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CONTRACTING ORGANIZATION: Ohio University

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14. ABSTRACT

Musculoskeletal injuries such as to the knee's anterior cruciate ligament (ACL) degrade the operational readiness of our U.S. Service members. These injuries cause decreased physical ability that leads to reduced performance and high re-injury risk. Changes in brain activity as the result of the injury is directly related to the decreased physical performance, affecting the Service member's motor performance capability in complex or highly reactive military training and operations environments. Unfortunately, current treatments do not restore post-injury Service member's physical performance, especially when under stress. This deficit has clear consequences for military personnel, as the intense stress and constant need of situational awareness can impair physical performance when returned to active duty. To that end, new therapies are needed to restore Service member performance after injury. Thus, the purpose of this proposal is to quantify how the brain changes after injury across the typical 6-month window of physical therapy. We are also testing new functional assessments that target the brain changes that limit Service member performance. These assessments will support the transition of this research to clinical practice. This applied research award will provide the knowledge of the time course of brain changes that influence function to implement these new impactful interventions. These synergistic outcomes provide an immediate product that can be clinically implemented and propel further investigations to ensure truly restored functional capacity of our nations Service members.

15. SUBJECT TERMS

NONE LISTED

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1. Introduction

Musculoskeletal injuries such as to the knee's anterior cruciate ligament (ACL) degrade the operational readiness of our U.S. Service members. These injuries cause decreased physical ability that leads to reduced performance and high re-injury risk. Changes in brain activity as the result of the injury is directly related to the decreased physical performance, affecting the Service member's motor performance capability in complex or highly reactive military training and operations environments. Unfortunately, current treatments do not restore post-injury Service member's physical performance, especially when under stress. This deficit has clear consequences for military personnel, as the intense stress and constant need of situational awareness can impair physical performance when returned to active duty. To that end, new therapies are needed to restore Service member performance after injury. Thus, the purpose of this proposal is to quantify how the brain changes after injury across the typical 6-month window of physical therapy. We are also testing new functional assessments that target the brain changes that limit Service member performance. These assessments will support the transition of this research to clinical practice. This applied research award will provide the knowledge of the time course of brain changes that influence function to implement these new impactful interventions. These synergistic outcomes provide an immediate product that can be clinically implemented and propel further investigations to ensure truly restored functional capacity of our nations Service members.

2. Keywords

Neuroimaging, lower extremity, biomechanics, knee injury, anterior cruciate ligament, tactical performance, neural control of movement, neuromuscular control, cognitive motor interaction

3. Accomplishments

Project Goals
The project is split into 2 primary goals\aims.
Goal 1: To determine when the maladaptive neuroplastic sensory reweighting occurs following ACL injury.
Local IRB Approval: Achieved – Year 3 Continuing Review Completed
HRPO Approval: Achieved – Year 3 Continuing Review Completed
Equipment preparation: Completed
New technology integration and initial development studies
(virtual reality and sensorimotor monitoring during neuroimaging): Completed (**initial data published**)

Participant recruitment: Ongoing
Injured cohort Neuroimaging data collection: Ongoing
(n=5 completed, n=8 currently enrolled or engaged in longitudinal follow-up) target sample size: 36

Control cohort Neuroimaging data collection: Ongoing (n=10 completed) target sample size: 36

Goal 2: To determine the functional correlates of neuroplastic sensory reweighting for motor performance.
Local IRB Approval: Achieved – Year 3 Continuing Review Completed
HRPO Approval: Achieved – Year 3 Continuing Review Completed
Equipment preparation: Completed
New technology integration and initial development studies
(functional virtual reality, proprioception, reactive motor control): Completed (**initial data published**)

Participant recruitment: Ongoing
Injured cohort Biomechanical data collection (muscle strength, proprioception, postural control, neuromuscular control and patient outcomes): Ongoing
(n=5 completed, n=8 currently enrolled or engaged in longitudinal follow-up) target sample size: 36

Control cohort Biomechanics data collection (muscle strength, proprioception, postural control, neuromuscular control and patient outcomes): Ongoing (n=10 completed) target sample size: 36

ROTC cohort tactical neuromuscular control performance data collection: Completed (n=33)

4. Impact

Work has completed development stage, as well as the ROTC arm of the study and is in currently in data collection for the ACL injured cohort. Two works have been published, 1) the neuroimaging development study and 2) an initial report from the ROTC arm.

5. Changes/Problems

No changes to the deliverables, general scope of work, expenditures or human subject experience were made during this reporting period. The local University IRB shutdown of all research has been lifted and we are currently operating under the local IRB approved COVID modifications requirements regarding contact tracing, masking, distancing etc. The COVID related research shutdown did force us to lose follow-up on 15 recruited patients, nearly half of our study cohort requiring new subjects to be recruited and enrolled to replace them to meet the scope of work for 6-month longitudinal follow-up. A supplemental award was granted to enable running the project for additional years to ensure the scope of work can be completed with these vital longitudinal follow-up visits. A no-cost extension was also granted to continue the work as due to COVID resulting in no allowed laboratory research activity with human subjects for over a year starting in March 2020, we reduced charges to the grant and reduced personnel effort to allow for increased effort and charges once human subject research activity was allowed to resume.

We did have to change personnel due to the project manager leaving the University in August 2020. Mr. Haggerty was offered a position with the Navy at much higher salary and benefits then we could compete with and he resigned his position with the University on the project effective August 21st. We replaced the position in late November. Dr. Steven Pfeiffer, research biomechanics specialist, added Co-I, also left the University in May 2021 (removed from scope of work) and responsibilities shifted to the research associate\project manager and PI (Grooms).

The volume of orthopedic surgery has yet to reach normal levels and we are finding patients are less interested to participate secondary to COVID related fears and general economic stress. However, we have had success recruiting at least 2 new subjects each month that have been engaged in the follow-up visits. We foresee this number increasing as the latest COVID variant wave is mitigated and orthopedic surgeries increase along with increasing sport participation rates. At times our orthopedic surgery and related medical staff has been pulled away to assist the local hospitals with COVID related outbreaks.

6. Products

Work has completed development stage initial studies is in currently in data collection on the primary longitudinal patient arm of the study.

Data from the initial development arm and ROTC arm of the work has been published since the last annual report:

Buckley S, Chaput M, Simon JE, Criss CR, Brazalovich P, McCarren G, Yom J, Grooms DR. Cognitive Load Impairs Time to Initiate and Complete Shooting Tasks in ROTC Members. *Military Medicine*. Published online July 9, 2021:usab276. doi:10.1093/milmed/usab276

Grooms DR, Criss CR, Simon JE, Haggerty AL, Wohl TR. Neural Correlates of Knee Extension and Flexion Force Control: A Kinetically-Instrumented Neuroimaging Study. *Front Hum Neurosci*. 2020;14. doi:10.3389/fnhum.2020.622637

1 Abstract has been presented or accepted at national scientific meetings related to the work since the last annual report

Chaput M, Farraye BT, Simon JE, Kim HW, Monfort SM, Grooms DR. Development and Reliability of a Gaze Controlled Visual-Cognitive Reactive Triple Hop Test. Combined Sections Meeting of the American Physical Therapy Association, San Antonio, TX. Feb 2022 National

7. Participants & Other Collaborating Organizations

Name: Dustin Grooms
Role: PI
Research identifier: 0000-0001-6102-8224
Person month worked: 3
Contribution: Coordinate overall project, IRB\HRPO approval, hire and train research assistants\project manager, secure technologies, patient and participant recruitment and data collection\analysis
Funding support: This award and university research release time

Name: Byrnadeen Farraye
Role: Project manager\research associate
Research identifier: *NA*
Person month worked: 10
Contribution: Undergo training in all data collection methods and CITI training for human subject interaction. Facilitate participant recruitment, data collection\analysis and manage research equipment.
Funding support: This award

Name: Janet Simon
Role: Co-I
Research identifier: *NA*
Person month worked: 1
Contribution: Project management, data analysis and experimental design, patient outcomes management
Funding support: This award and university research release time (in-kind)

Name: Brian Clark
Role: Co-I
Research identifier: *NA*
Person month worked: 0.75
Contribution: Strength and functional testing data collection and analysis.
Funding support: This award and university research release time (in-kind)

Name: Meredith Chaput
Role: Research assistant\PhD student
Person month worked: 9
Contribution: Data analysis, reporting and manuscript preparation on the phase 1 initial study data.
Funding support: This award and university

Name: Sergio Ulloa
Role: Physician
Person month worked: 0.5
Contribution: Patient recruitment
Funding support: This award and university and clinical practice

8. Special Reporting Requirements

Updated quad chart included

9. Appendices

Publications
Updated Scope of Work with percentage completed\ongoing

STATEMENT OF WORK – Month/Day/Yea`r
PROPOSED START DATE Sept 30, 2018

Site 1: Ohio University
E156 Grover Center
1 Ohio University
Athens, OH 45701
PI: Dustin Grooms

Site 2: Holzer Medical Center
Imaging & Radiology
2131 East State Street
Athens, OH 45701

Specific Aim 1: To determine when the maladaptive neuroplastic sensory reweighting occurs following ACL injury.	**Timeline (months) ORIGINAL**	**Timeline (months) Revised**	**Changes**	**Site 1**	**Site 2**	**Status**
Local IRB submission USAMRMC ORP HRPO submission Equipment preparation Training of study personnel	1-6		N\A	Dr. Grooms (PI) All Co-Is		Completed
Milestone Achieved: IRB & HRPO Approval	6		N\A	Dr. Grooms (PI)		Completed
Subject recruitment and enrollment	6-27	6-39	Extended duration	Dr. Grooms (PI) Dr. Sergio Ulloa		Ongoing (36%) 13 of 36 patients
Neuroimaging data collection	6-27	6-39	Extended duration		Grooms (PI) GRA	Ongoing (25%) 9 of 36 patients
Milestone Achieved: Data collection complete	27	39	Extended duration	Dr. Grooms (PI)		
Neuroimaging data analysis	6-30	6-42	Extended duration	Dr. Grooms (PI) GRA/PM		Ongoing (25%)
Milestone Achieved: Data analysis complete	30	42	Extended duration	Dr. Grooms (PI)		
Assessment of study data quality	12,18, 24	12,18, 24, 36	Extended duration	Dr. Grooms (PI) Dr. Masato Nakazawa All Co-Is		Ongoing (25%)
Statistical analysis	9-30	9-42	Extended duration	Dr. Grooms (PI) Dr. Masato Nakazawa All Co-Is		Not started
Milestones Achieved: Final study report • Deliverables: presentation of Aim 1 data at national meetings and publication of 1 peer reviewed paper	30-36	42-48	Extended duration	All investigators		

ACLR, anterior cruciate ligament reconstruction; GRA, graduate research assistant; PM, project manager

