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RESEARCH ARTICLE

# Sex differences in the neural underpinnings of unimanual and bimanual control in adults

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## Abstract

While many of the movements we make throughout our day involve just one upper limb, most daily movements require a certain degree of coordination between both upper limbs. Historically, sex differences in eye-hand coordination have been observed. As well, there are demonstrated sex-specific differences in hemisphere symmetry, interhemispheric connectivity, and motor cortex organization. While it has been suggested that these anatomical differences may underlie sex-related differences in performance, sex differences in the functional neural correlate underlying bimanual performance have not been explicitly investigated. In the current study we tested the hypothesis that the functional connectivity underlying bimanual movement control differed depending on the sex of an individual. Participants underwent MRI scanning to acquire anatomical and functional brain images. During the functional runs, participants performed unimanual and bimanual coordination tasks using two button boxes. The tasks included pressing the buttons in time to an auditory cue with either their left or their right hand individually (unimanual), or with both hands simultaneously (bimanual). The bimanual task was further divided into either an in-phase (mirror/symmetrical) or anti-phase (parallel/asymmetrical) condition. Participants were provided with extensive training to ensure task comprehension, and performance error rates were found to be equivalent between men and women. A generalized psychophysiological interaction (gPPI) analysis was implemented to examine how functional connectivity in each condition was modulated by sex. In support of our hypothesis, women and men demonstrated differences in the neural correlates underlying unimanual and bimanual movements. In line with previous literature, functional connectivity patterns showed sex-related differences for right- vs left-hand movements. Sex-specific functional connectivity during bimanual movements was not a sum of the functional connectivity underlying right- and left-hand unimanual movements. Further, women generally showed greater interhemispheric functional connectivity across all conditions compared to men and had greater connectivity between task-related cortical areas, while men had greater connectivity involving the cerebellum. Sex differences in brain connectivity were associated with both unimanual and bimanual movement control. Not only do these findings provide novel insight into the fundamentals of how the brain controls bimanual movements in both women and men, they also present potential clinical implications on how bimanual movement training used in rehabilitation can best be tailored to the needs of individuals.

**Keywords** Bimanual coordination · Sequential finger movements · Sex differences · Task-based functional connectivity

## Introduction

Bimanual coordination is essential for performing many everyday movements that require successful spatiotemporal interactions between both arms, such as typing or picking up a box (Kilbreath and Heard 2005; Howard et al. 2009). Indeed, healthy adults use both hands together in everyday functional activities more than either hand alone (Kilbreath and Heard 2005; Stone et al. 2013). Thus, gaining a better understanding of how the brain controls these movements is both important for fundamental insight into sensorimotor

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processing, and could provide a basis for clinical applications. For instance, bimanual movement training is being increasingly used as a potential post-stroke rehabilitation technique (Rose and Winstein 2004; Stewart et al. 2006; Kang and Cauraugh 2014; Wolf et al. 2014), although the results have been inconsistent (Cauraugh et al. 2010). Fundamental studies investigating sex differences in bimanual performance report contradictory findings with some showing a better performance in men (Mickevičienė et al. 2011; Shetty et al. 2014) and others a better performance in women (Albines et al. 2016; Khanjari and Arabameri 2021). These inconsistencies may be a result of the type of bimanual task used, as there appears to be a female advantage in some bimanual tasks and a male advantage in others (Rudisch et al. 2020). However, the neural underpinnings of these observed bimanual sex differences have never been examined. Thus, understanding how the neural correlates underlying bimanual movements differ between the sexes is not only important for fundamental motor control research, but may inform clinical practices since sex may be a potential factor in determining bimanual training success.

Bimanual coordination is associated with activation within a widespread network of brain regions similar to that involved in unimanual movements, including the primary sensorimotor cortex (S1/M1), dorsal premotor cortex (PMd), supplementary motor area (SMA), cingulate motor area (CMA), posterior parietal cortex (PPC), and the cerebellum (Jancke et al. 2000; Tracy et al. 2001; Swinnen 2002; Debaere et al. 2004a; Lin et al. 2017). There is a further increased activation in the PMd, SMA, CMA, PPC, and cerebellum during more complex anti-phase (asymmetrical/parallel) compared to in-phase (symmetrical/mirror) bimanual tasks (Sadato et al. 1997; Debaere et al. 2001, 2004a; Immisch et al. 2001; Nair et al. 2003; Ullén et al. 2003; Kraft et al. 2007; Wu et al. 2010; Kiyama et al. 2014; Lin et al. 2017). Several neuroimaging studies in humans have demonstrated that bimanual movements heavily rely on interhemispheric communication between these active brain regions (Sadato et al. 1997; Ehrsson et al. 2002; Serrien and Brown 2002; Meister et al. 2010; Liuzzi et al. 2011; Morishita et al. 2022).

Further support for the importance of intact interhemispheric connectivity for successful bimanual coordination comes from imaging studies investigating the integrity of the corpus callosum. The corpus callosum is a major white matter tract that connects the two hemispheres and facilitates interhemispheric communication (Bloom and Hynd 2005), crucial for motor control involving bimanual coordination (Gooijers et al. 2014; Rudisch et al. 2018) and damage to transcallosal pathways impairs bimanual performance (Serrien et al. 2001; Larson et al. 2002; Caeyenberghs et al. 2011). Increased bimanual performance of a finger tapping task was associated with increased white matter integrity (measured as greater fractional anisotropy) in the corpus callosum, likely reflecting increased myelination of the corpus callosum and consequently more efficient neuronal signal transmission (Muetzel et al. 2008). Callosal regions where white matter integrity was correlated with bimanual performance gave rise to pathways connecting the SMA and CMA between the two hemispheres (Johansen-Berg et al. 2007), both medial wall regions that are important for complex bimanual coordination. Together, these findings suggest that greater interhemispheric connectivity between brain regions involved in bimanual coordination is especially important for successful bimanual control.

