Lower Extremity Interlimb Coordination Associated Brain Activity in Young Female Athletes: A Biomechanically Instrumented Neuroimaging Study

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Abstract

Bilateral sensorimotor coordination is required for everyday activities, such as walking and sitting down/standing up from a chair. Sensorimotor coordination functional neuroimaging (fMRI) paradigms (e.g., stepping, cycling) increase activity in the sensorimotor cortex, supplementary motor area, insula, and cerebellum. Although these paradigms are designed to assay coordination, performance measures are rarely collected simultaneously with fMRI. Therefore, we aimed to identify neural correlates of lower extremity coordination using a bilateral, in-phase, multi-joint coordination task with concurrent MRI-compatible 3D motion analysis. Seventeen female athletes (15.0±1.4 years) completed a bilateral, multi-joint lower-extremity coordination task during brain fMRI. Interlimb coordination was quantified from kinematic data as the correlation

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between peak-to-peak knee flexion cycle time between legs. Standard preprocessing and whole-brain analyses for task-based fMRI were completed in FSL, controlling for total movement cycles and neuroanatomical differences, with interlimb coordination as a covariate of interest. A clusterwise multi-comparison correction was applied at $z > 3.1$ and $p < .05$. Less interlimb coordination during the task was associated with greater activation in the posterior cingulate and precuneus ($z_{max} = 6.41$, $p < .01$) and the lateral occipital cortex ($z_{max} = 7.55$, $p = .02$). The inability to maintain interlimb coordination alongside greater activity in attention- and sensory-related brain regions may indicate a failed compensatory neural strategy to execute the task. Alternatively, greater activity could be secondary to reduced afferent acuity that may be elevating central demand to maintain in-phase lower extremity motor coordination. Future research aiming to improve sensorimotor coordination should consider interventional approaches uniquely capable of promoting adaptive neuroplasticity to enhance motor control.

Keywords

fMRI; human movement; kinematics; central nervous system; in-phase

1. Introduction

Bilateral lower extremity sensorimotor coordination is necessary for activities of daily living, such as walking, sitting down/standing up from a chair, and ascending/descending stairs. Both coordinative in-phase (i.e., in sync) movements, such as standing up from a chair, and anti-phase (i.e., alternating) movements such as walking, depend on dynamic coupling of the neural activity within the left and right brain hemispheres. With use of functional magnetic resonance imaging (fMRI), a network of regions including the sensorimotor cortex (Fontes et al., 2015, 2020; Hollnagel et al., 2011; Jaeger et al., 2014, 2015, 2016; Mehta et al., 2009; Noble et al., 2014), supplementary motor area (SMA; Fontes et al., 2020; Jaeger et al., 2014, 2015; Mehta et al., 2012; Noble et al., 2014), insula (Fontes et al., 2020; Jaeger et al., 2015, 2016; Noble et al., 2014), and the cerebellum (Fontes et al., 2015, 2020; Jaeger et al., 2014; Mehta et al., 2009, 2012) are consistently activated during a variety of coordinated bilateral lower extremity movements. Further, with increased task movement rate (e.g., faster pedaling cadence) or complexity (e.g., unilateral versus bilateral), neural demand within this sensorimotor network is increased. However, assessing lower extremity coordination comes with inherent technological and methodological challenges, such as head motion artifact corrupting data quality and lack of MR-compatible lab equipment to assess motor control and performance (e.g., kinematic and kinetics). These combined technical and methodological limitations have historically limited the ability to probe lower extremity coordination, specifically concurrent with performance kinematics, which is a critical step to improve our understanding of neuromuscular control in healthy, injured, and diseased populations.