Specific Aim 2: <u>To determine the functional correlates of neuroplastic sensory reweighting for motor performance.</u>	**Timeline (months)**	**Timeline (months) Revised**	**Changes**	**Site 1**	**Status**
Local IRB approval, equipment preparation and training of study personnel	1-6		N\A	Dr. Grooms (PI) All Co-Is	Completed
Milestone Achieved: IRB Approval	6		N\A	Dr. Grooms (PI)	Completed
Subject recruitment and enrollment (concurrent with Aim 1)	6-27	6-39	Extended duration	Dr. Grooms (PI) Dr. Sergio Ulloa	Ongoing (36%)
Muscle strength data collection	6-27	6-39	Extended duration	Dr. Grooms (PI) GRA/PM	Ongoing (25%)
Knee joint proprioception data collection	6-27	39	Extended duration	Dr. Grooms (PI) Dr. Clark GRA/PM	Ongoing (25%)
Virtual reality postural control data collection	6-27	6-39	Extended duration Replace Yom (left University) with Pfeiffer	Dr. Grooms (PI) GRA/PM	Ongoing (25%)
Knee neuromuscular control data collection	6-27	6-39	Extended duration Replace Yom (left University) with Pfeiffer	Dr. Grooms (PI) GRA/PM	ACL cohort Ongoing (25%) ROTC cohort completed (100%)
Patient reported outcomes data collection	6-27	6-39	Extended duration	Dr. Grooms (PI) Dr. Simon GRA/PM	Ongoing (25%)
Milestone Achieved: Data collection complete	27	9-42	Extended duration	Dr. Grooms (PI)	
Muscle strength data analysis	9-30	42-48	Extended duration	Dr. Grooms (PI) GRA/PM	Ongoing (25%)
Knee joint proprioception data analysis	9-30	9-42	Extended duration	Dr. Grooms (PI) Dr. Clark GRA/PM	Ongoing (25%)
Virtual reality postural control data analysis	9-30	9-42	Extended duration Replace Yom (left University) with Pfeiffer	Dr. Grooms (PI) GRA/PM	Ongoing (25%)
Knee neuromuscular control data analysis	9-30	9-42	Extended duration Replace Yom (left	Dr. Grooms (PI) GRA/PM	Ongoing (25%) ROTC cohort completed (100%)

			University) with Pfeiffer		
Patient reported outcomes data analysis	9-30	9-42	Extended duration	Dr. Grooms (PI) Dr. Simon GRA/PM	Ongoing (25%)
Milestone Achieved: Data analysis complete	30	42	Extended duration	Dr. Grooms (PI)	
Assessment of study data quality	12,18, 24	12,18, 24, 36	Extended duration	Dr. Grooms (PI) Dr. Masato Nakazawa All Co-Is	Ongoing (25%)
Statistical analysis	9-30	9-42	Extended duration	Dr. Grooms (PI) Dr. Masato Nakazawa All Co-Is	ACL cohort Not started ROTC cohort completed (100%)
Milestones Achieved: Final study report • Deliverables: presentation of Aim 2 data at national meetings and 1 peer reviewed paper	30-36	42-48	Extended duration	All investigators	ROTC cohort completed (100%)

ACLR, anterior cruciate ligament reconstruction; GRA, graduate research assistant;

Human Subject Quarterly Enrollment Targets

Quarters	**Year 1**				**Year 2**				**Year 3**				**Year 4**			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
ACLR participants	0	0	0	0	3	0	0	0	0	3	7	7	8	8	Enrollment complete **Total:72**	Data collections complete with follow-ups
Healthy control participants	0	0	0	3	3	0	0	0	0	3	6	7	7	7		
Target cumulative enrollment	0	0	0	3	6	0	0	0	0	6	13	14	15	15		

* Power analysis for 72 already includes 10% attrition and 10% data quality loss.

We are 3 subjects behind for this quarter (recruiting and enrolling 2), however as fall sport participation has increased we have 6 potential new patients awaiting surgery in the next 2-4 weeks.

Highlight is COVID-19 pandemic research shutdown – All subjects recruited but not completed study activities (specifically the longitudinal follow-up) in year 2 Q1 lost to follow-up and require replacement and thus not counted here (n=15).

Preliminary reliability, optimization and ROTC development experiments not counted in this enrollment total. Only the primary study aims (longitudinal patient data collection) included here.

MILITARY MEDICINE, 00, 0/0:1, 2021

Cognitive Load Impairs Time to Initiate and Complete Shooting Tasks in ROTC Members

Sean Buckley, MS, AT[*]*; Meredith Chaput, DPT*[†]*; Janet E. Simon, PhD, AT*[*,†]*; Cody R. Criss, BS*[†]*;*
Philip Brazalovich, MS, AT[*]*; Gillian McCarren, MS, AT*[*]*; Jae Yom, PhD*[‡]*;*
Dustin R. Grooms, PhD, AT, CSCS[*,†,§]

ABSTRACT

Introduction:

Multitasking typically requires an individual to simultaneously process cognitive information while performing a motor task. Cognitive motor interference (CMi) is encountered when cognitive challenges negatively impact motor task performance. Military personnel encounter cognitively taxing situations, especially during combat or other tactical performance scenarios, which may lead to injury or motor performance deficits (i.e., shooting inaccuracy, delayed stimulus–response time, and slowed movement speed). The purpose of the current study was to develop four cognitive motor shooting paradigms to determine the effects of cognitive load on shooting performance in healthy Reserve Officers' Training Corps (ROTC) cadets.

Methods:

Thirty-two healthy collegiate ROTC members (24 male and 8 female; 20.47 ± 1.24 years, 174.95 ± 10.58 cm, and 77.99 ± 13.90 kg) were recruited to complete four simulated shooting tasks with additional "motor" challenge (180° turn, gait, weighted, and unweighted landing) and with and without a "cognitive" decision-making challenge requiring response selection and inhibition to both auditory and visual stimuli, totaling eight multi-task cognitive motor shooting conditions. The current study was approved by the university's Institutional Review Board. Task initiation (seconds), task completion (seconds), and number of misses were calculated to determine marksmanship efficiency and accuracy. For each task, a multivariate repeated-measures analysis of variance (ANOVA) was conducted for the combined dependent variables. If the overall multivariate repeated-measures ANOVA was significant, follow-up univariate ANOVAs were conducted for each dependent variable. Alpha was set at $\alpha = 0.05$ for all analyses.

Results:

Task initiation increased for the cognitive condition for the 180° turn (4.29 ± 1.22 seconds baseline, 5.09 ± 1.39 seconds cognitive; $P < .05$), gait (2.76 ± .60 seconds baseline, 3.93 ± .62 seconds cognitive; $P < .05$), unweighted (1.27 ± .57 seconds baseline, 3.39 ± .63 seconds cognitive; $P < .05$), and weighted landing (1.46 ± .72 seconds baseline, 3.35 ± .60 seconds cognitive; $P < .05$). Task completion time increased for the cognitive condition for the 180° turn (3.48 ± 1.53 seconds baseline, 4.85 ± 1.24 seconds cognitive; $P < .05$), gait (7.84 ± 2.07 seconds baseline, 9.23 ± 1.76 seconds cognitive; $P < .05$), unweighted (5.98 ± 1.55 seconds baseline, 7.45 ± 1.51 seconds cognitive; $P < .05$), and weighted landing (6.09 ± 1.42 seconds baseline, 7.25 ± 1.79 seconds cognitive; $P < .05$). There were no statistically significant differences in the number of misses for any of the tasks between conditions ($P > .05$).

Conclusions:

The addition of a cognitive load increased both task initiation and task completion times during cognitive motor simulated shooting. Adding cognitive loads to tactical performance tasks can result in CMi and negatively impact tactical performance. Thus, consideration for additional cognitive challenges into training may be warranted to reduce the potential CMi effect on tactical performance.

INTRODUCTION

Tactical (military and law enforcement personnel) roles often require managing intensive cognitive and physical stress. Physical skills such as rifle negotiation, jumping, and running across uneven terrain are commonly performed with cognitive loads such as rapid decision-making, visual-spatial processing, and team communication.[1] These cognitive challenges during intensive physical skills can reduce tactical performance and potentially contribute to tactical decision or physical errors, or even injury.[2] However, most tactical performance assessments are completed in isolation (i.e., shooting at a target, running an obstacle course, or completing a cognitive assessment) and rarely quantify the interaction of physical and cognitive challenges on tactical performance.

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Opinions, interpretations, conclusions, and recommendations presented here are those of the author and are not necessarily endorsed by the Department of Defense.

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Complex tactical situations require an individual to perform multiple motor and cognitive tasks simultaneously (multi-task) or alternate (task switching) between tasks for a given goal.[1,3] However, an individual has limited attentional capacity to perform both cognitive decision-making and plan complex motor skills,[4,5] potentially disrupting performance in either of them—a phenomenon referred to as cognitive motor interference (CMi).[6,7] Interference is due to an individual's limited ability to simultaneously cognitively process information and execute motor skills.[7–9] Reductions in performance from CMi are commonly described by the cognitive load theory subcomponents: the central bottleneck, capacity, and cross talk theories,[10] which represent various methods in which an individual may prioritize, organize, store, and act on information.[11] Experimental designs commonly target different cognitive load subcomponents (i.e., such as working memory, decision-making, and memory) to impose CMi by utilizing arithmetic problem-solving, choice-reaction tasks, or visual/verbal memory tasks while simultaneously performing a motor task.[12] However, concurrently assessed motor skills are typically static balance or straight-line walking, which may not simulate tactical occupational stressors.

A classic paradigm that can be used to induce CMi is the Stroop test.[13] The Stroop test assesses an individual's discrimination and decision-making capability through congruent and incongruent cognitive challenges and is commonly used simultaneously while performing motor tasks to assess CMi effects.[14–16] However, typical CMi assessments like the Stroop test do not incorporate a tactical performance component. There is a need for tactical modifications to increase ecological validity and occupational relevance.[12] Laboratory assessments have evaluated balance, gait, reaction time, shooting accuracy, and shooting decision errors[17]—all essential skills related to tactical occupational duties, but rarely in an integrated fashion that would better simulate in the field demands.[12,18] Therefore, the purpose of this study was to (1) develop four multi-task cognitive motor shooting paradigms for tactical athletes and (2) examine the influence of CMi on each task in healthy Reserve Officers' Training Corps (ROTC) cadets through both cognitive (task initiation and task completion times) and motor performance (shot accuracy) changes.[12] We hypothesized that under the cognitive challenge, shooting accuracy would diminish and time to start and complete the motor task would increase for all tasks (both indicating worse performance).

METHODS

Participants

Thirty-two students from XXXXX University's ROTC Army branch (24 male and 8 female; 20.5 ± 1.2 years, 175.0 ± 10.6 cm, and 78.0 ± 13.9 kg) volunteered to participate in this study. To be included in the study, participants had to be 18 years or older and participate in at least 1-hour of formal marksmanship training a month (2.7 ± 2.5 hours). Exclusion criteria consisted of individuals with any prior lower extremity surgery, any injury within the last 12 months, a neuromuscular deficiency that affected the upper or lower body coordination or balance, and color blindness. The current study was approved by the university's Institutional Review Board.

To determine differences in shooting accuracy between baseline (motor and shooting task) and CMi (motor and shooting task with cognitive challenge), an indoor simulated shooting system, Laser Ammo (Smokeless Range; Great Neck, NY, USA) was used. The shooting simulator projected numbers 1 to 9 in red, yellow, green, and blue colors onto an 80'' × 60'' EPSON screen as the intended targets. The Laser Ammo Smokeless Range software permits customized target location as well as number of shots needed to clear the target. For this study, the number of shots needed to clear one target was set to one, meaning one successful shot to a target would remove it from the projector screen. The Smokeless Range software was calibrated to the projector screen based on manufacturer's guidelines. A replica AR-15 rifle (KWA LM4 RIS; Great Neck, NY, USA) embedded with a battery-powered laser and biomethane cartridge was used to simulate ammunition and recoil. The laser was only displayed on the projector screen following a shot as a red dot marking where the shot hit. Participants could adjust the length of the stock and iron sights to fit their comfort.