There is direct evidence of a greater amount of interhemispheric connectivity in women, especially in the splenium (posterior portion of the corpus callosum) (Allen et al. 1991; Dubb et al. 2003), while men show greater intrahemispheric connectivity (Ingalhalikar et al. 2014). The corpus callosum specifically has been shown to have structural differences related to sex, where women have a significantly larger corpus callosum compared to men after adjusting for brain size (Shiino et al. 2017). Functional neuroimaging and electrophysiological studies have demonstrated that even when men and women show the equal performance of complex unimanual visuomotor tasks, the underlying brain activity associated with completing the tasks differs between the sexes with a more bilateral pattern of visuomotor brain activity in women relative to men (Grön et al. 2000; Gorbet and Sergio 2007; Gorbet et al. 2010; Gorbet and Staines 2011). Collectively, these findings predict sex-related differences in interhemispheric connectivity associated with bimanual movement coordination. In the current study, we directly tested the hypothesis that the neural correlates underlying the control of unimanual and bimanual movements differ in women and men. As mentioned above, sex differences in the neural underpinning of unimanual control have been reported in a variety of paradigms. Here, we were interested in comparing the sex differences in functional connectivity of unimanual and bimanual movements on comparable tasks. We predicted that regions known to be important for unimanual and bimanual control would be significantly more bilaterally connected in women compared to men.

## Methods

### Participants

Thirty right-handed participants were included in the experiment (see Table 1 for demographic information). Participants of the study were 15 women (mean age 25.3 ± SD 6.2 years) and 15 men (mean age 24.9 ± SD 4.7 years). Handedness was verified using the Edinburgh inventory, where the range of scores varies between − 100 (preference

**Table 1** Participant demographic features

| | Women | Men |
|---|---|---|
| *n* | 15 | 15 |
| Mean age (years) ± SD | 25.3 ± 6.20 | 24.9 ± 4.70 |
| Mean handedness score | 82.1 | 67.3 |
| Mean handedness score range | 28.6–100 | 5.26–100 |

of "strong left") and + 100 (preference of "strong right") (Oldfield 1971). There were no statistically significant differences observed between women and men on handedness scores ($p = 0.13$). Participants were asked to self-report sex on a binary scale (female/male) and gender on a non-binary scale where individuals marked a position on a line ranging between "strongly masculine" and "strongly feminine". None of the participants had any known neurological issues. All participants had a normal or corrected-to-normal vision. The study protocol was approved by the Human Participants Review Sub-Committee of York University's Ethics Review Board, and all participants provided informed written consent before data collection.

## Apparatus and MRI acquisition

MRI data were acquired using a 3 Tesla (3T) Siemens Magnetom Prisma Fit scanner at York University. Participants lay in a supine position in the scanner with a vertical screen behind them in the magnet bore. A mirror was attached to the MRI head coil in front of the participant's eyes to allow participants to view a fixation target being presented on the screen behind them. Participants wore MRI-compatible headphones (MR Confon audio system) to hear auditory cues, and eye movements were monitored using an MRI-compatible eye tracking system (Avotec Eye Tracking System RE-5721) solely to verify gaze fixation. Two button boxes with 4 buttons in a curved line (Current Designs fORP SKU#HHSC-2 × 4-C) were placed under the right and left hand in a position that allowed participants to press appropriate buttons using their fingers with minimal wrist and lower arm movements.

T1-weighted anatomical images were collected using a sagittal volumetric magnetization-prepared rapid gradient echo (MP-RAGE) sequence. The MP-RAGE consisted of 192 sagittal slices (slice thickness of 1 mm, with no gap), TR = 2300 ms, TE = 2.26 ms, flip angle = 8°, FoV = 256 mm, and voxel dimension of 1 × 1 × 1 mm. Functional images covered the entire brain and cerebellum, and were acquired using an echo planar imaging (EPI) sequence with TR = 1200 ms, TE = 30 ms, flip angle = 66°, and FoV = 240 mm. Fifty-four, 3.0-mm thick slices with a voxel dimension of 2.5 × 2.5 × 3.0 mm were collected with an interleaved acquisition sequence and zero gap between slices.

## Experimental paradigm

All participants were trained on the experimental tasks prior to scanning. After a demonstration of how to perform the tasks by the experimenter (DG), participants performed two blocks of each of the four task conditions (two unimanual and two bimanual) to ensure task comprehension. In addition, participants were provided with an illustrated description of the tasks several days prior to scanning. During MRI data collection, each participant performed five experimental runs. Each run consisted of a randomized order of four conditions, each presented twice, for a total of eight blocks. Each run began with 30 s of baseline data collection where participants fixated on a central dot. Each block was preceded by a 6 s instruction screen which informed participants which of the four conditions they would be performing in the following block. Instruction screens were followed by another 15.6 s central fixation trial to allow brain activity to return to baseline levels. There was then a 30 s experimental block where participants performed one of the four conditions, followed by a 15.6 s inter-block central fixation. The next instruction screen was presented for the next block condition.

