

**AWARD NUMBER: W81XWH-17-1-0490**

**TITLE: Using Multimodal Imaging to Examine the Neural Mechanisms of an Integrative Exercise Program for Individuals with Dementia**

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**CONTRACTING ORGANIZATION: Northern California Institute for Research and Education (NCIRE)**

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The goal of this project is to investigate whether participation in the Preventing Loss of Independence through Exercise (PLIÉ) program for 4 months will result in neurobiological changes that improve cognitive function, leading to improvements in physical function and quality of life (QOL). We will estimate the impact of PLIÉ on brain atrophy rates, Default Mode Network (DMN) functional connectivity, and cerebral perfusion and determine if improvements in cognition, function, and QOL are associated with changes in brain volume, DMN functional connectivity, and cerebral perfusion in individuals who participated in PLIÉ.					
<b>15. SUBJECT TERMS</b> Exercise, Alzheimer's disease, other dementias, mild cognitive impairment, quality of life, neuroimaging					
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## TABLE OF CONTENTS

	<u>Page No.</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4-6
4. Impact	6-7
5. Changes/Problems	7-9
6. Products	9-10
7. Participants & Other Collaborating Organizations	10-14
8. Special Reporting Requirements	14
9. Appendices	14

## 1. INTRODUCTION:

The goal of this project is to investigate whether participation in the Preventing Loss of Independence through Exercise (PLIÉ) program for 3 months will result in neurobiological changes that improve cognitive function, leading to improvements in physical function and quality of life (QOL). We will estimate the impact of PLIÉ on brain atrophy rates, Default Mode Network (DMN) functional connectivity, and cerebral perfusion and determine if improvements in cognition, function, and QOL are associated with changes in brain volume, DMN functional connectivity, and cerebral perfusion in individuals who participated in PLIÉ.

## 2. KEYWORDS:

Exercise, Alzheimer's disease, other dementias, mild cognitive impairment, quality of life, neuroimaging.

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

1. Obtain local and HRPO IRB approval (local approval: 11/15/2017; HRPO approval: 1/25/2018)
2. Obtain neuroimaging data from MRI-eligible MCI participants of VA-funded trial of PLIÉ (3/29/18 and 7/19/18).
3. Recruit first DOD PLIÉ cohort of MCI participants where neuroimaging will be obligatory part of study (January, February 2019).
4. Obtain behavioral and clinical data before and after PLIÉ intervention in first DOD MCI cohort (February, June 2019).
5. Obtain neuroimaging data from MCI participants in first DOD PLIÉ cohort (February, June 2019).
6. Recruit second DOD PLIÉ cohort of MCI participants where neuroimaging will be obligatory part of study (May-June 2019).
7. Obtain behavioral and clinical data before and after PLIÉ intervention in second DOD MCI cohort (June, July, October 2019).
8. Obtain neuroimaging data from MCI participants in second DOD PLIÉ cohort (June, July, October 2019).
9. Process imaging data (ongoing: started March 2018).
10. Analyze imaging data together with PLIÉ behavioral outcome measures (months 32-35).
11. Disseminate study findings (months 24, 26).
12. Write final report for DOD (month 36).

### What was accomplished under these goals?

Major activities and achievements:

- Obtained baseline and follow-up neuroimaging data from one MRI-eligible MCI participant from VA-funded PLIÉ trial (3/29/18; 7/19/18)
- Recruited MCI participants for the three DOD PLIÉ cohorts where neuroimaging is obligatory (January – March 2020)
  - Seven participants were enrolled in Cohort 1 (3/12/19-6/6/19); 8 participants were enrolled in Cohort 2 (7/16/19 – 10/3/19); 10 participants were enrolled in Cohort 3 (11/12/19 – 2/20/20)
  - Four participants were enrolled for Cohort 4 before COVID-19 related shelter-in-place orders went into effect, halting recruitment.
- Obtained baseline and post-PLIÉ behavioral, clinical, and neuroimaging data from Cohort 1 (March - June 2019), Cohort 2 (July - October 2019), and Cohort 3 (November 2020 – February 2020).
- We have processed and analyzed the imaging data together with the PLIÉ behavioral outcome measures.
- We have disseminated the PLIÉ behavioral and imaging results at the following meetings:
  - 2020 virtual Alzheimer’s Association International Conference (poster and oral presentation. 7/30/20)
  - Children’s Hospital of Philadelphia 4<sup>th</sup> Annual Integrative Health Symposium (virtual conference, 9/25/2020)
  - Submitted abstract to present findings at 2021 American Academy of Neurology conference

**What opportunities for training and professional development has the project provided?**

Nothing to report.