Much work has gone into overcoming the MRI-related limitations associated with examining brain activity during multi-joint lower limb movements, including the development of novel devices such as an MR-compatible pedaling device (Fontes et al., 2015; Mehta et al., 2009), a Magnetic Resonance Compatible Stepper (MARCOS;

Hollnagel et al., 2011; Jaeger et al., 2015), a device to assess hip, knee, and ankle torque during isometric contractions(Newton et al., 2008), a device to complete unilateral leg press-like movements (Grooms et al., 2019), and a lower extremity isometric force matching device (Grooms et al., 2021). Although these devices, combined with improvements to immobilizing participants trunk and head during neuroimaging, have made it possible to assay lower extremity coordination, the ability to precisely quantify motor performance data concurrent with fMRI has remained a considerable limitation to prior work. Some recent investigators have implemented neuroimaging paradigms with MRI-compatible kinematics during an anti-phase stepping task (Jaeger et al., 2014) and a unilateral leg press-like task (Anand et al., 2021). Jaeger et al. (2014) found that during stepping, there was activation in expected sensorimotor areas, however there was no relationship between stepping performance (knee amplitude, stepping frequency, maximal knee and foot force) and neural activation throughout a network of *a priori* defined regions-of-interest (ROI). The lack of association was potentially due to the ROI-based approach, it remains unclear if performance was not related to *any* neural activation or just not related within the defined ROIs. Using a whole-brain analytic approach, concurrent frontal plane range of motion (ROM) was modelled with neural activation during a unilateral leg press fMRI paradigm (Anand et al., 2021). The authors uniquely found that greater frontal plane ROM was associated with bi-directional activation in a variety of regions important for attention, sensorimotor control, and sensorimotor integration (Anand et al., 2021). The identified neural correlates provided initial evidence of the neural activation pattern associated with precise metrics of knee neuromuscular control that could have been missed with a sensorimotor network only ROI-based approach. Whole-brain analytic approaches allow for the recognition of distinct neural markers that can provide targets for clinical interventions based on precise lower extremity motor performance metrics. To our knowledge, no prior literature has collected concurrent sensorimotor motor performance measures (kinematics) and used a whole brain approach to identify neural correlates of bimanual lower extremity interlimb coordination for in-phase coordination of the ankle, knee, and hip during combined flexion-extension movements. Integrated biomechanical and fMRI approaches for lower extremity motor control would enable a better understanding of interlimb lower-extremity coordination during activities of daily living ranging from chair rising and squatting to athletic activities such as jumping and landing. Further, examination of this relationship in young female athletes, who are recognized at a high risk for sensorimotor coordination failures (e.g., anterior cruciate ligament [ACL] injury when landing from a jump; Swanik, 2015) is of particular interest.

Therefore, our purpose was to identify the neural regions involved in controlling bilateral in-phase lower extremity movements and to determine the neural correlates of lower extremity coordination during a bilateral multi-joint in-phase coordination task with a whole-brain analytic approach in young female athletes. We hypothesize that during task performance, the sensorimotor cortex, SMA, insula, and cerebellum will increase activity and there will be unique activation associated with the ability to maintain precise synchrony with the auditory cue across both limbs.

2. Method

2.1 Participants

Eighteen female high-school basketball and volleyball players (14.7 ± 1.4 years, 169.5 ± 7 cm, 65.8 ± 20.5 kg) completed the study. One athlete's data was excluded due to excessive head motion (*a priori* standard >2 mm absolute head motion), thus seventeen were included in the analyses. This experiment was approved by the institutional review board at Cincinnati Children's Hospital Medical Center and all participants/parents signed written informed consent prior to completing MRI screening.

2.2 Procedure

Participants completed a bilateral multi-joint in-phase coordination task during a whole-brain fMRI (Figure 1). A vital aspect of the study to ensure data quality, reliability, and minimal dropout due to head motion or participant discomfort was the completion of a mock scanner session before actual scanning, whereby the participants were trained on all aspects of the in-phase coordination task prior to entering the MRI. First, a standardized video was played that explained and illustrated the task. Then, participants had an opportunity to practice the task with guidance from the experimenter. All participants wore standardized shorts and socks without shoes to control for skin tactile feedback. Participants were positioned supine on the MRI table with customized padding and straps to reduce head motion. Handlebars were attached to the MRI table to standardize hand position and minimize accessory motion. Our methods sufficiently reduced head motion for bilateral lower extremity movement during fMRI and produced robustly usable data, like our previously published unilateral lower extremity fMRI paradigm that exhibited good to high reliability for eliciting sensorimotor region neural activity (Grooms et al., 2019).