The four conditions were two unimanual and two bimanual coordination tasks using two button boxes. The conditions involved pressing the buttons in time to an auditory cue presented at 1 s intervals with just their left hand (unimanual), pressing the buttons with just their right hand (unimanual), or using both hands to press buttons simultaneously (bimanual) for a total of 7 repetitions of the full movement pattern for each condition (Fig. 1). The auditory cue ensured that all participants pressed the buttons at the same rate and the same number of times. All instructions were provided as shown in Fig. 1, with an additional animation showing clear buttons switching to red in the correct sequence for the task. The unimanual left and unimanual right hand conditions involved fingers moving from inside to outside (i.e., index, middle, ring, pinky). The bimanual coordination task was further divided into two conditions, in-phase (mirror/symmetrical) or anti-phase (parallel/asymmetrical). The symmetrical bimanual condition involved the same fingers moving on both hands simultaneously (i.e., index, middle, ring, pinky). The asymmetrical bimanual condition involved both hands moving fingers from the left side of the hand to the right simultaneously (i.e., left pink + right index, left ring + right middle, left middle + right ring, left index + right pinky). For all four conditions, hand positions were kept constant with both hands resting over both button boxes regardless of condition. During scanning, participants were monitored to ensure they were correctly completing the

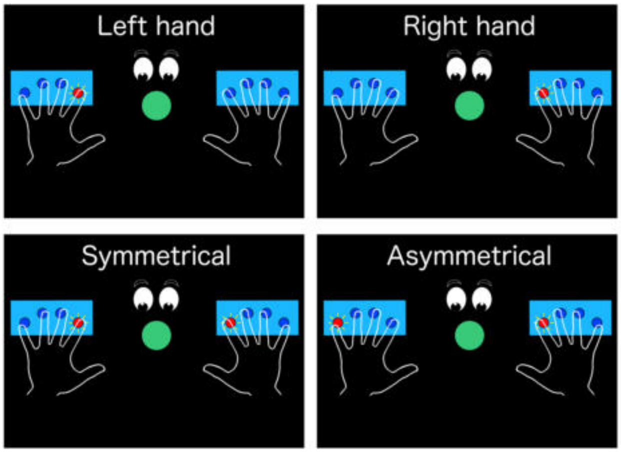

**Fig. 1** Schematic representation of the four task conditions. Participants pressed buttons on two button boxes in time to an auditory stimulus. The two unimanual tasks involved using either the left hand or right hand. The two bimanual tasks involved using both hands simultaneously in a symmetrical pattern (same fingers moving on both hands), or asymmetrical pattern (both hands moving fingers from the left side of the hand to the right simultaneously)

tasks by monitoring both eye position as well as the accuracy of button presses. The goal of the task across all conditions was similar task proficiency between all participants, with the task intentionally made to be very simple and easy to perform. Participants were specifically told to move slowly and smoothly to limit the amount of head movement associated with the task. As both the unimanual and bimanual task conditions were easy following a full functional run of training outside the scanner, and participants had an auditory cue to guide the rate of button presses, the performance error rate was expected to be equivalent between men and women. With each participant ($n = 30$) performing five experimental runs of 8 condition blocks, there was a total of 1200 condition blocks for all conditions and all participants. Of these, 8 blocks contained errors (e.g., performing the right-hand condition during a block in which they were instructed to perform the asymmetrical condition; performing the symmetrical condition during a block in which they were instructed to perform the left-hand condition; etc.). The error rate was therefore defined as the total number of blocks in which a participant performed the task incorrectly. A two-tailed $t$ test was performed to compare error rates between men and women. Men and women did not differ in their ability to successfully perform the task ($p = 0.17$).

## Preprocessing of MRI data

MRI data were analysed with the CONN toolbox (version 21a; https://www.nitrc.org/projects/conn) in Matlab R2019a (Mathworks Inc., Natick, MA) using the default preprocessing pipeline and denoising procedure (Whitfield-Gabrieli and Nieto-Castanon 2012). The pipeline included realignment of the functional data using the SPM12 *realign & unwrap procedure* (Andersson et al. 2001) to coregister and resample all scans to a reference image (first scan of the first session). Temporal distortions between slices in the functional data were corrected using the SPM12 *slice-timing correction procedure* (Henson et al. 1999). Scans with a framewise displacement $> 0.9$ mm or global BOLD signal changes of $> 5$ SD of each participant's mean were identified and flagged as outliers. Functional and anatomical data were then normalized into MNI space and segmented into grey matter, white matter, and cerebrospinal fluid tissue classes based on the SPM12 unified segmentation and normalization procedure (Ashburner and Friston 2005). Smoothing of fMRI data was performed by applying a spatial convolution with a Gaussian kernel of 8 mm full-width half-maximum (FWHM).

Functional data were then denoised using Ordinary Least Squares (OLS) regression to remove the following confounding effects for each voxel's time-series: (a) White matter and cerebrospinal fluid areas that were computed by applying a one-voxel binary erosion to the masks of voxels with values above 50% in white matter and cerebrospinal fluid posterior probability maps. Within each of these two regions, 5 potential noise components were estimated. These included the average BOLD signal and the first four components in a Principal Component Analysis of the covariance within the subspace orthogonal to the average BOLD signal; (b) 12 head motion parameter estimates (3 translation, 3 rotation, and their associated first-order derivatives); (c) all identified outlier scans from the preprocessing pipeline (i.e., scans with a framewise displacement $> 0.9$ mm or global BOLD signal changes $> 5$ SD); and (d) linear BOLD signal trends within each session. Last, following nuisance regression, functional data were temporally filtered by applying a bandpass of 0.008—0.09 Hz.

## Generalized psychophysiological interaction (gPPI) analysis to measure functional connectivity

Several brain regions of interest (ROIs) were chosen for this study based on their importance in bimanual coordination, or that have demonstrated sex-related differences associated with motor control. Neuroimaging studies have identified a distributed sensorimotor network involved in bimanual coordination consisting of the dorsal premotor cortex (PMd), primary sensorimotor cortex (S1/M1), supplementary motor area (SMA), cingulate motor area (CMA), superior parietal lobule (SPL), inferior parietal lobule (IPL), and cerebellum (Sadato et al. 1997; Jancke et al. 2000; Immisch et al. 2001; Tracy et al. 2001; Swinnen 2002; Nair et al. 2003; Ullén et al. 2003; Debaere et al. 2004a; Kraft et al. 2007; Wu et al. 2010; Lin et al. 2017).