**How were the results disseminated to communities of interest?**

- Oral presentation at the Dementia Care Research: Behavioral Interventions session at the 2020 (virtual) Alzheimer’s Association International Conference (7/30/20)
- Virtual poster presented at the 2020 Alzheimer’s Association International Conference (7/30/20)
- Oral presentation at finding at FY20 PRARP In Progress Review Meeting (9/9/20)
- Oral presentation at the Children’s Hospital of Philadelphia 4<sup>th</sup> Annual Integrative Health Symposium (virtual conference, 9/25/2020)
- Oral presentation Western Region Chapter-Aging Life Care Association Conference (9/26/20)
- Submitted abstract to present findings at 2021 American Academy of Neurology Conference

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

- Modify IRB protocol to conduct third follow-up time point with 18 participants who have completed pre-post PLIÉ assessments.
- Nine of these participants have continued to practice PLIE through Together Senior Health's virtual program.

**4. IMPACT:**

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

Eighteen older adults (mean age 75 years) with mild cognitive impairment (MCI) completed 12 weeks of PLIÉ. After PLIÉ, there were significant improvements in cognition, as assessed by the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog, paired t-test,  $p=0.01$ ), physical function, as assessed by the Short Physical Performance Battery (paired t-test,  $p<0.05$ ), ability to regulate distress by increasing attention to body sensations (e.g., self-regulation, paired t-test,  $p=0.006$ ), and reduced feelings of social isolation, as assessed by the PROMIS social isolation measure (paired t-test,  $p=0.009$ ).

After 12 weeks of PLIÉ, there were also trends of improvements in feelings of well-being, as assessed by the PROMIS positive affect and social well-being measure (paired t-test,  $p=0.05$ ) and ability to sustain and control attention to body sensations (e.g., attention regulation, paired t-test,  $p=0.05$ ).

After 12 weeks of PLIÉ, there were increased functional connectivity between nodes of the default mode network, specifically between the hippocampus and anterior cingulate cortex and between the posterior cingulate cortex and bilateral parietal cortex.

Although there were no significant pre-post PLIÉ changes in cerebral perfusion, post-PLIÉ increases in hippocampal perfusion was positively and significantly correlated with post-PLIÉ improvements in Quality of Life Neurological Disorders (Neuro QoL) mobility measure (Spearman's  $\rho=0.64$ ,  $p=0.036$ ). Post-PLIÉ increases in posterior cingulate (PCC) and ventral inferior prefrontal cortex (viPFC) perfusion were positively and significantly correlated with post-PLIÉ improvement in the verbal recall measure of the ADAS-cog (Spearman's  $\rho=0.60$ ,  $p=0.01$  for the PCC and Spearman's  $\rho=0.61$ ,  $p=0.01$  for the viPFC). These findings are consistent with research evidence supporting the PCC role in episodic memory processing and the ventral inferior prefrontal cortex in memory retrieval.

Although there were no significant pre-post PLIÉ changes in hippocampal subfield volumes, post-PLIÉ increases in presubiculum volume was positively and significantly correlated with post-PLIÉ improvements in delayed verbal recall on the ADAS-cog (Spearman's  $\rho=0.52$ ,  $p=0.03$ ). This finding is consistent with recent report by Jacobs et al. (2020) that the presubiculum links incipient amyloid and tau pathology to memory function in older adults.

#### **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?**

Improving public knowledge about and attitude towards integrative movement programs for senior citizens and people with mild cognitive impairment and early dementia.

### **5. CHANGES/PROBLEMS:**

#### **Changes in approach and reasons for change**

We were in the middle of enrolling and assessing participants for our fourth PLIÉ group when the COVID-19 related shelter-in-place orders went into effect in San Francisco. Presently, in-person research activities have yet to resume at the San Francisco VA, therefore, we have decided to close recruitment and focus on finishing image data analysis and writing up the findings for publication. Because COVID will impact our ability to deliver PLIÉ in person, we plan to modify the study protocol to bring back the 18 study completers for a third and final behavioral and neuroimaging assessment. Nine of these completers have continued to practice PLIÉ through Together Senior Health's on-line virtual PLIÉ program.