Procedures

Participants were asked to complete a randomized series of four occupational specific rifle shooting tasks (Fig. 1A–C). Before each task, participants were required to complete two practice attempts and were given additional trials if needed for task familiarization. Three trials of each task were performed at baseline (without cognitive load) followed by three trials performed with cognitive load. Task initiation (time to first rifle shot [second]), task completion (time from first to last rifle shot [second]), and the number of missed targets (accuracy) were recorded for each trial.

Baseline and Cognitive Load Conditions

At baseline for all shooting tasks (180° turn, forward drop landing weighted and unweighted, or gait), six targets appeared on the projector screen organized horizontally in random order for color and number (Fig. 2A). Participants were asked to clear the targets from left to right as quickly and as accurately as possible. For the cognitive condition, there were six targets scattered across the shooting screen with one indicator target at the bottom (Fig. 2B). The most inferior number (number 2 in the example figure) was considered the indicator number and cue for the initial shot. This indicator was always presented in the center bottom of the screen for all trials. An auditory beep stimulus at the beginning of the

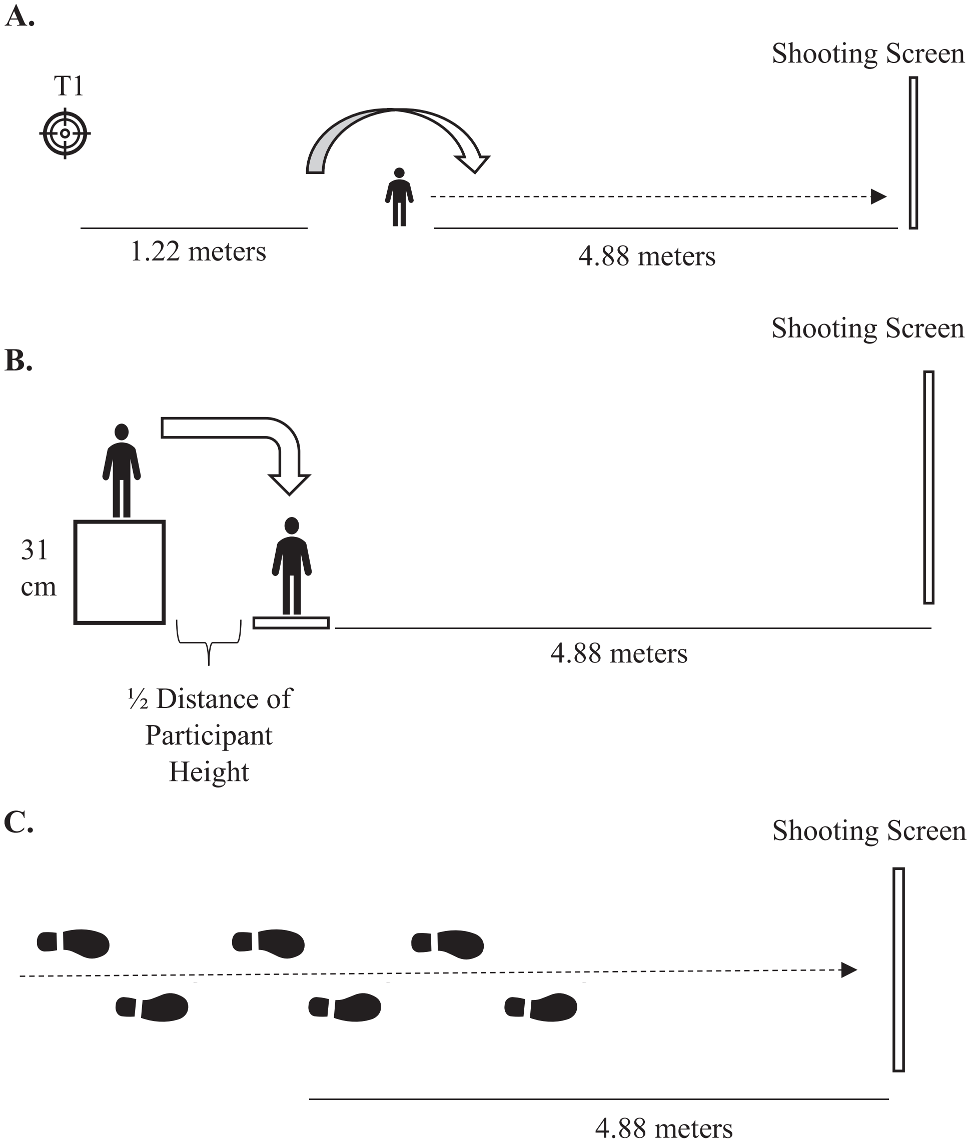

FIGURE 1. Shooting task schematics. (A) 180° turn task schematic. T1 represents an electronic target that the participants began facing in ready-to-shoot position. After the initial auditory stimulus, T1 was shot and participants immediately performed a 180° turn to face the shooting screen. (B) Forward drop landing task schematic. Participants stood on a 31-cm box. Following the task initiation auditory stimulus, participants acquired three targets. Participants then performed a forward drop landing. After landing, the remaining three targets would be acquired to complete the task. (C) Gait task schematic. Participants began facing the shooting screen. After the task initiation auditory stimulus, participants stepped forward twice toward the shooting screen, shot two targets, and then stepped two more steps forward. This sequence was repeated three times (i.e., six total steps) or until all targets were successfully eliminated.

task would indicate when the participant could begin shooting. A second auditory stimulus approximately 0.5 seconds later (“breaking glass” or “buzzer”) indicated what order the six scattered targets were to be acquired. Participants were instructed to begin with the same “number” as the indicator if they heard the “breaking glass” sound and begin with the same “color” target as the indicator number if they heard the “buzzer” sound. After hitting a target that corresponded to the indicator, participants would alternate shooting between the indicator color and indicator number until the six targets above the indicator were cleared (i.e., for buzzer: blue 1, green 2, blue 4, red 2, and so forth in the example figure). The task ended when all the targets on the screen were acquired. The cognitive motor task consisted of shooting performance (accuracy; i.e., shooting errors), during simultaneous movement (180° turn, forward drop landing weighted and unweighted, or gait), and with cognitive load (attending to auditory stimulus and sequencing decision). The cognitive interference effect was quantified by task initiation time and time from the first shot to task completion.

The cognitive load was designed to engage participants in visuospatial search, response inhibition, and rapid reactive decision-making processes. The initial central processing required attending to the auditory stimulus (cognitive task 1),

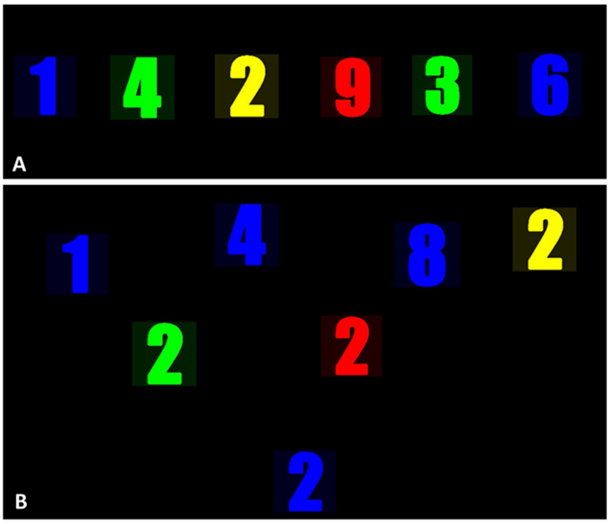

FIGURE 2. Baseline and cognitive conditions. In the print version the color of the numbers will not be apparent.

followed by sequentially processing the visual target stimulus of the indicator number (cognitive task 2). The rifle navigation (accuracy) was the primary motor skill of interest, which was layered with cognitive challenge and coupled with a secondary motor skill (180° turn, forward drop landing weighted and unweighted, and gait). Employing a task with multiple motor components better simulates occupational requirements that entail both environmental navigation and rifle manipulation. Additionally, coupling visual search with auditory stimuli required participants to continuously process target position and order throughout the task duration, resulting in not only an initial decision-making challenge but requiring working memory during the entire task as well.

180° Turn

The 180° turn task schematic can be found in Figure 1A and Supplementary Videos S1 and S2. The 180° turn was designed to challenge rapid rotation and immediate target acquisition. An electronic target (T1) was positioned 180° from the projector screen of the intended targets. The participant started by facing T1 in a ready-to-shoot position, with their nondominant foot within a square 4.88 m from the shooting screen. The shooting software provided a stimulus by the sound of a beep tone in which the individual would first acquire T1 and then perform a 180° turn to the shooting screen for the remaining targets. Participants then completed the baseline and cognitive conditions as described previously.

Forward Drop Landing (Weighted and Unweighted)

The forward drop landing resembles deploying from a vehicle or dropping from an obstacle in the field. Participants stand on a box 31 cm in height and drop onto landing indicators (squares) located one-half the participant's height in front of the box (Fig. 1B and Supplementary Videos S3-S6). The first three targets were acquired while on top of the box before the forward drop movement, and upon landing the final three targets were acquired. The procedures were performed for the baseline and under cognitive constraints. After six trials, the participants repeated the procedure with the addition of a weighted vest (35% of bodyweight; Rogue, Columbus, Ohio, USA) used to simulate the rucksack load that soldiers may wear during military duty.[19] The weight in the vest was evenly distributed throughout the vest. The weighted forward drop landing was always performed following the unweighted task. Participants completed the baseline and cognitive conditions as described previously.

Gait

The gait task aimed to assess movement with shooting interruption and added target acquisition during movement. Participants began facing the projector screen in a ready-to-shoot position at a standardized starting position to complete six steps with the second set of steps being 4.88 m from the projector. At the sound of the beep tone, they took two steps forward and acquired two targets, followed by two additional steps and two more targets (Fig. 1C and Supplementary Videos S7 and S8). The pattern was repeated until all six targets were cleared from the screen successfully for both baseline and cognitive load conditions.

Statistical Analysis

For each task, a multivariate repeated-measures analysis of variance (ANOVA) was conducted for the combined dependent variables (task initiation time, task completion time, and misses) with the within-subject factor condition (baseline and cognitive). If the overall multivariate repeated-measures ANOVA was significant for the main effect of condition, follow-up univariate ANOVAs were conducted for each dependent variable. The α level was set at 0.05. Cohen's effect sizes (d) were calculated between each condition and interpreted as small ($d = 0.20$), medium ($d = 0.50$), and large ($d = 0.80$) effects.[20] Multi-task cost was calculated as the percentage of change for each variable from the baseline to the cognitive condition for each task ([{baseline − cognitive}/baseline] × 100%). An increase in multi-task cost (positive numerical value) is associated with slower or decreased performance under the cognitive condition than at baseline, whereas a decrease in multi-task cost (negative numerical value) implies faster or improved performance during the cognitive condition.