Within the cerebellum, cerebellar lobules IV, V, VI, and VIII, and vermis regions V, VI, and VIII were specifically identified as being involved in bimanual coordination (Debaere et al. 2004a, b; Boisgontier et al. 2018). Sex-differences have been reported in premotor regions, S1, SPL, and regions of the lateral sulcus (superior temporal gyrus (STG) and parietal operculum (PO)) during eye-hand coordination tasks (Gorbet and Sergio 2007). The CONN toolbox uses the FSL Harvard–Oxford atlas (distributed with FSL http://www.fmrib.ox.ac.uk/fsl/) and AAL atlas (Tzourio-Mazoyer et al. 2002) for cortical and cerebellar parcellation, respectively. Therefore, the following cortical regions from the FSL Harvard–Oxford atlas were used as seed regions for analysis: right/left precentral gyrus, right/left postcentral gyrus, right/left superior parietal lobule, right/left supramarginal gyrus, right/left angular gyrus, right/left supplementary motor cortex, right/left parietal operculum cortex, and right/left superior temporal gyrus. The following cerebellar regions from the AAL atlas were chosen as seed regions: right/left lobule IV/V, right/left lobule VI, right/left lobule VIII, vermis IV/V, vermis VI, and vermis VIII.

First-level seed-to-voxel generalized psychophysiological interaction (gPPI) analysis was then implemented in CONN to examine how sex modulates functional connectivity during bimanual coordination. A gPPI analysis computes how functional association strength between a seed region and all other voxels in the brain covaries with an external or experimental factor (in this case, task condition). In CONN, gPPI analysis involves computation of separate multiple regression models for each target voxel BOLD time series, and included (a) all of the selected task effects convolved with a canonical hemodynamic response function (psychological term), (b) seed ROI BOLD time-series (physiological term), and (c) the interaction term specified as the product of (a) and (b) (PPI term). Second-level analyses were then performed to control for multiple comparisons at the level of individual clusters using parametric statistics based on Gaussian Random Field Theory (Worsley et al. 1996). Sex was used as a covariate in the second-level analysis, with a contrast of female > male set for each of the seed regions for all four task conditions (left unimanual, right unimanual, in-phase/symmetrical, anti-phase/asymmetrical). Active clusters were reported only when surviving a voxel-level a priori $p < 0.001$ uncorrected height threshold and a false discovery rate (FDR)-corrected cluster-level $p < 0.05$ threshold. The uncorrected height threshold p-value is defined as the likelihood of a randomly selected cluster being its size or higher and the FDR-corrected $p$ value is defined as the expected proportion of false discoveries among all clusters of this size or larger over the entire analysis volume, both under the null hypothesis.

## Results

Functional connectivity between our seed ROIs and the whole brain differed between men and women during our four task conditions (see Table 2). During the right-hand unimanual condition (Fig. 2a), women demonstrated increased connectivity relative to men between the right SPL (seed) and voxels covering the right central opercular cortex/PMd, as well as between the left SPL (seed) and bilateral anterior CMA. Men showed greater functional connectivity between the bilateral anterior CMA (seed) and voxels covering the right lateral occipital cortex/IPL (angular gyrus) and between the right cerebellar lobule VIII (seed) and right lateral occipital cortex/precuneus. The effects reported in the right-hand condition reflect a more intra-hemispheric connectivity pattern in both women and men, and that it is the connectivity within the ipsilateral (right) hemisphere that differs between the sexes.

During the left-hand unimanual condition (Fig. 2b), women had increased functional connectivity between the right SMA (seed) and voxels covering bilateral IPL (supramarginal gyrus) and primary sensorimotor cortex (S1/M1). Vermis VI (seed) also had greater connectivity to the left lateral occipital cortex and left lingual gyrus/cerebellar lobule IV/V. In men, greater functional connectivity was demonstrated between right STG to the right lateral occipital cortex/precuneus, left cerebellar lobule IV/V (seed) to the left frontal cortex and left IPL (angular gyrus/supramarginal gyrus), between right cerebellar lobule VI (seed) to left PMd, and between vermis VIII (seed) to left middle temporal gyrus. These results from the left-hand condition, similarly to the right-hand condition, show a greater involvement of the hemisphere ipsilateral to the hand movement (i.e., left hemisphere for left-hand movements) in both men and women. In contrast to the right-hand condition, however, the findings from the left-hand show both intra- and interhemispheric connections.

The effects shown in the two bimanual tasks generally reflect a more interhemispheric connectivity pattern. Greater interhemispheric connectivity was demonstrated in both sexes in the in-phase (symmetrical/mirror) condition (Fig. 2c). Specifically, women showed greater functional connectivity between the right IPL (supramarginal gyrus; seed) and the left CMA. Women also had higher connectivity between vermis IV/V (seed) and other subcortical structures in the left hemisphere (including the left cerebellar Crus I and II, thalamus, and hippocampus). Men had greater functional connectivity between right PMd (seed) and right PMd/SMA, as well as right SMA (seed) and left lingual gyrus/occipital fusiform gyrus. Women also showed interhemispheric connections in the anti-phase

**Table 2** Results of the seed-based generalized psychophysiological interaction (gPPI) analysis for the contrast female vs male