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

We were in the middle of enrolling and assessing participants for our fourth PLIÉ group when the COVID-19 related shelter-in-place orders went into effect in San Francisco. Presently, in-person research activities have yet to resume at the San Francisco VA, therefore, we have decided to close recruitment and focus on finishing image data analysis and writing up the findings for publication. Because COVID will impact our ability to deliver PLIÉ in person, we plan to modify the study protocol to bring back the 18 study completers for a third and final behavioral and neuroimaging assessment. Nine of these completers have continued to practice PLIÉ through Together Senior Health's on-line virtual PLIÉ program.

**Changes that had a significant impact on expenditures**

Due to COVID-19, we were not able to run a fourth group of participants through the PLIÉ intervention. Consequently, we have funds remaining that we intend to use to bring back all the 18 study completers for a third study timepoint.

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

**Significant changes in use or care of human subjects.**

There have been no significant deviations or changes in approved protocols for the use of human subjects. The current IRB approval dates are:

Study #17-23517 (imaging VA-PLIÉ participants): approved: 11/15/2017; expires 9/11/2021

Study # 17-23034 (DOD- PLIÉ): approved: 12/15/2017; expires: 9/06/2021

**Significant changes in use or care of vertebrate animals.**

N/A

**Significant changes in use of biohazards and/or select agents**

N/A

**6. PRODUCTS:**

- **Publications, conference papers, and presentations**

**Journal publications.**

Nothing to report.

**Books or other non-periodical, one-time publications.**

Nothing to report.

**Other publications, conference papers, and presentations.**

1. Martinez SM, Barnes DE, Mehling W, Chesney M, Lee J, Lee A, Chao LL. Preventing Loss of Independence through Exercise (PLIE) Improves Cognitive, Behavioral, and Neuroimaging Outcomes. 2020 Alzheimer's Association International Conference, July 30, 2020 (online poster).
2. Barnes DE. Preventing Loss of Independence through Exercise (PLIE) for Persons with Dementia. 2020 Alzheimer's Association International Conference, July 30, 2020 (online talk).
3. Chao LL. Using Multimodal Imaging to Examine the Neural Mechanisms of an Integrative Exercise Program for Individuals with Mild Cognitive Impairment. FY20 PRARP In Progress Review Meeting, September 9, 2020 (online talk).
4. Chesney M. Integrative Approaches to Brain Health: Lessons from Research on Integrative Movement Therapies for Mild Cognitive Impairment. Children's Hospital of Philadelphia 4<sup>th</sup> Annual Integrative Health Program Symposium, September 25, 2020 (online talk).
5. Barnes DE and Lee J. PLIE & Moving Together - In-Person and Online Group Movement Programs for People Living with Dementia. Western Region Chapter-Aging Life Care Association Conference, September 26, 2020 (online talk).

- **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**

Video tapes of the PLIÉ classes were created for graduates of the PLIÉ classes so that they can continue to practice PLIÉ on their own after the study/classes are over.

## **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

Name:	Linda Chao
Project Role:	PI
Researcher Identifier:	(eRA Commons: lindachao)
Nearest person month worked:	1.2 calendar months
Contribution to Project:	Dr. Chao has worked closely with the study co-investigators to ensure the successful coordination of all aspects of project, from study procedures, data collection, data quality control, and data analyses. She has held monthly meetings with the research team to discuss progress, technical. and scientific issues, and subject flow issues.
Name:	Deborah Barnes
Project Role:	Co-Investigator
Researcher Identifier:	(eRA Commons: BANESD)
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Barnes has worked closely with Dr. Chao to oversee the conduct of the proposed research Dr. Barnes has also assisted with data analysis and interpretation of the study results.
Name:	Margaret Chesney
Project Role:	Co-Investigator
Researcher Identifier:	(eRA Commons: chesneymar)
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Chensey has worked closely with Dr. Chao interpret the study results.
Name:	Wolf Mehling
Project Role:	Co-Investigator
Researcher Identifier:	(eRA Commons: mehling)
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Mehling has worked closely with Dr. Chao to interpret the study results
Name:	Steven Martinez
Project Role:	Study Coordinator
Researcher Identifier:	N/A
Nearest person month worked:	6.0 calendar months
Contribution to Project:	Mr. Martinez was involved with recruiting and assessing participants in the second and third PLIÉ cohorts. He has also been involved in data quality control and data analysis.
Name:	Gary Tarasovsky
Project Role:	database manager
Researcher Identifier:	N/A
Nearest person month worked:	0.4 calendar months
Contribution to Project:	Mr. Tarasovsky has built a customized database for the specific needs of this project and has ensured that behavioral and demographic data generated by this project is stored in a timely manner and accessible at all times.