RESULTS

Table I contains the descriptive statistics, effect sizes, and multi-task cost for each task and dependent variable by condition. The multivariate repeated-measures ANOVA conducted for the combined dependent variables were significant for all tasks (Supplemental Materials Table S1). Follow-up univariate ANOVAs were significant for initiation time

TABLE I. Mean and Standard Deviation for Time to Shoot, Complete Task, and Number of Misses per Task at Baseline and during Cognitive Challenge

Task		Baseline (Mean ± SD)	Cognitive (Mean ± SD)	Multi-task cost[a] (% mean; range)	Effect size
180	Initiation time (seconds)	4.3 ± 1.2	5.19 ± 1.4*	21.56; −23.10; 76.53	0.60
	First shot to task completion (seconds)	3.5 ± 1.5	4.9 ± 1.2*	54.89; −19.55, 174.13	0.98
	Misses (count)	0.4 ± 0.7	0.4 ± 0.6	2.73; −100, 400	0.01
Gait	Initiation time (seconds)	2.8 ± 0.6	3.9 ± 0.6*	47.06; −21.67; 138.72	1.89
	First shot to task completion (seconds)	7.8 ± 2.1	9.2 ± 1.8*	16.96; −24.99; 39.34	0.72
	Misses (count)	0.6 ± 0.6	0.4 ± 0.7	−32.77; −100, 100	0.29
Landing	Initiation time (seconds)	1.3 ± .6	3.4 ± .6*	211.04; 30.77, 569.46	3.49
	First shot to task completion (seconds)	6.0 ± 1.6	7.5 ± 1.5*	27.39; −0.89; 86.04	0.94
	Misses (count)	0.6 ± 0.6	0.7 ± 0.7	1.00; −100, 300	0.12
Weighted landing	Initiation time (seconds)	1.5 ± 0.7	3.4 ± 0.6*	166.71; −3.11, 386.77	2.82
	First shot to task completion (seconds)	6.1 ± 1.4	7.3 ± 1.8*	21.27; −38.53, 72.37	0.72
	Misses (count)	0.5 ± 0.9	0.7 ± 0.7	22.95; −100; 300	0.24

*Indicates statistical significance ($P < .05$).

[a] An increase in multi-task cost (positive numerical value) is associated with slower performance under the cognitive condition. A decrease in multi-task cost (negative numerical value) implies faster performance or better accuracy during the cognitive condition.

and completion time for all tasks (Table I for descriptive statistics of all dependent variables by condition and Supplemental Materials Table S2 for individual ANOVA results). In summary, cognitive load slowed the initiation time for all tasks (180° turn [mean difference between conditions (MD) = 0.8 second], gait [MD = 1.17 second], forward drop landing [MD = 2.12 second], and weighted forward landing [MD = 1.89 second]). For completion time, the cognitive load increased time to completion for all tasks (180° turn [MD = 1.37 second], gait [MD = 1.39 second], forward drop landing [MD = 1.47 second], and weighted forward landing [MD = 1.16 second]). Shooting accuracy indicated by target misses was not significant between conditions for any shooting task ($P > .05$).

DISCUSSION

This study assessed CMi effects via multi-task cost on shooting accuracy, task initiation, and task completion times during four simulated shooting paradigms. Our results indicate that cognitive load significantly increased the initiation and completion times for all tasks supporting our hypothesis. However, contrary to our hypothesis, the cognitive load did not affect the accuracy of any task. Task initiation had the greatest multi-task cost for all tasks except the 180° turn. Overall, our results support the limited capacity theory of attention,[10] where cognitive load delayed task initiation and prolonged motor performance.[21,22]

CMi Effects

The CMi effect was captured by the increase in task initiation and task completion times when the motor skill was performed with additional decision-making, working memory, and response selection and inhibition constraints.[6] Previous studies have attempted to induce CMi with shooting tasks using arithmetic,[23] memorization, and target decision (Shoot/Do not Shoot) paradigms.[12,24] The drawback of arithmetic or memorization paradigms is the emphasis on working memory in isolation without online decision-making[15] and a lack of occupational translation. Our methodology aimed to improve occupational translation by employing multiple cognitive components during simulated move and shoot paradigms that required situational decision-making, integration of both auditory and visual stimuli, and response inhibition common to tactical situations.

The forward drop landing tasks (unweighted and weighted) and gait were designed as motor interruption paradigms where the ROTC member first acquired targets, executed a separate motor skill (land or step), and then resolved remaining targets, and repeated until task completion. These three paradigms resulted in a greater multi-task cost for task initiation (211% unweighted, 166% weighted, and 47% gait) than task completion time (27% unweighted, 21% weighted, and 17% gait). Delayed task completion for both forward drop landing and gait cognitive motor paradigms suggest that cognitive demand of target sequencing had an effect throughout the task; however, task initiation was affected to a far greater degree (effect size for initiation: 1.89 gait, 3.49 landing vs. completion: 0.72 gait, 0.94 landing).

While completing the 180° turn, there was a greater CMi effect for completion (55% multi-task cost) relative to initiation time (22% multi-task cost), indicating that most of the cognitive processing occurred while properly sequencing target order “after” the first shot was fired—the opposite of the landing and gait tasks. This difference is likely because the 180° turn is the only paradigm in which participants began and acquired the first target facing away from the projector screen, giving time to process the auditory target acquisition stimuli during the turn before taking the first shot. In all other paradigms, the first motor task was to shoot at projector targets and then complete the additional motor task (forward drop or gait), whereas for the 180° turn task, the first motor task was the turn followed by shooting at the projector targets. No differences were seen between conditions for all cognitive motor tasks for target accuracy; therefore, cadets likely prioritized shooting accuracy over speed for all paradigms.

Cognitive Load Theory

Of the three cognitive load theories (capacity, bottleneck, and cross talk), the capacity theory recognizes that with each additional cognitive load (i.e., summation of challenges) the central nervous system has less capacity to prioritize the motor output and redistribute attention.[5,10] In the current study, an auditory stimuli (cognitive task 1) dictated the order in which targets were sequenced and then the indicator target (cognitive task 2) dictated visual attention to either color or number for target sequence. Thus, CMi effects could be secondary to limited capacity to process temporally overlapping cognitive loads while performing the motor task, resulting in delayed shot initiation and completion.[5,7] The slowing or reduced performance of both task initiation and completion aligns with the capacity theory of attention, suggesting that cognitive task 1 (second auditory stimulus) and cognitive task 2 (indicator target) were processed in parallel while participants planned target acquisition. The first cognitive task required participants to engage in short-term memory through the task duration to remember the order in which targets were sequenced, as well as engage in working memory to plan future target sequences. For tactical operations, efficient integration of environmental sensory stimuli (auditory and visual) and concurrent cognitive decision-making is paramount for efficient movement. By slowing both initiation and completion times of the cognitive motor shooting paradigms, the cognitive load was challenging enough to slow the overall motor performance however did not hinder the shooting accuracy. Since target shooting is highly practiced in ROTC members, it is likely that participants redistributed their cognitive capacity to the unfamiliar tasks of the motor and cognitive demands.

The central bottleneck theory speculates that central organization for performing multiple cognitive tasks occurs in sequence when stimuli are presented almost simultaneously,[10] resulting in delays in processing the second stimulus and not the first.[10,21] Our paradigm was not experimentally designed in a fashion to have the multi-task cost be due to limitations in bottleneck theory processing, as the stimuli were presented and acted upon sequentially and not simultaneously.[7,25] The resulting performance deficits in both task initiation and task completion time further support limited capacity as the likely driving factor. Bottleneck theory limitations would primarily present as task completion cost, not initiation cost. The cross talk model is also not represented in our cognitive paradigm because it did not require backward processing of a second cognitive stimulus before the complete processing of the first stimulus (i.e., predictive processing).[26] Therefore, due to the nature of the cognitive stimuli timing, the CMi effects from this experimental design are likely attributed primarily to the capacity theory of attention.

Cognitive Load Effects on Performance

We inferred that our participants chose to prioritize shot accuracy over speed as CMi effects were found for task time and not accuracy. Raisbeck et al.[24] examined the effects of a shoot-reload-shoot task on marksmanship and upper extremity kinematics of law enforcement shooters.[24] They utilized a dual-task choice-reaction paradigm with auditory tones. Participants were to report pitch tone (extraneous focus) or trigger finger position (skill focused) based on the stimuli they heard simultaneously while shooting at targets, finding that expert shooters (5+ years’ experience with advanced firearm training) were able to maintain high performance accuracy despite the cognitive load, and the accuracy of novice shooters (law enforcement recruits) declined under both dual-task conditions.[24] Our study used participants of similar marksmanship experience level to Raisbeck et al.’s[24] novice participants group. However, in contrast to their results, we did not find a decline in shooting accuracy with any task, likely because in our study accuracy was defined as binary hit\no hit with increased error allowance, whereas Raisbeck et al. used distance from the target center. Our participants were instructed to maximize speed and accuracy, while Raisbeck et al.’s participants were told to focus on accuracy.[24] Further, although both studies used cognitive loads with auditory stimuli, ours was employed to initiate a task and sequence target acquisition order at various spatial locations, whereas Raisbeck et al.’s[24] study required continuous verbal report of the stimulus throughout task duration with a single spatial location, likely challenging different attention process.

Cognitive and aerobic fatigue has also been shown to degrade shooting performance in tactical athletes.[27,28] By adding aerobic fatigue, Davidson et al.[27] observed decreased angular velocity of the body, rifle, and target acquisition accuracy during a 180° turn task.[27] Tenan et al.[19] also investigated marksmanship accuracy following aerobic activity with and without a rucksack and found decreased shooting accuracy with aerobic fatigue; however, their methodology did not incorporate a cognitive load. Although the participants in the studies by Davidson et al.[27] and Tenan et al.[19] were similar to ours, we did not employ a fatiguing component limiting comparison. Interestingly, the 180° turn task in the current study and Davidson et al.'s[27] study aimed to evaluate shooting accuracy by means of different constructs, target accuracy, and stability on target. Davidson et al.[27] found the greatest performance deficit in initial time to stabilize on target while physically fatigued, whereas our study results suggest that the greatest multi-task cost deficits occur during task completion time with the addition of cognitive load. Therefore, physical fatigue may impair an individual's fine motor ability to stabilize a rifle, and cognitive load may impair the overall speed of task performance. Furthermore, Head and colleagues[28] measured response inhibition[29] and mental fatigue before a shooting task in expert performers. They found that the overall ability to inhibit motor responses to shoot based on visual stimuli was reduced when cognitively fatigued.[28] Thus, cognitive fatigue may more directly impair decision accuracy while direct cognitive load may delay performance but maintain accuracy. However, it is important to note that the participants in the study by Head et al.[28] were infantry soldiers whereas our participants were ROTC members. The ROTC participants are in the novice stages of skill acquisition relative to active infantry; thus, expertise could contribute to the CMi effect of decreased motor speed as a compensation for increased attention to cognitive task.[30]

Limitations and Future Research

Simulation of military-specific tasks/constructs is difficult to replicate in a controlled laboratory, and we developed the motor tasks to simulate typical field challenges like turning to acquire a target, jumping from a height, or maintaining target acquisition while moving. However, other factors like aerobic and/or cognitive fatigue and load carriage may also impact translation of our results to occupational reality. It is important to note that the tactical utility of weapons such as a rifle is for protected threats. In real-life scenarios, various confounding factors such as "target" size, spatial location, previous interactions/knowledge, and situational anxiety can impact both cognitive and physical performance that were beyond the scope of our investigation.

Future research should consider the combination of cognitive loading with aerobic capacity during marksmanship tasks to better simulate the duty requirements of ROTC or active military participants. Possible implications of adding a cardiorespiratory component would better simulate duty demands and may result in decreased target acquisition accuracy. Prior work demonstrates that elevated physical or cognitive stress or added cognitive demand can contribute to altered motor control strategies; thus, future studies should consider examining tactical task-specific biomechanics or movement patterns associated with CMi.[12,31]

CONCLUSION

Our findings suggest that the addition of a cognitive load delays both task initiation and task completion compared to baseline performance in ROTC cadets. All cognitive motor paradigms exhibited performance deficits in both task initiation and task completion, and the multi-task cost was found to be the greatest for task completion for most paradigms. In the current study, cognitive load had no effect on shooting accuracy; however, delayed shooting performance may have negative occupational relevance in tactical athletes. Scarce research integrating cognitive motor (dual movement and shooting) paradigms has been conducted. The current study provides insight to meaningful contributions for understanding CMi on tactical performance in healthy ROTC cadets.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY

Data will be made available on request.