The in-phase coordination task was completed from resting 0° full extension (without locking out the joint to avoid jerking movement) to approximately 45° knee flexion standardized at 0.6 Hz. This movement pace was found after extensive optimization experiments to minimize head motion. This motion was completed continuously for 30 seconds with 30 seconds of rest for 4 cycles. Each scan session started with 30 seconds of a blank screen. The subject saw a countdown of "2", "1", and then "MOVE" was displayed, then a metronome started to standardize the movement pace at 1.27 Hz. At the end of each movement block, the participant saw "2", "1", "STOP" to allow a gentle return to the rest position to minimize head motion during transitions. The movement was completed on a custom apparatus comprised of two separate foot pedals that run on tracks and allow each limb to move independently. The feet of the participant were strapped to the pedals and moved horizontally with flexion and extension of the ankle, knee, and hip. Rubber resistance bands were put around the pedals and connected to the unit to provide tension when the participant extends and flexes. A standardized resistance band (manufacturer rated peak force ~9.1kgs) was anchored to the lateral side of both legs and in the center of the leg press apparatus. This resistance was found to be a challenging resistance without inducing motion artifact that would corrupt data quality.

2.3 Biomechanics data acquisition and analysis

Lower-extremity kinematics were captured concurrently with brain activation data using an MRI-compatible motion capture system (Metria Innovation Inc., Milwaukee, Wisconsin, USA) that was validated against a traditional 3D motion analysis (Anand, Diekfuss, Bonnette, et al., 2020). This system tracked four markers that were affixed to the participants' thighs and shins using Velcro straps. Each marker has characteristic coordinate axes that define its orientation during movement. The markers were placed on both thighs and shins and were oriented such that the x-axis of the markers was aligned along the long axis (z-axis) of the limb segment, and the markers were parallel to the frontal plane of the segment. The marker axes were thus aligned with the segment coordinate axis like standard 3D motion analysis methods. The system captured data at 85 Hz and transmitted data corresponding to each frame and marker which was captured on a collection computer using customized software developed in MATLAB (2018a) (MathWorks, Natick, Massachusetts, USA). The system reported the orientation of each marker (in quaternions) in the camera coordinate system. Subsequent data processing was performed using custom software developed in MATLAB. The orientations were filtered using a low pass 12 Hz 4th order Butterworth filter (Anand, Diekfuss, Bonnette, et al., 2020).

Knee joint angles were calculated as the shank coordinate system relative to the thigh coordinate system. To assess interlimb correlation, cycle time was computed for each leg as the time between two consecutive peak flexion angles for every movement repetition. Corresponding cycle times between the left and right leg, and across all four movement blocks, were linearly correlated and the coefficient of correlation was used as an indicator of interlimb coordination, with lower values of correlation indicating poorer coordination/synchronicity.

2.4 Neuroimaging data acquisition and analysis

Neuroimaging of the in-phase coordination task was performed on Philips 3T Ingenia scanner (Philips Medical Systems, Best, Netherlands) using a 32-channel phased-array head coil. The MRI protocol included a 3-dimensional high-resolution T1-weighted image (repetition time: 8.3 ms, echo time: 3.7 ms, field of view: 256×256 mm; matrix: 256×256; slice thickness 1 mm, 176 slices) for image registration. fMRI data were acquired with a gradient-echo EPI sequence following a periodic block design in which the 30 s motor task (4 blocks) was interleaved with 30 s of rest (5 blocks) acquired with a 2 s repetition time, a 3.75×3.75 mm in-plane resolution, and a 5 mm slice thickness for 38 axial slices (field of view 240 mm and 64×64 matrix).

2.5 Preprocessing

Neuroimaging analyses were performed using the Oxford Centre for Functional MRI of the Brain software package, FSL 6.0 (FMRIB, Oxford UK; Jenkinson et al., 2012)). Initial processing of data was completed in three steps to prepare the imaging data for automated removal of motion artifact with an independent component analysis (ICA-AROMA; Pruim et al., 2015), removal of the artifact-ridden components, and complete processing on denoised data. Pre-ICA-AROMA steps included robust brain extraction, motion correction using MCFLIRT, ascending slice timing correction, spatial smoothing with a gaussian kernel

of 6 mm full-width-half-max (FWHM), and multiplicative mean intensity normalization of the volume at each timepoint. Functional images were first registered with a linear transformation to the high-resolution 3D T1-weighted structural images and then a non-linear approach was used for registration to standard space (T1 2mm brain). Then we used an open-source graphical user **In**terface **For Ba**tch processing fMRI datasets using ICA-**AR**OMA (INFOBAR; Anand, Diekfuss, Slutsky-Ganesh, et al., 2020), which allows for preprocessed/postprocessed data inspection and efficient ICA-AROMA completion. During the task, participants had an average absolute head motion of 0.50 ± 0.34 mm and relative head motion was 0.14 ± 0.07 mm. Following ICA-AROMA, a high-pass filter of 100 s was applied to the denoised data and again linear and non-linear registration methods were applied to structural images and standard space, respectively.