| Condition | Seed (hemi) | Target (hemi) | Cluster size (no. of voxels) | MNI coordinates (*x*, *y*, *z*) | p-FDR[a] | Higher connectivity |
|---|---|---|---|---|---|---|
| Right | Superior parietal lobule (right) | 26% Central opercular cortex (right); 20% Inferior frontal gyrus, pars opercularis (right); 20% Precentral gyrus (right) | 429 | 48, 6, 4 | < 0.001 | Women |
| | Superior parietal lobule (left) | 99% Cingulate gyrus, anterior division (mid) | 165 | − 2, 10, 36 | 0.011 | Women |
| | Cingulate gyrus, anterior division (mid) | 50% Lateral occipital cortex, superior division (right); 39% Angular gyrus (right) | 155 | 42, − 58, 24 | 0.018 | Men |
| | Cerebellar lobule VIII (right) | 66% Lateral occipital cortex, superior division (right); 10% Precuneus (mid); 6% Cuneus (right) | 163 | 18, − 78, 40 | 0.025 | Men |
| Left | Superior temporal gyrus, posterior division (right) | 55% Cerebellar lobule 6 (left); 28% Lingual gyrus (left); 15% Cerebellar lobule 4/5 (left) | 101 | − 10, − 64, − 14 | 0.049 | Men |
| | Supplementary motor area (right) | 31% Supramarginal gyrus, anterior division (right); 24% Parietal operculum (right); 18% Postcentral gyrus (right) | 193 | 56, − 16, 22 | 0.009 | Women |
| | | 70% Supramarginal gyrus, anterior division (left); 27% Postcentral gyrus (left) | 149 | − 62, − 26, 24 | 0.017 | Women |
| | Cerebellar lobule IV/V (left) | 50% Frontal pole (left); 34% Superior frontal gyrus (left) | 137 | − 6, 56, 28 | 0.018 | Men |
| | | 65% Angular gyrus (left); 20% Supramarginal gyrus, posterior division (left) | 130 | − 56, − 54, 22 | 0.018 | Men |
| | Cerebellar lobule VI (right) | 57% Precentral gyrus (left); 38% Middle frontal gyrus (left) | 136 | − 38, − 4, 54 | 0.024 | Men |
| | Cerebellar vermis VI (mid) | 64% Lateral occipital cortex, superior division (left); 34% Occipital pole (left) | 173 | − 26, − 90, 30 | 0.007 | Women |
| | | 71% Lingual gyrus (left); 25% Cerebellar lobule 4/5 (left) | 150 | − 8, − 54, − 8 | 0.007 | Women |
| | Cerebellar vermis VIII (mid) | 51% Middle temporal gyrus, posterior division (left); 35% Middle temporal gyrus, temporooccipital part (left) | 137 | − 58, − 44, 2 | 0.009 | Men |
| In-phase | Precentral gyrus (right) | 60% Precentral gyrus (right); 9% Supplementary motor cortex (right) | 134 | 10, − 18, 56 | 0.033 | Men |

**Table 2** (continued)

| Condition | Seed (hemi) | Target (hemi) | Cluster size (no. of voxels) | MNI coordinates (*x*, *y*, *z*) | p-FDR[a] | Higher connectivity |
|---|---|---|---|---|---|---|
| | Supramarginal gyrus, posterior division (right) | 34% Paracingulate gyrus (left); 30% Subcallosal cortex; 23% Cingulate gyrus, anterior division (mid); 3% Paracingulate gyrus (right) | 145 | − 6, 42, − 8 | 0.029 | Women |
| | Supplementary motor area (right) | 55% Lingual gyrus (left); 43% Occipital fusiform gyrus (left) | 155 | − 20, − 79, − 10 | 0.049 | Men |
| | Cerebellar vermis IV/V (mid) | 18% Cerebellar Crus 2 (left); 16% Cerebellar Crus 1 (left) | 180 | − 2, − 84, − 18 | 0.018 | Women |
| | | 37% Thalamus (left); 20% Hippocampus (left) | 126 | − 20, − 28, − 4 | 0.044 | Women |
| Anti-phase | Supplementary motor area (right) | 77% Insular cortex (left); 12% Planum polare (left) | 131 | − 38, − 18, − 86 | 0.032 | Women |

Percentages in the Target column indicate what percentage of that significant cluster corresponds to regions in the Harvard–Oxford atlas