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Neural Correlates of Knee Extension and Flexion Force Control: A Kinetically-Instrumented Neuroimaging Study

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Background: The regulation of muscle force is a vital aspect of sensorimotor control, requiring intricate neural processes. While neural activity associated with upper extremity force control has been documented, extrapolation to lower extremity force control is limited. Knowledge of how the brain regulates force control for knee extension and flexion may provide insights as to how pathology or intervention impacts central control of movement.

Objectives: To develop and implement a neuroimaging-compatible force control paradigm for knee extension and flexion.

Methods: A magnetic resonance imaging (MRI) safe load cell was used in a customized apparatus to quantify force (N) during neuroimaging (Philips Achieva 3T). Visual biofeedback and a target sinusoidal wave that fluctuated between 0 and 5 N was provided *via* an MRI-safe virtual reality display. Fifteen right leg dominant female participants (age = 20.3 ± 1.2 years, height = 1.6 ± 0.10 m, weight = 64.8 ± 6.4 kg) completed a knee extension and flexion force matching paradigm during neuroimaging. The force-matching error was calculated based on the difference between the visual target and actual performance. Brain activation patterns were calculated and associated with force-matching error and the difference between quadriceps and hamstring force-matching tasks were evaluated with a mixed-effects model ($z > 3.1$, $p < 0.05$, cluster corrected).

Results: Knee extension and flexion force-matching tasks increased BOLD signal among cerebellar, sensorimotor, and visual-processing regions. Increased knee extension force-matching error was associated with greater right frontal cortex and left parietal cortex activity and reduced left lingual gyrus activity. Increased knee flexion force-matching error was associated with reduced left frontal and right parietal region activity. Knee flexion force control increased bilateral premotor, secondary somatosensory, and right anterior temporal activity relative to knee extension. The force-matching error was not statistically different between tasks.

Conclusion: Lower extremity force control results in unique activation strategies depending on if engaging knee extension or flexion, with knee flexion requiring increased neural activity (BOLD signal) for the same level of force and no difference in relative error. These fMRI compatible force control paradigms allow precise behavioral quantification of motor performance concurrent with brain activity for lower extremity sensorimotor function and may serve as a method for future research to investigate how pathologies affect lower extremity neuromuscular function.

Keywords: force sense, functional magnetic resonance imaging, quadriceps, hamstring, lower extremity, sensorimotor control

INTRODUCTION

Determining how the central nervous system regulates force is vital for understanding the neural control of biomechanical action. The integration of neuroimaging techniques with simultaneous biomechanical recording has allowed for concurrent capture of joint position and force with neural activity (Liu et al., 2000; Ward et al., 2008; Naufel et al., 2019). However, the majority of investigations have focused on the upper extremity and the primary motor cortex to elucidate the relationship between muscle force and neural activity (Georgopoulos et al., 1992; Ashe, 1997; Ward et al., 2008). Studies examining neural activity associated with lower extremity motor control have not quantified motor performance beyond movement timing (Luft et al., 2002; Kapreli et al., 2007; Grooms et al., 2019) or have been limited to electroencephalography paradigms, which provide excellent temporal resolution but lack the spatial resolution of functional magnetic resonance imaging (fMRI; Poortvliet et al., 2015). Prior work specific to fMRI has examined neural correlates of quadriceps force regulation in patients with knee osteoarthritis (Shanahan et al., 2015) using an isometric, force-matching paradigm, finding an anterior shift of the knee representation within the primary motor cortex in those with knee osteoarthritis. Various research groups have also employed cycle ergometers (Mehta et al., 2009), gait simulations (Jaeger et al., 2016), or leg press (Grooms et al., 2019) movement paradigms to quantify lower extremity movement with brain imaging. While these paradigms demonstrated success to activate the sensorimotor network and do so reliably, many fMRI lower extremity paradigms are metronome-paced and do not attempt to quantify motor performance (Luft et al., 2002; Kapreli et al., 2006). Therefore, the development of lower extremity paradigms that can concurrently measure neural activity *via* fMRI and biomechanical performance may offer more precise methods to investigate central strategies for force regulation, with implications for pathologies affecting sensorimotor control of the lower extremity (Hortobágyi et al., 2004; Ward et al., 2019).

Prior biomechanically isolated work has demonstrated force control deficits in a variety of orthopedic and neurological pathologies of the lower extremity (Hortobágyi et al., 2004; Docherty and Arnold, 2008; Telianidis et al., 2014) but a clear brain-behavioral interaction has yet to be established (Baumeister et al., 2011). Further, no study to our knowledge has attempted to contrast how the brain regulates force when engaged in knee extension (quadriceps-dominant activity) relative to knee flexion (hamstring-dominant activity). Unique deficits in quadriceps and hamstring function have been reported in a variety of orthopedic and neurological conditions, and the restoration of respective muscle and joint function is vital for the recovery and resumption of activities of daily living, adequate mobility, and mitigating the development of chronic conditions such as osteoarthritis (Manini et al., 2007; Manini and Clark, 2012; Tourville et al., 2014; Arhos et al., 2020). As lower extremity pathologies have been found to manipulate both quadriceps and hamstring muscle activity, timing, and function, determining the neural mechanisms for each is vital to better understand how lower extremity motor control is centrally governed (Telianidis et al., 2014; Abourezk et al., 2017; Blackburn et al., 2017; Hohmann et al., 2019). Isolating neural correlates of quadriceps and hamstring force generation and control may highlight central mechanisms for function following injury and permit the development of novel therapies that restore function. Therefore, our purpose was to: (1) develop and test a lower extremity neuroimaging paradigm for knee extension and flexion force control to better understand how the nervous system regulates lower extremity forces; and (2) determine differences between knee extension and flexion neural activity during a force control task.

MATERIALS AND METHODS

Participants

This study was approved by Ohio University's Institutional Review Board and all participants signed the informed consent document. We included female recreational athletes (at least 3 h of moderate to vigorous exercise per week, including 1 h of running, cutting, pivoting, or decelerating every week) aged 18–30 years. This population was selected for the following investigative work as they are at unique increased risk for noncontact knee injuries, whereby during athletics, exercise, or activities of daily living that require rapid movement, sensorimotor control of the knee is compromised, resulting in positions that put excessive strain on the joint ligaments (Beynnon et al., 2014; Montalvo et al., 2019).

A sample size estimate was calculated based on effects reported by Shanahan et al. (2015) for the correlation to force-error, and Trinastic et al. (2010) for the contrast between movement conditions. For the force-error correlate analysis, an $r = 0.83$ was reported for the relationship between error and motor cortex peak activation location (Shanahan et al., 2015). A sample size estimate was calculated based on $r = 0.83$, $\alpha = 0.05$, and $1 - \beta = 0.8$ indicating a total sample size of 8 is required. For the motor condition analysis, the effect size between ankle plantarflexion and dorsiflexion was calculated as $d = 1.42$ (Trinastic et al., 2010). A sample size estimate was calculated based on $d = 1.42$, $\alpha = 0.05$, and $1 - \beta = 0.8$ resulting in needing a sample size of 7. Additionally, we modeled our study on previous literature of Newton et al. (2008) and Mehta et al. (2009) regarding paradigm development who enrolled 9 and 10 participants, respectively. Therefore, enrolling 15 participants provided adequate power for the proposed study. We enrolled 15 participants (15 F; age = 20.3 ± 1.2 years, height = 1.6 ± 0.10 m, and weight = 64.8 ± 6.4 kg) in this study. All participants were right leg dominant and met the exercise requirement criteria, as determined by the Marx Activity Rating Scale (**Table 1**; Marx et al., 2001).

We excluded participants who were contraindicated for fMRI (e.g., pregnancy, implanted metal devices, claustrophobia, and any other criteria as determined by the MRI operator), have a visual impairment, have a history of seizures or epilepsy, or have a history of surgery on the back, hip, leg, knee, etc. Other screening criteria included: primary sport, leg dominance, previous leg injury, medical history anxiety disorder, ADHD, depression, diabetic neuropathy, concussion or traumatic brain injury, cerebral palsy, balance disorder, vertigo, Parkinson's disease, multiple sclerosis, substance abuse or dependence, heart disease/defect, and prescription medication use within the 24 h before data collection. No individuals reported any of the previous medical conditions or consumed any medications impacting the data collection.

fMRI Data Collection

Data collection was completed in a single neuroimaging session (∼45 min including set-up, instruction, and scan time). During imaging, all participants wore standardized shorts and socks without shoes to reduce the possibility of altered skin tactile feedback. Participants also wore a splint to lock their right (dominant leg) ankle at neutral (∼90°) to minimize ankle movement throughout the scan. Headphone and hearing protection was provided for subject comfort and safety and to facilitate communication during scanning. While lying supine in the fMRI scanner, participants were strapped down to the table with four straps, one across the thighs at the mid-point between the greater trochanter and knee joint line, one across the hips at the anterior superior iliac spines, and two across the chest, from each shoulder to the pelvis at the iliac crest. The knee was fixed near terminal extension between 10° and 15° of flexion. Participants were also fitted with customized padding to reduce head motion. This padding was high-density MRI-safe foam that was inserted around the sides and top of the head to remove space between the skull and head coil. This was customized based on skull size, with those with larger skulls requiring less padding and smaller skulls requiring more padding.

TABLE 1 | Demographics and force error.

Data	Mean ± SD
Age (years)	20.3 ± 1.2
Height (m)	1.6 ± 0.10
Weight (kg)	64.8 ± 6.4
Activity level (Marx)	9.93 ± 5.50
Run	3.00 ± 0.85
Cut	2.07 ± 1.62
Decelerate	2.40 ± 1.64
Pivot	2.27 ± 1.49
Knee extension error (*N*)	1.068 ± 0.327
Knee flexion error (*N*)	0.999 ± 0.189

fMRI scans were collected with a 16-channel head coil. Before the functional data collection, a three-dimensional high-resolution T1-weighted image (repetition time (TR): 2,000 ms, echo time (TE): 4.58 ms, field of view: 256 × 256 mm; matrix: 256 × 256; slice thickness 1 mm, 176 slices, 8° flip-angle) was collected for image registration (∼8 min). fMRI collection parameters include 10 whole-brain gradient-echo-echo planar scans per block (four force-matching blocks, five rest blocks) acquired with a 3 s TR with anterior-posterior phase encoding and a 3.75 × 3.75 in-plane resolution, 5 mm slice thickness for 38 axial slices with a 35 ms TE, 90° flip angle, the field of view 240 mm and 64 × 64 matrix. Each functional force-matching run lasted 4 min and 30 s. fMRI measured regional brain activity during rest and motor control conditions, which were contrasted to isolate the regional brain activity to the isometric knee extension and flexion force-matching tasks.