2.6 Overall Activation and Neural Correlate Analyses

Subject-level time-series statistical analyses were carried out using a linear model with local autocorrelation correction during a 30 s block design (30 s move/ 30 s rest). Cluster-wise multiple comparison corrections were applied with significance thresholds set at $z=3.1$ and $p<.05$. Group-level analyses were completed with FSL's 2-stage local analysis of mixed-effects model (FLAME 1+2) model to evaluate overall activation during the multi-joint in-phase coordination task. The biomechanical variable (interlimb coordination) was demeaned and added into the FLAME 1+2 model as a covariate of interest to determine respective relationship to brain activity. Covariates of no interest included in each model included a voxelwise covariate for gray matter (Oakes et al., 2007) and the demeaned total number of movement cycles completed across four blocks. To visualize findings for those with relatively greater interlimb coordination versus those with relatively lesser interlimb coordination we computed a median split on the 17 participants, discarding the median from the split, resulting in n=8 for each interlimb coordination group. Using FSL's Featquery tool, percent blood oxygen level dependent (BOLD) signal was extracted for each subject from the resultant clusters of the overall activation analysis and the interlimb coordination neural correlate analysis to visualize the activation in these regions across the entire sample, as well as within the higher interlimb coordination and lower interlimb coordination median split groups. Given the median split was conducted on the neural correlate of interest for visualization purposes only, no between group statistics on activation was completed to avoid circularity.

3. Results

During the bilateral multi-joint in-phase coordination task there was significant neural activation in six clusters (Table 1, Figure 2). Average interlimb coordination (correlation between right and left lower extremity cycle times) during the in-phase coordination task was $r=0.49 \pm 0.25$ (range $r = 0.08 – 0.92$). During movement, lower interlimb coordination was associated with greater neural activity in the precuneus/posterior cingulate cortex (PCC) and the lateral occipital cortex (Table 1, Figure 3). To visualize findings across participants with relatively high or low interlimb coordination, a median split was conducted and centered at $r=0.43$, resulting in high interlimb coordination (n=8, $r=0.74 \pm 0.11$) and low interlimb coordination (n=8, $r=0.25 \pm 0.10$) groups (Figures 2 and 3).

4. Discussion

Overall, the results from the current report indicate that a bilateral multi-joint in-phase coordination task increases neural activity in a similar network of regions as previously described during bilateral anti-phase tasks, bilateral single-joint tasks, and unilateral single- and multi-joint tasks. Specifically, there were task-related increases of activation in the sensorimotor cortex, somatosensory cortex, bilateral insula, temporal pole, and the cerebellum. Extending beyond previous reports, we have demonstrated that reduced lower extremity interlimb motor coordination during an in-phase movement was associated with greater activity in the posterior cingulate gyrus and precuneus, as well as the lateral occipital cortex.

Greater activation within the PCC and precuneus has previously been associated with greater ratings of perceived exertion during a lower extremity cycling task (Fontes et al., 2015), as well as poorer motor control during a unilateral leg press task (Anand et al., 2021). The relatively higher PCC and precuneus activation with lesser interlimb coordination may be indicative of those who have reduced interlimb coordination capacity, or find the task relatively more challenging, may require additional neural resources to try and maintain desired sensorimotor performance. This framework is similar to the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008) which suggests that increased brain activity can be a method of compensation that is secondary to differences in central structural or morphological (e.g., gray and white matter degradation) and\or peripheral capability (e.g., reduce strength, proprioception, injury). However, as task complexity or demand increases, eventually this compensation may fail and result in poorer sensorimotor performance. Those with lesser interlimb coordination in the present study may have been engaged in a compensation neural strategy that partially failed given the complexity of motor task demands associated with the in-phase coordination task (e.g., timing constraints, added resistance, maintaining head stability).