[a] False discovery rate (FDR)-corrected cluster-level $p < 0.05$ threshold

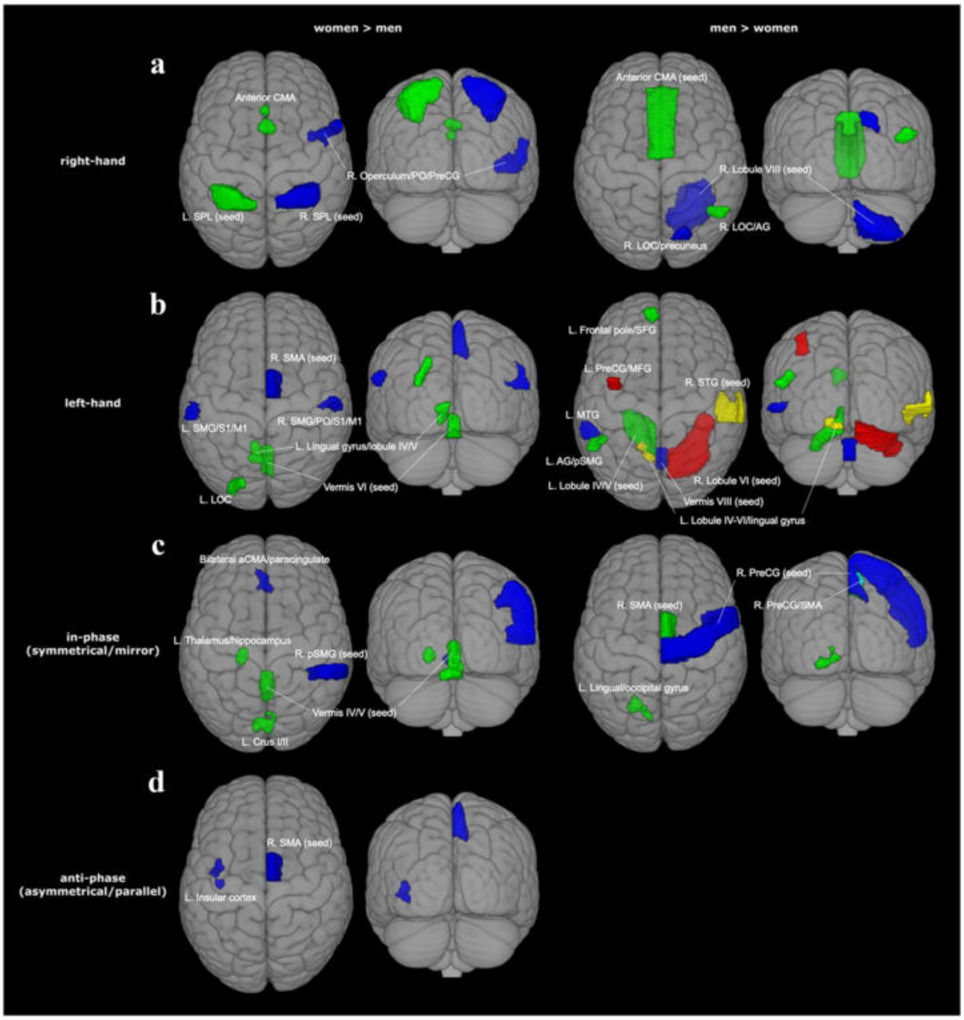

**Fig. 2** Regions of interest (seeds) and the corresponding significant clusters showing increased functional connectivity with that seed for the contrast female vs male. Colours of the seed regions match their respective target regions. Women > male indicate regions that showed increased functional connectivity in women and men > women indicate regions that showed increased functional connectivity in men in the **a** right-hand unimanual, **b** left-hand unimanual, **c** in-phase (symmetrical/mirror) bimanual, and **d** anti-phase (asymmetrical/parallel) bimanual conditions. *CMA* cingulate motor area, *SPL* superior parietal lobule, *PO* parietal operculum, *PreCG* precentral gyrus, *LOC* lateral occipital cortex, *AG* angular gyrus, *SMG* supramarginal gyrus, *SMA* supplementary motor area, *S1/M1* primary sensorimotor cortex, *SFG* superior frontal gyrus, *MFG* middle frontal gyrus, *MTG* middle temporal gyrus, *STG* superior temporal gyrus

(asymmetrical/parallel) condition (Fig. 2d), with greater functional connectivity between the right SMA (seed) and left insular cortex.

## Discussion

The main goal of the current study was to assess whether there were sex differences in the functional connectivity underlying bimanual control even in the absence of behavioural performance differences. The key findings of this paper were that (1) functional connectivity sex differences exist during unimanual and bimanual movements and are distinct for each task condition, and (2) functional connectivity differences where women had greater connectivity than men tended to involve cortical areas, while functional connectivity differences where men had greater connectivity than women were more likely to involve the cerebellum.

### Functional connectivity is distinct for right- vs left-hand unimanual conditions in women and men

It has been well established that unimanual movements rely on a bilateral motor network (Chettouf et al. 2020) where right-handed movements typically involve greater activity within the contralateral motor areas (Kawashima et al. 1993; Kim et al. 1993; Li et al. 1996; Stephan et al. 1999). In both women and men the findings from the right-hand condition reflect a largely intrahemispheric pattern of connectivity, while the left-hand condition shows both intra- and interhemispheric connections. The sex differences observed in the current study in the right-hand condition suggest that it is connectivity within the ipsilateral hemisphere that largely differs between men and women. Women had greater functional connectivity between bilateral SPL and motor regions including the anterior CMA and right PMd. Neuroimaging studies in humans have shown that the SPL is interconnected with the CMA (Rushworth et al. 2006), which has been linked to manual action (Paus et al. 1993), as well as both anatomically and functionally with the PMd (Wise et al. 1997; Tanné-Gariépy et al. 2002). Together, the SPL and PMd form part of the visuomotor network important for the selection, preparation, and execution of movements (Caminiti et al. 2017). Similar to the increased connectivity between right parietal and right premotor regions we reported in women, a study looking at visually guided arm movements demonstrated that activity in parietal and premotor regions tended to be more bilateral in women with greater activation of the right (ipsilateral) hemisphere during right-handed movements (Gorbet and Sergio 2007). They also found that the right PMd was more active in women than in men. The SPL in particular was previously shown to be more activated for simple finger sequencing in 11 year old fifth-grade girls compared to boys (Richards et al. 2009) and more bilaterally activated in women compared to men during various motor tasks (Jordan et al. 2002; Gorbet and Sergio 2007). When tapping with the dominant hand, women showed higher activation in the contralateral parietal cortex, ipsilateral premotor cortex, and ipsilateral anterior CMA (Lissek et al. 2007). Findings from these studies align with the greater connectivity between bilateral SPL and motor regions we reported in women when performing a right-handed finger pressing task.

Findings from the right-hand condition revealed that men had greater functional connectivity between anterior CMA and the right angular gyrus extending into the right lateral occipital cortex, as well as between the right cerebellar lobule VIII and the precuneus extending into the right lateral occipital cortex. Relative to a rest control, right-hand finger tapping has been shown to produce activation in lobule VIII, with greater activation occurring ipsilaterally (Desmond et al. 1997). In another study that looked only at male participants, activation during right-hand movements was observed in the ipsilateral cerebellar hemisphere of lobule VIII (Habas et al. 2004), which is activated during hand movements (Grodd et al. 2001). These findings coincide well with our results showing greater connectivity between this area and medial PPC in men performing the right-hand condition.