The isometric force-matching motor task required the participant to either "kick up" or "press down" against a load cell (Biopac Systems Inc., TSD121B-MRI, 1,000 Hz sampling frequency) at the ankle (**Figure 1C**). Both knees rested upon a foam roller, while only the dominant, right leg was additionally strapped to a device against the load cell. Participants had to match their force output (visualized with biofeedback provided by MRI-safe virtual reality) with a sine wave that oscillated (1.2 Hz) from 0 to 5 N for 30 s with 30 s of rest for four total cycles, resulting in four force-matching blocks interspersed with five rest blocks of 30 s each (with the paradigm starting and ending with rest) for a total run time of 4 min and 30 s (**Figures 1A,B**). Standardized auditory cues informed participants when to begin and end force-matching. The force-matching error was calculated based on the difference between the visual target (sine wave) and actual performance (biofeedback). The force level for this study was low and we recruited a young active cohort to minimize the potential influence of fatigue; however, fatigue was monitored regularly and breaks were offered. No participants indicated fatigue or needed a break beyond the few minutes between scans.

Participants practiced the force-matching task for a full run with immediate examiner feedback if instructions were not

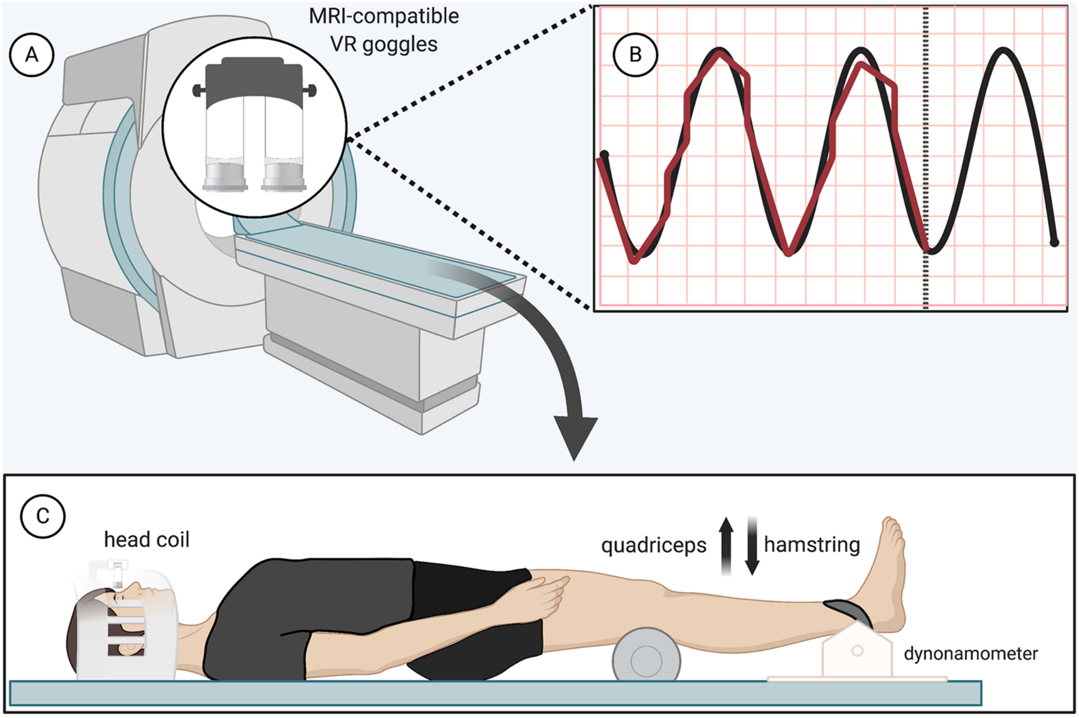

FIGURE 1 | Functional magnetic resonance imaging (fMRI) force-matching task—**(A)** magnetic resonance imaging (MRI)-compatible virtual reality display **(B)** black, Sinewave graph (0–5 N, 1.2 Hz); red, real-time display of participant force **(C)** load cell apparatus and patient position (participant restraints not pictured). Created with Biorender.

understood before completing the task during scanning. Also before data collection at the MRI, participants completed a mock MRI session where they familiarized themselves with the MRI environment, restraints to reduce head motion, and the lower extremity motor task. The participants were permitted to ask questions and practice the tasks with feedback from the experimenter. The practice session included three practice blocks (30 s each) of each force-matching task with examiner cueing to ensure the participant understood the task, followed by a complete run of each task with the same feedback and timing as during the actual MRI data collection session.

Error Calculation and Statistical Analysis

The force-matching error was recorded continuously throughout the force-matching tasks. For statistical analysis, error across the 30-s blocks was partitioned into 3-s intervals (the time interval for one sine wave). The first 3-s interval of each 30-s block was removed from the data analysis, as participants commonly required a few seconds to become acclimated to the task during the initiation of the movement block and thus, was shown to bias the overall average of the remaining nine intervals. The average error for each block was determined by the root mean square of the differential from target force to actual force on the remaining nine sets of 3-s intervals within each block, and the average error across the four blocks was computed for each participant for statistical analyses. Average knee extension and flexion force-matching error were compared with a paired samples *t*-test with an alpha set at 0.05.

fMRI Data and Statistical Analysis

The fMRI technique used in this study quantified the blood-oxygen-level-dependent (BOLD) signal *via* the hemodynamic response by contrasting the respective force-matching condition with interspersed rest conditions (Friston et al., 1995). We controlled for the additional sensory feedback of the strap across the shank by ensuring it was tightly pressed during both the rest and force-matching conditions, but the pressure of this tactile stimulus unavoidably changes with contraction and may thus contribute to the overall BOLD response. The BOLD response, quantified *via* fMRI collection and analysis, has been validated against direct neural recordings, demonstrating a very high correlation between blood flow and neural activity (Logothetis et al., 2001; Goense and Logothetis, 2008). The reliability of fMRI quantification of the BOLD signal is generally high and specific to knee movement and has high inter-session reliability (Newton et al., 2008; McGregor et al., 2012).

The fMRI statistical analyses were performed using the Oxford Centre for Functional MRI of the Brain Software Library (Smith et al., 2004; Jenkinson et al., 2012). Image analysis began with standard pre-statistic processing applied to individual data in the standardized FSL recommended order (Jenkinson et al., 2012), which included nonbrain removal, slice timing correction, standard motion correction, and realignment parameters (three rotations and three translations) as covariates to limit confounding effects of head movement and spatial smoothing at 6 mm before statistical analysis (Jenkinson et al., 2002). One participant was removed from the knee extension force-matching analysis due to excessive head motion ($>$0.5 mm) and two removed from the knee flexion force-matching analysis, resulting in $n = 14$ for knee extension, $n = 13$ for knee flexion, and $n = 13$ for comparison between knee extension and knee flexion. High-pass temporal filtering at 90 Hz and time-series statistical analyses were carried out using a linear model with local autocorrelation correction. Functional images were co-registered with the respective high-resolution T1 image and the standard Montreal Neurological Institute template 152 using linear image registration. This registration process allowed data from each participant to be spatially aligned on a standardized brain template for comparison.

The subject-level analysis of knee sensorimotor control relative to rest was completed using a z score greater than 3.1 and a (corrected) cluster significance threshold of $\alpha < 0.05$. The cluster correction for multiple comparisons uses a variant of the Gaussian random field theory to decrease type I error in the statistical parametric mapping of imaging data by evaluating the activation not only at each voxel but also at the surrounding voxel cluster (as it is unlikely that the voxel tested and surrounding voxels are active above the threshold due to chance; Poldrack et al., 2011). The paired contrast between each individual's quadriceps vs. hamstring force control neural activity was performed with group z statistic images set at a threshold of z scores of greater than 3.1 and a corrected cluster significance level of $\alpha < 0.05$. As this was a brain activity correlate identification study, the effect size (r-value) of the relationship between brain activity and behavior are not reported to avoid circularity (voxel selection and magnitude estimation on the same data) and a follow-up validation study is required to estimate effect size with the identified regions from this work (Kriegeskorte et al., 2009, 2010).

RESULTS

Regional brain activation is reported as contralateral [indicating activation on the opposite side of the task, or the left hemisphere, as the task was always completed with the right (dominant) lower extremity] or ipsilateral (being the same side as the task, or the right hemisphere; **Tables 2–4**). Regions of brain activity are reported that were identified in FSLeyes based on peak-voxel with the Harvard-Oxford Cortical and Subcortical Structural Atlas (Desikan et al., 2006), Juelich Histological Atlas (Eickhoff et al., 2006, 2007) and the Cerebellar Atlas in MNI152 space after normalization with FNIRT (Diedrichsen et al., 2009) and with FSL tool atlasquery (Jenkinson et al., 2012). The atlasquery function from FSL utilizes the averaged probability across all voxels in the cluster to identify probabilistic anatomy across the cluster ensuring reporting of peak voxel location and overall cluster spatial representation.

Both knee extension and flexion force-matching tasks elicited increased bilateral BOLD signal among cerebellar, sensorimotor, and visual-processing regions (**Figures 2**, **4**). Increased knee extension force-matching error was associated with increased BOLD signal within the ipsilateral frontal cortex and contralateral parietal cortex and decreased contralateral BOLD signal within the lingual gyrus and intracalcarine cortex (**Figure 3**). Increased knee flexion force-matching error was related to decreased contralateral frontal and ipsilateral parietal region activity (**Figure 5**). Knee flexion force control had increased bilateral premotor, secondary somatosensory, and right anterior temporal activity relative to knee extension force control (**Figure 6**). Force-matching error performance was not statistically different between the knee extension and flexion tasks (**Table 1**). Head motion during the knee extension task was: 0.28 ± 0.17 mm absolute motion and 0.11 ± 0.10 mm relative motion. Head motion during the knee flexion task was: 0.22 ± 0.13 mm absolute motion and 0.10 ± 0.09 mm relative motion.

DISCUSSION

Lower extremity force control results in unique neural activation strategies depending on if engaging the quadriceps for knee extension or the hamstrings for knee flexion, with knee flexion requiring more sensorimotor neural activity for the same level of force generation and relative error. This paradigm allows precise behavioral quantification of motor performance concurrent with brain activity for lower extremity sensorimotor function, which may serve as a method for future research to investigate how pathologies or interventions affect lower extremity neuromuscular function.

Neural Correlates of Knee Extension Force Control

Knee extension force-matching had a neural activation pattern similar to prior reports of lower extremity knee-focused and quadriceps-dominant movements, with activation across the cortical and subcortical sensorimotor network (Luft et al., 2002; Kapreli et al., 2007). Quadriceps force error was associated with increased activity in frontal and parietal regions and associated with decreased crossmodal (Calvert, 2001) region activity (intracalcarine cortex and lingual gyrus) along the border of the occipital and parietal cortex.

Increased activation of frontal regions with increased error could indicate force control is more complex for those with a higher force-matching error, as previous research has identified an association between increased frontal activity with increased task complexity error (Schubotz and von Cramon, 2002; Mehta et al., 2012; Dunst et al., 2014). It is also possible that as a participant began to perform poorly and visualize their error, they engaged in more extensive or rapid recalibration to attempt to remain on target, requiring greater levels of attentive neural processing (Tracy, 2007; Tracy et al., 2007; Baweja et al., 2009). However, despite increased neural activity among attention and executive function-related brain regions, the relative error was higher which could also be simply a byproduct of more actively attending to their mismatched biofeedback and not secondary to employing a strategy to correct it (Tracy, 2007).

TABLE 2 | Regions of increased brain activity during the knee extension force-matching task.