An important note, however, is that the regression findings—greater neural activity associated with less interlimb coordination—could reflect either hyperactivity or reduced deactivation with poorer interlimb coordination. To parse this hypothesis out, we extracted the percent BOLD signal change from all participants and plotted the percent change within each resultant cluster for the entire sample, as well as for the median split high and low coordination groups. It appears that the low coordination participants had greater BOLD signal within the precuneus/PCC and almost no apparent change in activation in the lateral occipital cortex, whereas the high coordination group deactivated (less activity during task relative to rest) in both clusters. The precuneus and PCC are anatomically located within the medial aspect of the parietal cortex and have distinct functional sensory integration, cross modal visual spatial processing and motor planning roles (Wang et al., 2019), potentially supporting a specific sensory-based compensation (CRUNCH) to maintain coordination. Greater somatosensory activity may be reflective of reduced afferent acuity or peripheral contributions to proprioception, or muscle capability, requiring increased central integration to maintain body and spatial representation for accurate motor planning (Chaput et al., 2022; Criss et al., 2020; Oliveira et al., 2017). However, there is considerable literature identifying the PCC and precuneus as key regions involved in the default mode network

(DMN; Utevsky et al., 2014). The DMN– sometimes referred to as the task negative network – is most active at rest and deactivates in response to increases in attentional demand. Though we did not assess connectivity or perform network-related analyses in this study, hypothetical inferences may be made from the different activation profiles across the coordination groups within the precuneus and PCC. A potential alternative hypothesis for these data is that those who displayed relatively higher interlimb coordination may have better attended to task-relevant stimuli (e.g., the auditory metronome) and thus had the network flexibility to successfully suppress the DMN to achieve the task constraints imposed by the in-phase task. Whereas those with lower interlimb coordination may have either consciously or subconsciously not attended to the task-relevant stimuli, thus failing to suppress the DMN and impairing successful motor performance. Further, the lateral occipital cortex is primarily associated with visual integration (Beauchamp, 2005; Mullin & Steeves, 2011), which would not appear to benefit coordination with an auditory metronome, thus deactivation by the more coordinated group may have allowed for greater availability of neurocognitive resources to task-relevant regions.

4.1 Limitations

While the current study reports novel findings, the authors acknowledge study limitations that should be considered in interpretation of the current results. First, this study lacked concurrent force data acquisition and relied on positional data to determine interlimb coordination. Future work should consider inclusion of force data, as well as a direct assessment of overall deactivation during the motor task (as suggested by Fontes et al., 2020) and connectivity analyses within the resting-state and active state (psycho-physiological interaction analyses [PPI]) to assess network flexibility during shifts of processing states relative to task performance. Further, this study is limited to a sample of adolescent females, thus not generalizable to males or across different age groups. This study was a secondary data analysis from which the primary study's focus was put on female adolescent athletes due to their high risk for anterior cruciate ligament (ACL) injury (Griffin et al., 2000), theorized to occur because of sensorimotor coordination errors whereby the central nervous system fails to maintain safe knee positioning during dynamic movements with high neurocognitive demands (landing from a jump while distracted by a defender; Swanik, 2015). Thus, the present findings may be an initial step towards identifying a neural marker underlying sensorimotor coordination failures of the lower extremity (e.g., ACL injury) and/or could be used to evaluate the efficacy of training programs designed to optimize brain function to support injury-resistant movement (Diekfuss et al., 2019, 2020; Grooms et al., 2018, 2022). Though this study is not without limitations, our inferences here to discuss our findings in the context of previous literature are theoretical constructs and sets the stage for targeted research to further deconstruct the neural mechanisms underlying interlimb coordination.