Production of left-hand unimanual movement involved sex differences in connectivity between brain regions that were distinct from, and not a mirror of, the functional connectivity differences observed for right-hand unimanual movement. Previous findings suggest that activity in the left hemisphere is essential for controlling more complex movements, such as left-hand use in right-handed individuals (Serrien and Spapé 2009). Several imaging studies have demonstrated a greater engagement of the ipsilateral hemisphere during left-hand movements (Kawashima et al. 1993; Kim et al. 1993; Li et al. 1996; Stephan et al. 1999). In the present study, there was greater involvement of the ipsilateral (left) hemisphere in both men and women in the left-hand condition, and taken together with findings from the right-hand condition suggests that sex differences are more prominent in functional connectivity with the ipsilateral hemisphere to the movement. Women generally showed significantly greater connectivity between ipsi- and contralateral task-related cortical areas than men, while men mainly had greater connectivity involving the cerebellum and this connectivity was mainly ipsilateral. The right SMA was bilaterally connected to the supramarginal gyrus and sensorimotor regions to a greater degree in women and has been shown to be a brain area with increased activation during motor and sensory tasks using the left hand (Chung et al. 2005). Both the primary sensorimotor and posterior parietal areas are also activated during sequential finger movements paced with an auditory cue (Catalan et al. 1998). Men had greater connectivity between the contralateral STG and precuneus/lateral occipital cortex, and regions of the cerebellum with the ipsilateral frontal cortex, IPL (angular and supramarginal gyri), and MTG. The connectivity between these regions is very similar to patterns of activation previously reported in men during tapping sequences with the non-dominant hand, where there was higher activation in ipsilateral IPL, STG, MTG, and regions of the frontal gyrus (Lissek et al. 2007). The STG is thought to be involved in the processing of auditory timing (Bueti et al. 2008), and the STG along with the inferior frontal cortex are activated during the performance of rhythmic sequences (Ullen et al. 2005). TMS over the right STG in particular has been shown to decrease performance accuracy and increase response uncertainty (Bueti et al. 2008). Activation of the IPL has also been observed in the performance of sequential finger-tapping movements (Hanakawa et al. 2003). Our findings demonstrate that different regions of the lateral and medial PPC, including the SPL, IPL (composed of the angular and supramarginal gyri), and precuneus are important for both men and women in performing both right and left-hand movements. This is not surprising given the vital role the PPC plays in multiple cognitive and motor processes including planned movements, sensorimotor integration, and spatial attention (Whitlock 2017).

Both men and women also showed greater involvement of the cerebellum in left-handed movements, with more cerebellar regions showing distinct functional connectivity in men compared to women suggesting that the cerebellum is especially important for left-handed movements in men. The cerebellar motor regions span the hemispheres of lobules IV–VIII (Habas et al. 2009; Krienen and Buckner 2009; Stoodley and Schmahmann 2009, 2010), corresponding to hand representation in these lobules (Grodd et al. 2001; Wiestler et al. 2011). Activation in these regions has been reported during different finger movement tasks including tapping and flexion/extension (Rijntjes et al. 1999; Ramnani et al. 2001; Blouin et al. 2004). Sex differences have also been reported in the cerebellum, where the cerebellar lobule and vermis VIII have a larger relative volume in men compared to women (Steele and Chakravarty 2018) and may explain the greater involvement of this motor cerebellar lobule in the two unimanual tasks in men.

## Sex differences in the functional connectivity underlying bimanual control

The two bimanual conditions were not a combination of results from the two unimanual conditions, suggesting that different neural activity underlies unimanual and bimanual tasks in men and women. This coincides with other studies suggesting that while there is overlap in areas activated during bimanual and unimanual tasks, bimanual movements show distinct patterns of activation and are not simply a summation of independent movements (Jancke et al. 2000; Cardoso de Oliveira et al. 2001; Swinnen 2002; Walsh et al. 2008; Lin et al. 2017). In the current study, the regions showing differences in functional connectivity tended to be in the opposite hemisphere to the seed region rather than within the same hemisphere as the seed. This in part supported our hypothesis as women showed greater interhemispheric functional connectivity in both bimanual conditions, although we report that men did also have greater interhemispheric connectivity during the in-phase task. While we expected greater bilateral connectivity for bimanual performance in women based on previous corpus callosum structural findings (Allen et al. 1991; Dubb et al. 2003), our findings of greater interhemispheric functional connectivity underlying the in-phase task in men are not surprising given the general importance of interhemispheric connectivity for bimanual movements (Johansen-Berg et al. 2007; Muetzel et al. 2008).

Sex differences in functional connectivity existed between distinct regions depending on the bimanual mode used. In the in-phase task, women had increased functional connectivity between the right supramarginal gyrus and left anterior CMA. Compared to unimanual movements, bimanual movements have previously been shown to have a stronger activation of an area corresponding to the anterior CMA (Wenderoth et al. 2005). Women also showed greater connectivity between vermis IV/V and left cerebellar Crus I/II, thalamus, and hippocampus in the in-phase condition. To perform the bimanual movement, online monitoring of finger positions is necessary (Sadato et al. 1997) and suggests that activation of brain regions involved in spatial attention and spatial working memory may therefore be important for successful bimanual control. The cerebellum has been shown to be important in the visual guidance of movement, as well as for feedback loops and online correction and control of movement (Bastian 2006; Manto et al. 2012; Patel and Zee 2015). Women have larger cerebellar Crus II volumes compared to men (Steele and Chakravarty 2018), which along with Crus I is a cerebellar region implicated in spatial processing (Stoodley and Schmahmann 2009). There is increased activation of cerebellar lobules IV/VI during successful bimanual control (Debaere et al. 2004a; Boisgontier et al. 2018), with lobules V/VIII and vermis V/VI/VIII increasingly activated in more complex bimanual tasks (Tracy et al. 2001; Blouin et al. 2004; Debaere et al. 2004b). This may explain the increased connectivity between vermis IV/V and Crus II that we saw in women.

We found that men had greater functional connectivity between the right SMA and left lingual gyrus/occipital fusiform gyrus in the in-phase condition, as well as greater within-seed region functional connectivity in the right PMd with the significant target cluster further overlapping with the right SMA. The right SMA also had greater interhemispheric connectivity with the left insular cortex, which is involved in a variety of functions including cognitive control and sensorimotor processing (Uddin et al. 2017), in the anti-phase task in women. The SMA participates in the execution of sequential unimanual and bimanual movements (Shibasaki et al. 1993; Gerloff et al. 1997; Sadato et al. 1997), demonstrating further increased activity during more complex bimanual movements such as in anti-phase compared to in-phase tasks (Sadato et al. 1997; Debaere et al. 2001, 2004a; Immisch et al. 2001; Ullén et al. 2003; Wu et al. 2010). The SMA also appears to be involved in the control of interhemispheric interactions by adjusting the coupling of both primary motor cortices during the coordination of bimanual tasks (Serrien et al. 2002). Our data are therefore concurrent with previous findings suggesting that the right SMA is particularly important for bimanual movements in both men and women, and further demonstrates that it has different interhemispheric connectivity patterns with the rest of the brain depending on the type of bimanual task used.

