommended for clinical application in their current form. Regardless, we demonstrated their ability to diagnose MCI in OEF /OIF veterans by a brief telephone interview.

Given a larger sample of servicemen and women with and without TBI exposure, similar dTEL homologs could be used to assess the impact of non-dementing TBI exposure on cognitive performance in the field, and by lay personnel from a remote location.

Only one manuscript has been published to date from these data. However, it garnered the highest rating of any article published in *Journal of Neuropsychiatry and Clinical Neurosciences* for the month of February, 2018. Altmetric scores the quality and quantity of article mentions in traditional and social media, as well as researcher to researcher sharing. Additional manuscripts are anticipated.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. Changes/Problems

Changes in approach and reasons for change

A no cost extension (NCE) was approved 06 MAY, 2019. However, funding expired on 30 SEP 2019, before we could complete enrollment. We therefore closed recruitment and submitted our biomarkers for processing in anticipation of the final analyses.

Actual or anticipated problems of delays and actions or plans to resolve them

We encountered difficulties recruiting demented veteran subjects. Few presented for outpatient VA treatment. Some subjects failed to attend all their study-related visits, resulting in missing data. Some were lost to follow-up by moving, homelessness or incarceration. Multiple study sites required multiple regulatory reviews. Changes in personnel affiliation(s) necessitated even more regulatory submissions. One personnel relocation resulted in the loss of access to planned neuroimaging resources and their renegotiation with other providers, at increased expense. The new neuroimaging provider mistakenly attempted to bill subjects for study-related procedures. The use of non-VA staff required VA Without Compensation (WOC) credentialing imposing additional delay and obstacles to staff hiring and retention. These delays forced two NCE which pushed the project to the deadline for fund expiration.

Changes that had a significant impact on expenditures

Termination of recruitment before full enrollment left us with a surplus of funds, which have been returned to USAMRAA.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and /or select agents

Nothing to report.

6. Products

Publications, conference papers and presentations

Published Manuscripts: 1 (Royall & Palmer, 2018)
Manuscripts in press: 0
Manuscripts in review: 1 (Royall et al., in review)
Anticipated manuscripts: ≥3 in 2020
Two presentations to U.S. Army Medical Research and Development Command (USAMRDC) Congressionally Directed Medical Research Programs (CDMRP) Peer Reviewed Alzheimer's Research Program (PRARP) Fiscal Year 2016 (FY16) and 2019 (FY19) In-Progress Review Meetings at Ft. Detrick, MD.

Manuscripts:

1. Royall DR, Jaramillo CA, Tate DF, Palmer RF. δ Validation in OEF /OIF Veterans of a δ Homolog for Telephone Assessment of TBI-related Cognitive Change. *Neuropsychology*. In review.

2. Royall DR, Palmer RF. A potential telephone assessment of dementia diagnosis and severity. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2018; 30:202-207.

Website(s) or other internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other products

Nothing to report.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	*Donald R. Royall, MD*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-6475-0300*
Nearest person month worked:	*3*
Contribution to Project:	*Study oversight, statistical modelling and manuscript development*
Name:	*Carlos A. Jaramillo, MD, PhD*
Project Role:	*Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-2424-6326*
Nearest person month worked:	*2*
Contribution to Project:	*Subject referral and recruitment*
Name:	*Raymond F. Palmer, PhD*
Project Role:	*Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-6621-9038*

Nearest person month worked:	*1*
Contribution to Project:	*Statistical analyses and PI of UTHSCSA subaward*
Name:	*David F. Tate, PhD*
Project Role:	*Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-0213-1920*
Nearest person month worked:	*1*
Contribution to Project:	*Imaging analyses and PI of USOM subaward*
Name:	*Marsha J. Polk*
Project Role:	*Study Coordinator*
Researcher Identifier (e.g. ORCID ID):	*Not applicable*
Nearest person month worked:	*1*
Contribution to Project:	*Study Administration*
Name:	*Maria Sanchez*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*Not applicable*
Nearest person month worked:	*1*
Contribution to Project:	*Subject scheduling and assessment*
Name:	*Javier Gallegos*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*Not applicable*
Nearest person month worked:	*12*
Contribution to Project:	*Subject recruitment and assessment*
Name:	*Nancy Vergara*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*Not applicable*
Nearest person month worked:	*6*
Contribution to Project:	*Subject recruitment and assessment*

Has there been a change in the active other support of the PD/PIs or senior key personnel sine the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Site 1: The South Texas Veterans Health Care System (STVHCS)
5300 Merton Minter
San Antonio, TX 78229

- In kind salary support for PI (DRR) and Co- investigator (CJ)
- Facilities (Polytrauma Clinic)
- Administrative Support

Site 2: University of Texas Health Science Center at San Antonio (UTHSCSA)
7703 Floyd Curl Dr.
San Antonio, TX, 78229-3900

- Facilities (Texas Alzheimer's Research and Care Consortium (TARCC)
- Statistical Support

Site 3: University Hospital System (UHS)
7703 Floyd Curl Drive
San Antonio, TX 78229-3900

- Neuroimaging

Site4: University of Missouri, St. Louis (UMSL)
4633 World Parkway Circle
Berkeley, MO 63134-3115

- Image Processing

Site5: The University of Utah School of Medicine (UUSM)
30 N 1900 E, Salt Lake City, UT 84132

- Image Processing

8. Special Reporting Requirements

Nothing to report

9. Appendices

Royall & Palmer, 2018