4.2 Conclusion

In conclusion, a bilateral multi-joint in-phase coordination task elicited common sensorimotor activation, as demonstrated in previous fMRI studies of the lower extremities (Fontes et al., 2015, 2020; Hollnagel et al., 2011; Jaeger et al., 2014, 2015, 2016; Mehta et al., 2009, 2012; Noble et al., 2014). We extended prior work by quantifying concurrent

motor control behavior (i.e., 3D motion analysis of the bilateral knee joint position during in-phase movement), permitting the novel exploration of lower extremity interlimb coordination and its relationship with neural activity. We identified the precuneus/PCC and lateral occipital cortex as key neural regions that may support sensory integration to regulate in-phase lower extremity bilateral multi joint interlimb coordination. The inability to maintain interlimb coordination alongside greater activity in attention- and sensory-related brain regions may indicate a failed compensatory neural strategy to execute the task. Alternatively, the greater activity could be secondary to reduced proprioceptive or afferent acuity or motor planning ability resulting in elevated central demand to maintain in-phase coordination of the lower extremity. The current results set the stage for future research aiming to improve lower extremity sensorimotor coordination with adjunctive strategies capable of promoting adaptive neuroplasticity during exercise.

Data Availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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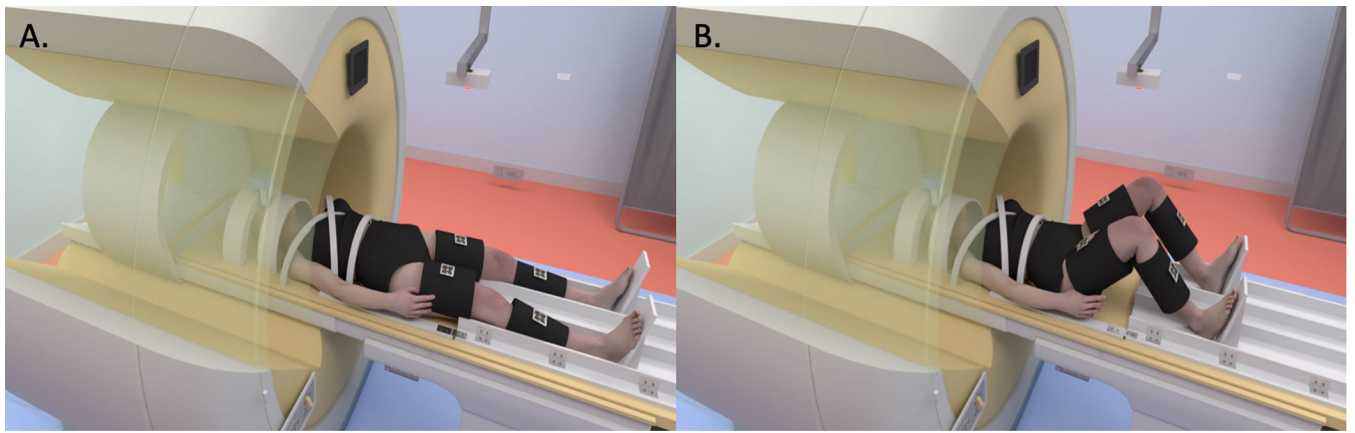
Figure 1:
3D Rendering of the bilateral multi-joint in-phase coordination task during fMRI conditions rest (A) and move (B).
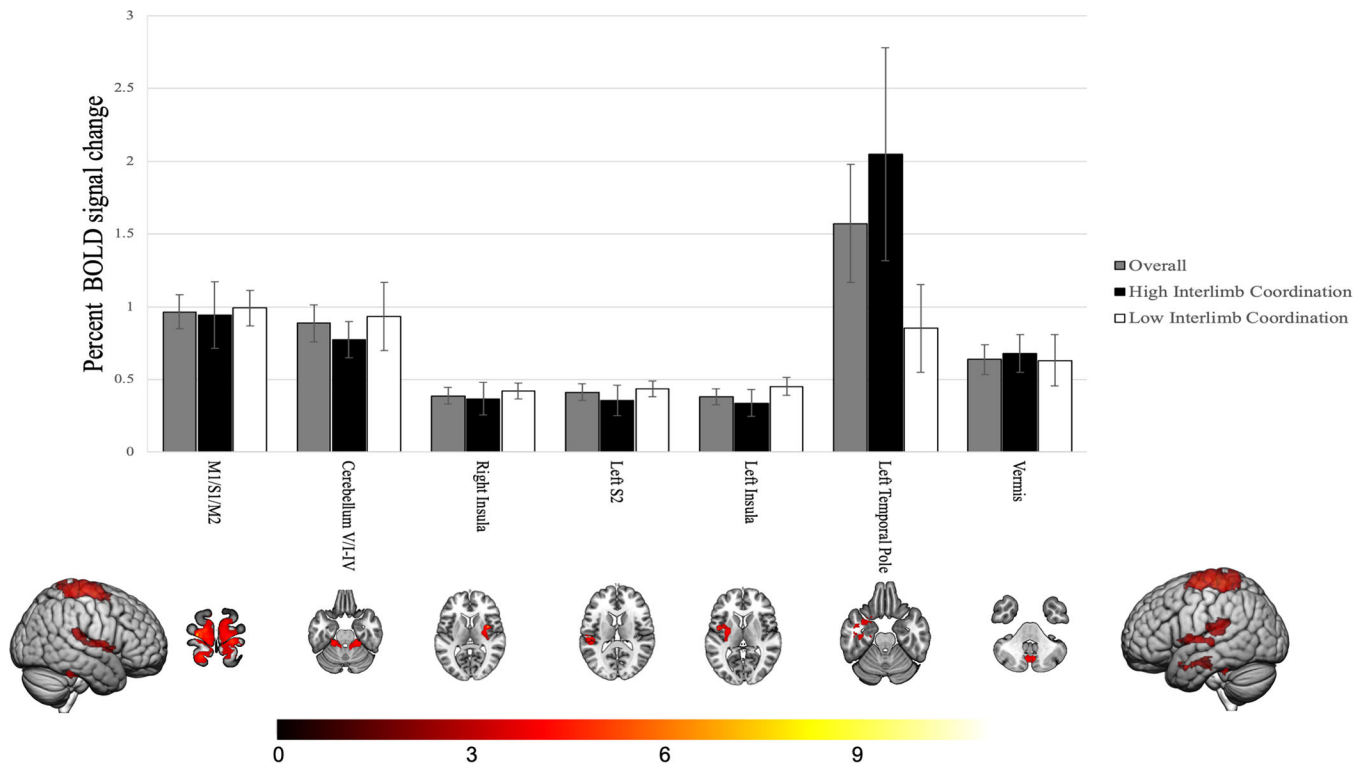
Figure 2:
Overall activation map of the bilateral task. Significant clusters are depicted in axial slices (numbers represent Z coordinate in MNI space) and are shown in rendered brains. All images shown in neurological convention (i.e., image left is the left side of the brain). Color bar represents z-statistics, which included a cluster-based correction for multiple comparisons of $z > 3.1$ and $p < .05$.