Thus, women showed overall greater bilateral connectivity not only in the left-hand condition but in the two bimanual conditions as well. Although there is still some debate as to whether sex contributes to cerebral lateralization, sex has been found to be associated with functional asymmetry with stronger laterality in men than in women (Liu et al. 2009). In cerebral regions, males have shown greater within-hemispheric connectivity, while females had predominantly between-hemispheric connectivity (Ingalhalikar et al. 2014). This relationship was reversed in the cerebellum, with greater interhemispheric cerebellar connectivity in men. These findings were supported by graph theory measures demonstrating that male brains generally had higher clustering coefficients and higher local efficiency in nodes within the cerebral cortex, while these measures were higher for female participants only in the cerebellum (Zhang et al. 2016). The findings from these studies support the notion that within females, connections are more widespread between the two hemispheres and the network is less modular thus facilitating functional integration, whereas men prevail in functional segregation. Integration refers to the efficiency of global information communication or the ability to combine distributed information, while segregation provides insight into the degree to which network elements form specialized communities (e.g., modules of anatomically or functionally connected areas) (Watts and Strogatz 1998; Farahani et al. 2019).

In conclusion, the observed sex differences in functional connectivity included differences with respect to intra- vs interhemispheric connectivity, differences in supra- vs infratentorial connectivity, and differences in lateralization of areas in one sex compared to the other. These between-sex differences in cerebral and cerebellar activation patterns during unimanual and bimanual movements existed even when women and men had similar error rates, suggesting that patterns of brain activity differ in women and men even when performing equivalent movements. Gaining knowledge of how neural activity may differ between men and women during bimanual movement is important not only for our fundamental understanding of how the brain works but also from a clinical perspective. Stroke is the leading cause of long-term motor impairments, with approximately 80% of unilateral stroke patients initially experiencing hemiparesis (a weakness of one side of the body) in their contralesional upper extremities (Virani et al. 2021). Bimanual movement training has been tested for many years as a promising rehabilitation technique for hemiparesis (Rose and Winstein 2004; Wolf et al. 2014). The goal of this approach is to encourage corresponding intact brain regions in the undamaged brain hemisphere to stimulate damaged areas via interhemispheric connections. However, many studies have produced inconsistent results (Cauraugh et al. 2010) and, to our knowledge, no studies have examined sex as a potential factor in bimanual training success. Understanding how the sex of an individual contributes to the neural control of different bimanual movements could inform clinical practice regarding how approaches can best be tailored to the needs of individuals, by individualizing the types of tasks used in bimanual movement training.

## Limitations and future directions

The results presented in this study should be considered preliminary, as the data set used was relatively small due to the financial costs associated with MRI not allowing for additional participants to be recruited. Despite these constraints on the number of participants that could be included, we have tried to eliminate as many differences between the two experimental groups as possible. Participants' eye movements were tracked, and mean ages, handedness scores, and performance error rates did not differ significantly between men and women. While it is difficult to eliminate all non-sex-related differences between groups, we argue that the findings presented here are largely attributable to sex-specific group differences. As mentioned in the introductory section of this study, sex-related discrepancies in bimanual coordination performance that have been reported in the literature may be due to differences in the bimanual tasks used (Rudisch et al. 2020). While we acknowledge that we have used two very simple paradigms to investigate the neural underpinnings of bimanual control, we argue that this is an advantage as it allows for a clear interpretation of the results and we believe that the findings in this study represent an important starting point. The purpose of the task was not to be a reaction time test, as participants were specifically told to move slowly and smoothly in order to limit the amount of head movement associated with the task. Participants were also given extensive practice including an illustrated guide to how to perform the tasks in the scanner, a demonstration of the tasks, and they each completed a full functional run outside of the scanner where the experimenter verified that each participant understood the tasks and could perform them correctly. However, we acknowledge the limitation that this poses on the ability to ascertain whether task performance was equivalent between the sexes beyond reporting similar error rates between women and men. Further, it is important to recognize that bimanual movement control is something that typically entails the full span of perception, sensory processing, motor preparation and execution, and feedback processing. While we demonstrate sex-related differences in the underlying neural control of this behaviour as a whole, we are unable to examine specifically which aspect of these processes may underly the observed control differences. We cannot disentangle all of the stages of perception to action involved in stimulus-cued voluntary movement production and this is a limitation; however, no voluntary movement task is completely free from perceptual or cognitive components. Future work will be needed to characterize which aspects of this complex behaviour—or indeed if it is all of them—differ as a function of biological sex. Although gender and its impact on functional connectivity underlying motor control was beyond the scope of the current study, we hope to investigate this relationship in the future. While the purpose of the study was to examine whether sex differences in functional connectivity associated with bimanual movement do, in fact, exist, the findings we report in the manuscript do not allow us to speculate on *why* there may be sex differences in functional connectivity. Further studies will be needed to elucidate what mechanisms may underlie the differences in connectivity that we demonstrate here for the first time. We have also collected diffusion-weighted scans for all participants in the study that could potentially be used to expand on previous reports of greater interhemispheric structural connectivity in women (Allen et al. 1991; Dubb et al. 2003) by exploring potential sex-related differences in structural connectivity underlying bimanual movement control.

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

## Declarations

**Conflict of interest** The authors have no competing interests to declare that are relevant to the content of this article.

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