Cluster index	Brain regions	Voxel count	*P*-value	Peak MNI voxel			*Z* stat-max
				x	*y*	*z*	
	Overall activation during knee extension force-matching						
6	B Precentral gyrus, Postcentral gyrus, Superior parietal lobule, Lateral occipital cortex	17,662	<0.00001	0	−34	56	10.1
5	B Precentral gyrus, Corticospinal tract, R Thalamus	1,567	<0.00001	10	−16	4	4.99
4	Corticospinal tract, L Thalamus	1,137	<0.00001	−8	−18	16	5.57
3	Precentral Gyrus, Inferior frontal gyrus, Premotor cortex	375	0.000116	−56	0	38	7.22
2	R Cerebellum VIIIA, VIIB, IX	284	0.000882	32	−50	−48	4.79
1	L Cerebellum VIIB, VIIIA, VIIIB, IX	182	0.0113	−20	−70	−44	6.26
	Neural activity increase associated with knee extension force error						
3	L Postcentral gyrus, Superior parietal lobule	206	0.00598	−20	−40	76	4.89
2	R Frontal pole	142	0.0344	30	52	20	5.02
1	R Middle frontal gyrus	130	0.0489	46	12	40	4.24
	Neural activity decrease associated with knee extension force error						
1	Intracalcarine cortex, Lingual gyrus	161	0.0201	−14	−82	10	4.68

Regions of brain activity are reported that were identified in FSLeyes with the Harvard-Oxford cortical and subcortical structural atlas, Julich histological atlas, and the Cerebellar atlas in MNI152 space after normalization with FNIRT by peak voxel and with FSL tool atlasquery. B, bilateral; L, left; R, right.

TABLE 3 | Regions of increased brain activity during the knee flexion force-matching task.

Cluster index	Brain regions	Voxel count	*P*-value	Peak MNI voxel			*Z* stat-max
				x	*y*	*z*	
	Overall activation during knee flexion force-matching						
3	B Postcentral gyrus, Precentral gyrus, Superior parietal lobule, Lateral occipital cortex, Supplementary motor cortex, Cingulate gyrus	16,647	<0.00001	−42	−78	−8	11.3
2	B Precentral gyrus, Supramarginal gyrus, Lateral occipital cortex, Lingual gyrus, Occipital fusiform gyrus, Cerebellum Right I-V, VIIB, VIIIA, Left VIIB, VIIIA	12,626	<0.00001	24	−70	−56	10.3
1	R Frontal pole, Frontal orbital cortex	189	0.008	26	34	−22	4.91
	Neural activity decrease associated with knee flexion force error						
2	R Precuneus, Postcentral gyrus, Posterior cingulate gyrus, Superior parietal lobule	257	0.00138	6	−40	50	5.91
1	L Frontal pole, Superior frontal gyrus, Middle frontal gyrus	215	0.00402	−36	30	40	5.25

Regions of brain activity are reported that were identified in FSLeyes with the Harvard-Oxford cortical and subcortical structural atlas, Julich histological atlas, and the cerebellar atlas in MNI152 space after normalization with FNIRT by peak voxel and with FSL tool atlasquery. There was no significant increased neural activity associated with knee flexion error. B, bilateral; L, left; R, right.

TABLE 4 | Regions of difference between knee extension and flexion force-matching.

Cluster index	Brain regions	Voxel count	*P*-value	Peak MNI voxel			*Z* stat-max
				x	*y*	*z*	
	Increased neural activity knee flexion > knee extension force control						
6	L Precentral and Postcentral gyrus	741	<0.00001	−62	−8	42	5.99
5	L Middle temporal gyrus, Angular gyrus, Inferior parietal lobule	259	0.00112	−62	−52	16	5.19
4	R Temporal pole	245	0.0016	44	22	−34	5.55
3	R Superior temporal gyrus, Supramarginal gyrus, Middle temporal gyrus	239	0.00187	48	−38	2	5.16
2	L Supplementary motor cortex, Paracingulate gyrus	194	0.00619	−6	10	48	4.44
1	B Corticospinal tract, L Thalamus	134	0.0354	−4	−10	−6	4.17

Regions of brain activity are reported that were identified in FSLeyes with the Harvard-Oxford cortical and subcortical structural atlas, Julich histological atlas, and the cerebellar atlas in MNI152 space after normalization with FNIRT by peak voxel and with FSL tool atlasquery. B, bilateral; L, left; R, right.

By contrast, those with less force-matching error had increased crossmodal visual-spatial and somatosensory region processing (or increased error had decreased relative activity), which may be involved in aligning and maintaining visual feedback with force regulation from peripheral afferent signals to minimize discrepancy. Previous work within the upper extremity has identified the lingual gyrus and intracalcarine regions to respond to congruent visual and somatosensory feedback (crossmodal; Driver and Spence, 1998; Macaluso et al., 2000). Further, extrastriate activity in the lingual gyrus and intracalcarine cortex has been implicated to be involved in body perception, and active during both visual and limb movements (Astafiev et al., 2004). Therefore, increased extrastriatal activity may correspond with a superior ability to align visual stimuli with proprioceptive afferent signals to minimize force-matching discrepancy. However, the increased

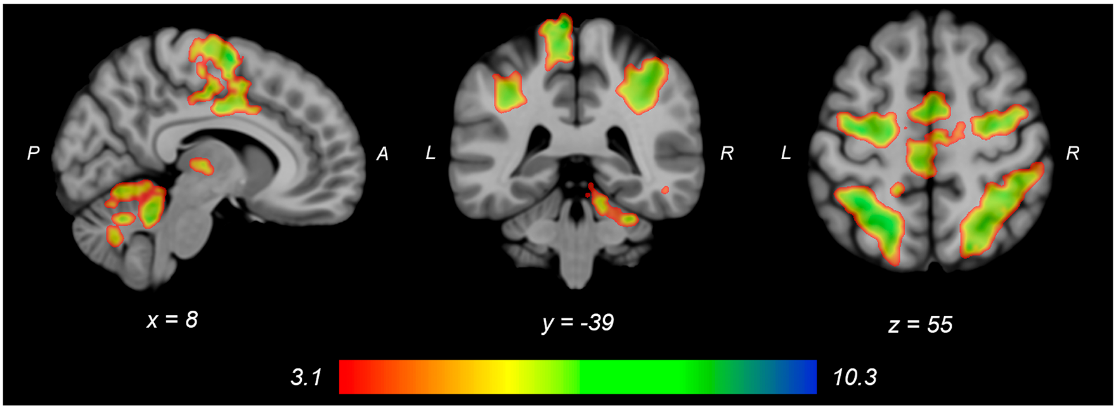

FIGURE 2 | Group average neural activity for knee extension force-matching from **Table 2**. P, posterior; A, anterior; L, left; R, right.

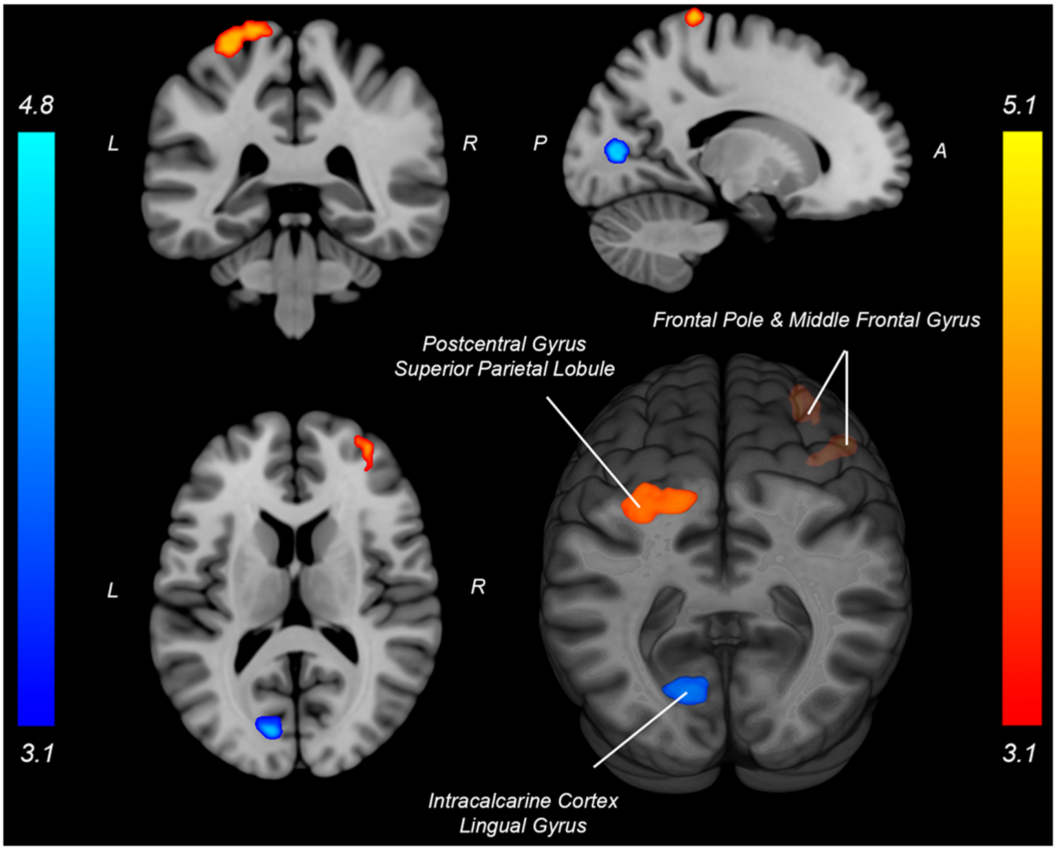

FIGURE 3 | Neural activity associated with knee extension force-matching error from **Table 2** (Red: brain activity positively associated with an error. Blue: brain activity negatively associated with an error). P, posterior; A, anterior; L, left; R, right.

extrastriatal activity could also be secondary to visualizing good performance *via* alignment of the target and participant force and not be the mechanism for reduced error. As intracalcarine cortex and lingual gyrus have greater levels of activity when such crossmodal stimuli are congruent compared to incongruent stimuli (e.g., spatial and temporal correspondence of visual presentation and tactile stimulation) and low error results in a visual stimulus that is congruent with proprioceptive sensed force generation and tactile cues (Driver and Spence, 1998; Macaluso et al., 2000).

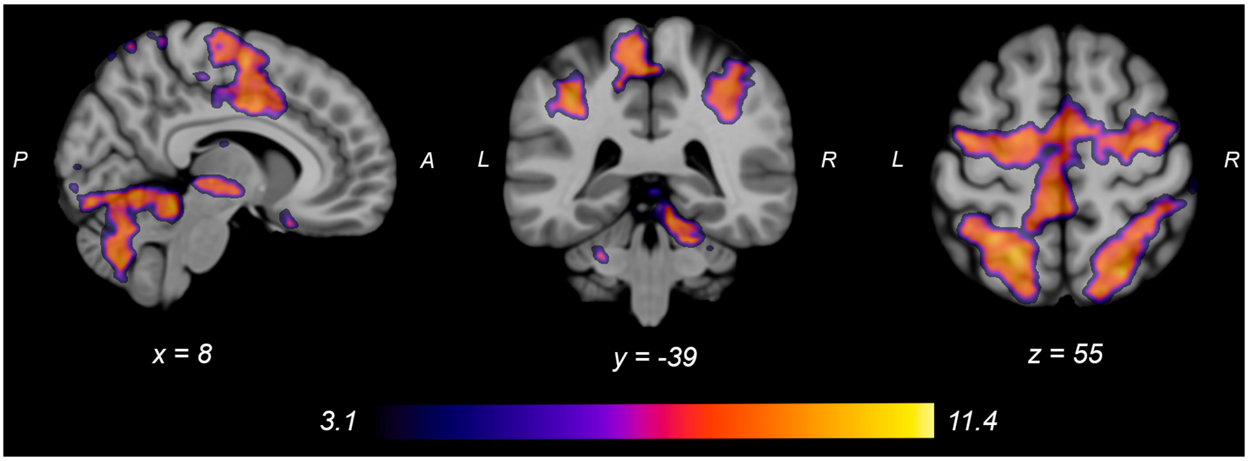

FIGURE 4 | Group average neural activity for knee flexion force-matching from **Table 3**. P, posterior; A, anterior; L, left; R, right.