Name:	Jennifer Lee
Project Role:	Primary PLIÉ Instructor
Researcher Identifier:	N/A
Nearest person month worked:	8 calendar months
Contribution to Project:	Ms. Lee has been the main PLIÉ instructor for all of the cohorts.
Name:	Amanda Lee
Project Role:	Assistant PLIÉ Instructor
Researcher Identifier:	N/A
Nearest person month worked:	8 calendar months
Contribution to Project:	Ms. Lee has been the assistant PLIÉ instructor for all of the cohorts. In addition to assisting Ms. Jennifer Lee in teaching the PLIÉ classes, Ms. Amanda Lee had also been calling participants prior to the PLIÉ classes to inquire about their goals for class and calling them each month during the study to check on adverse events.
Name:	Suyash Bhogawar
Project Role:	Imaging database manager
Researcher Identifier:	N/A
Nearest person month worked:	2.4 calendar months
Contribution to Project:	Mr. Bhogawar has built a customized imaging database for the specific needs of this project and has ensured that neuroimaging data generated by this project is stored in a timely manner and accessible at all times.

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Name: Linda Chao

- Changes:
1. Effort on this grant was increased from 0.66 calendar months to 1.2 calendar months.
  2. DOD/CDMRP grant W81XWH-16-1-0558 has been granted a no cost extension (NCE). Effort on this grant has been reduced from 0.66 calendar months to 0.12 calendar months in the NCE year.

Name: Deborah Barnes

- Changes:
1. Dr. Barnes stopped drawing salary support for her effort on this project in the NCE year.
  2. VA grant I0RX001507 ended in 12/31/2019.
  3. VA grant 1I01HX002764 has been funded. Dr. Barnes is PI at 5.1 calendar months.
  4. Dr. Barnes is a co-investigator on VA grant I01CX001761 at 0.6 calendar months.
  5. Dr. Barnes is a co-investigator on VA grant I01CX002946 at 0.6 calendar months.
  6. Dr. Barnes is a co-investigator on VA grant I01CX002096 at 1.2 calendar months
  7. Dr. Barnes is co-investigator on NIH/NIA grant R44AG059520 at 2.4 calendar months.
  8. Dr. Barnes is co-investigator on NIH/NIA grant R01AG057751 at 1.2 calendar months.
  9. Dr. Barnes is pilot core executive committee member on NIH/NIA grant U54 AG063546 at 1.5 calendar months.
  10. Dr. Barnes is PI of a California Department of Public Health grant (no award number) at 3.6 calendar months. The performance dates of the grant “Identifying Key Modifiable Risk Factors for Alzheimer's Disease in California” is April 1, 2020 to June 30, 2022.

Name:	Margaret Chesney
Changes:	1. Dr. Chesney stopped drawing salary support for her effort on this project in the NCE year.
	2. Effort on VA grant I01 RX001939-01A1 increased from 0.5 calendar months to 0.74 calendar months
	3. VA grant 1I01HX002764 has been funded. Dr. Chesney is co-investigator at 0.06 calendar months
	4. Dr. Chesney is co-investigator on NIH/NIDDK grant 1R01 DK116712 at 0.54calendar months.
Name:	Wolf Mehling
	1. Dr. Mehling stopped drawing salary support for her effort on this project in the NCE year.
	2. Dr. Mehling is co-investigator on NIH/NIAMS grant 1U19AR076737 at 1.8 calendar months.

**What other organizations were involved as partners?**

**Nothing to Report**

**8. SPECIAL REPORTING REQUIREMENTS:**

N/A

**9. APPENDICES:**

N/A