Figure 3:

Neural correlates of lower extremity coordination. Less coordination resulted in greater activation of clusters in the posterior cingulate cortex (PCC) and precuneus and the left lateral occipital cortex. Image is shown in neurological convention (i.e., image left is the left side of the brain). Color bar represents z-statistics, which included a cluster-based correction for multiple comparisons of $z > 3.1$ and $p < .05$.
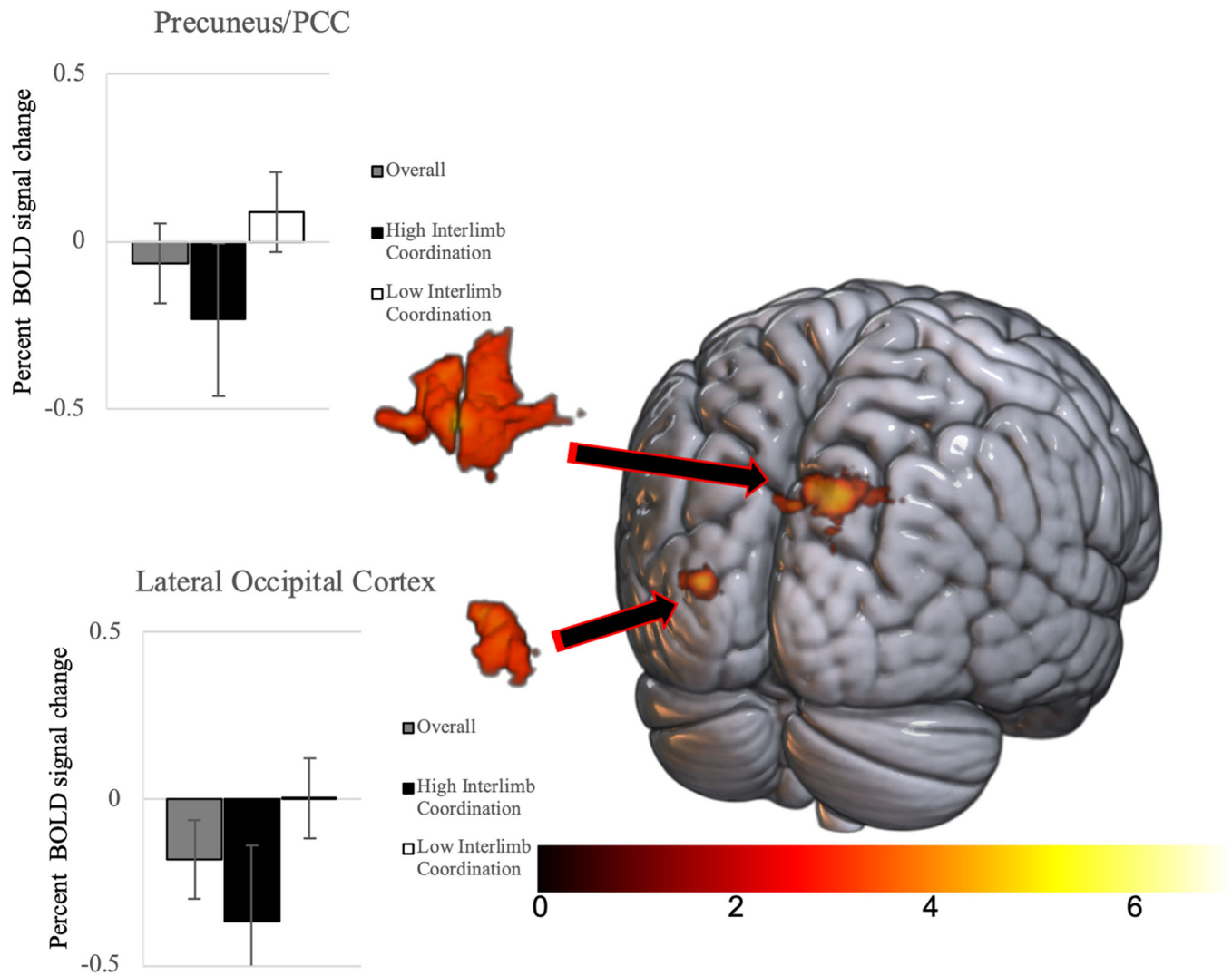
Table 1

Resultant Clusters from Neuroimaging Analyses

Cluster Index	Brain Regions	Voxel	P-value	Peak MNI Voxel			Z stat-max
				x	*y*	*z*	
	Overall Activation During Bilateral Leg Press						
1	Bilateral Premotor Cortex Primary Motor Cortex Primary Somatosensory Cortex	6313	<.0001	−20	−24	76	10.7
2	Bilateral Cerebellum V Cerebellum I-IV	1205	<.0001	−20	−36	−26	4.52
3	Right Insula Putamen	754	<.0001	36	2	8	7.11
4	Left Secondary Somatosensory Cortex (Parietal Operculum) Primary Auditory Cortex	637	<.0001	−50	−24	14	5.01
5	Left Central Opercular Cortex Insula Putamen	403	<.0001	−46	−2	6	5.54
6	Left Temporal Pole	346	<.0001	−28	6	−24	4.56
7	Central Vermis VIIb Vermis VIIIa Vermis Crus II	233	.0003	−6	−72	−40	4.56
	Neural Activity Negatively Associated with Leg Synchrony						
1	Bilateral PCC Precuneus	437	<.0001	2	−60	30	6.41
2	Left Lateral Occipital Cortex	115	.0241	−26	−82	8	7.55

Areas of increased brain activity during the bilateral leg press relative to rest (top), activity associated with the correlation between right and left leg cycle time (e.g., leg synchrony; bottom). Voxel #: indicates number of activated voxels in this cluster. The clusters are identified statically using Gaussian random field theory to correct for multiple comparisons and identify the number of contiguous voxels whose voxel wise stats are above threshold MNI Montreal Neurologic Institute provides a standardized reference atlas for region location and identification. x, y, z indicates 3D location of voxel with highest activity level in the cluster. Z stat max: Z-score of the voxel with highest activity. No regions were positively associated with leg synchrony.