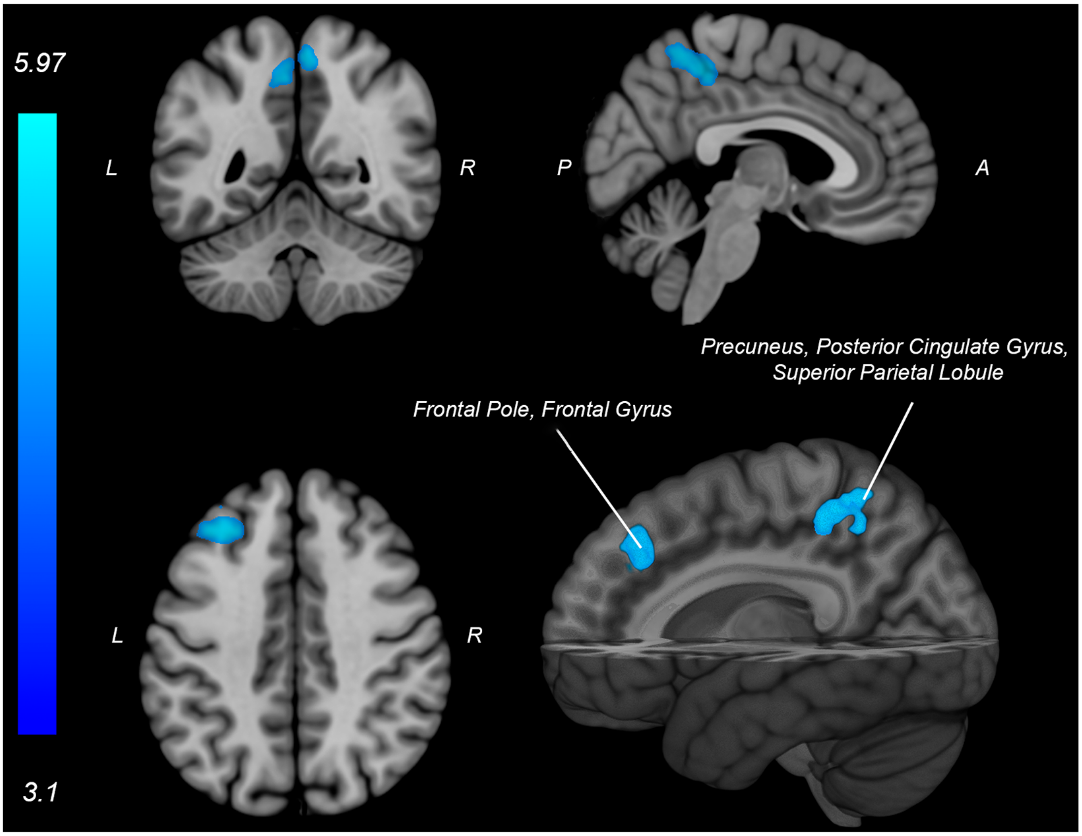

FIGURE 5 | Neural activity (blue) is negatively associated with knee flexion force-matching error from **Table 3**. P, posterior; A, anterior L, left; R, right.

Neural Correlates of Knee Flexion Force Control

The knee flexion force-matching task also had a neural activation pattern similar to prior lower extremity neuroimaging paradigms, with activation across the cortical and cerebellar sensorimotor network (Jaeger et al., 2014; Grooms et al., 2019). Knee flexion force error was associated with decreased activity in frontal and parietal regions, however, no increased neural activity was associated with knee flexion error. This contrasts with the knee extension force control error, which had increased

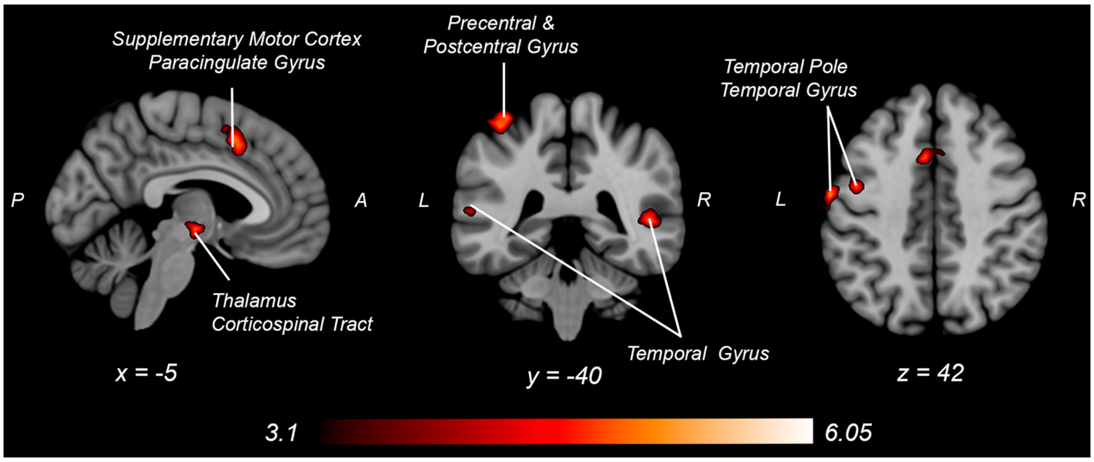

FIGURE 6 | Neural activity increases with knee flexion force matching relative to knee extension from **Table 4**. P, posterior; A, anterior L, left; R, right.

frontal and parietal lobe activity associated with increased force error.

This opposition may seem contradictory as one might expect more general alignment for the neural activity underlying force error between knee flexion and extension activities. However, the musculature enabling isolated knee flexion (primarily hamstring) vs. isolated knee extension (primarily quadriceps) have unique neural representation, peripheral nerve innervation, and spinal reflex structure (Jennings and Seedhom, 1994; Mrachacz-Kersting et al., 2006). Thus, the brain differences for error correction between knee extension and flexion may be secondary to mediation at the spinal level. The hamstrings are also typically weaker than the quadriceps (Wyatt and Edwards, 1981; Aagaard et al., 1995; Pincivero et al., 1997) and have a greater proprioceptive error (Relph and Herrington, 2016), potentially secondary to decreased relative cortical representation (Davies, 2020) and less muscle spindle innervation relative to the quadriceps (Banks, 2006).

Anecdotally, the participants in this study had a more difficult time learning how to perform the knee flexion task relative to the knee extension task as many needed more practice trials for the hamstring task than the quadriceps task to achieve reliable performance. The constrained action hypothesis posits that when you attend to a motor task, you constrain the automatic, implicit motor programs that would have otherwise facilitated the movement (Wulf et al., 2001; Kal et al., 2013; Vidal et al., 2018). However, if there is no automatic, implicit motor plan present to guide the movement, then attention to the motor task may improve performance. Therefore, the knee extension task may have been more "intuitive" (implicit) in this sample, contributing to decreased frontal cortex activity not constraining the automatic motor program and facilitating reduced extension error. Conversely, if the knee flexion task is anecdotally less implicit (lacking a well-established, implicit motor program), the association between increased frontal activity and improved performance for flexion may be attributable to the necessity of cognitive-attentive neural processes to drive the motor plan.

Neural Activity Differences Between Knee Extension and Flexion Force Control

Engaging in knee flexion force control required increased cortical and subcortical activation, including primary sensorimotor cortex, secondary motor cortex, temporal regions, parietal supramarginal gyrus, and corticospinal tract, whereas no brain regions had increased activity for relative knee extension force control. These findings may partially explain the apparent paradoxical similar activation pattern associated with increased knee extension force error, yet decreased knee flexion force error, as the knee flexion force-matching task required greater overall neural activity for similar force-matching performance. This could be secondary to the relatively greater demand on the hamstrings, as they are typically weaker than the quadriceps, requiring elevated neural activity to produce the same force level. Alternatively, the position of the knee may have influenced the result as a near-terminal extension may bias toward quadriceps shortened position and improved steadiness (Krishnan et al., 2011) compared to the hamstring position (lengthened). A likely neurophysiologic contributor is the relatively increased spinal reflexive innervation of the hamstring (Shahani and Young, 1971; Roy et al., 2014; Mackey et al., 2016) requiring increased cortical activity to overcome potential spinal inhibition. The increased knee flexor force-matching neural activity could also be secondary to the task being more atypical, as concentric precise force control of the hamstrings is not as common to be engaged during locomotion, where the quadriceps is primarily engaged in concentric positioning and the hamstrings act eccentrically to decelerate before heel strike. Thus, the nature of the concentric force matching task may result in increased activation for knee flexion that would not be the case with an eccentric force-matching task (Koohestani et al., 2020).

LIMITATIONS

This investigation was limited to a single joint position and an isometric contraction at a low force level, primarily to minimize head motion for fMRI. Possibly, synergist muscle groups that contribute to hip flexion or extension may reduce the ability to isolate the quadriceps for knee extension or the hamstring for knee flexion (though at the low force level required in this study, accessory muscle activity is unlikely), so future work may consider recording electromyography measures to ensure muscle group contributions. The force level was selected to ensure a sufficient fluctuation range to test force-sense but also keep head motion minimal. We used a low absolute value of 5 N, as opposed to a low relative force such as 5% of a maximal voluntary contraction. Prior works have employed both a ∼5 N absolute threshold (Newton et al., 2008) and similar relative thresholds (Shanahan et al., 2015). As our sample was homogeneous in terms of fitness, activity level, age, and BMI, there is a minimal indication the results would be different if scaled to a relative % for capability. Nonetheless, future work across varied samples may consider employing a relative metric for the force target. While we enrolled young and physically active females to better understand knee force control in this population at a unique high-risk for sensorimotor-related coordination errors that contribute to knee ligament injuries such as the anterior cruciate ligament, our participant selection criteria limit generalization to males or aging populations. Future investigations may consider heterogenous demographical recruitment of participants to increase generalizability or determine if changes in neural activity are present with various ages or pathological populations. Additionally, the use of a variety of joint angles and intensities may also highlight how limb position and magnitude plays a role in central mechanisms of force regulation.

CONCLUSION

This investigation employed a novel lower extremity force-matching neuroimaging-compatible paradigm to examine motor control of the knee extensors and flexors. The paradigm was found to activate the sensorimotor network with unique neural correlates to force-matching error across parietal and frontal regions. This paradigm may allow for future research to better understand the neural correlates of lower extremity neuromuscular control across varied pathologies or interventions. Specifically, this foundational work can support a future investigation into the unique contribution of the nervous system to lower extremity force regulation in pathologies that disrupt proprioception and sensorimotor function such as knee anterior cruciate ligament injury (Laboute et al., 2019), osteoarthritis (Shanahan, 2015), and patella-femoral pain (Te et al., 2017). As the evidence base for the role of the nervous system in these musculoskeletal conditions grows, the need for such paradigms that bridge neural activity and motor performance of the knee as described here are needed to provide pathology specific therapeutic targets (Silfies et al., 2017; Armijo-Olivo, 2018).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ohio University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DG, CC, and TW: conception. DG, CC, JS, and TW: experimental design and data analysis. DG, CC, AH, and TW: data collection. DG, CC, JS, AH, and TW: writing and review. All authors contributed to the article and approved the submitted version.

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