

Electronic Thesis and Dissertation Repository

10-4-2022 10:30 AM

Virtual hand actions show behavioural and neural signatures of right handedness

Jaana Leppala, *The University of Western Ontario*

Supervisor: Culham, Jody C., *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

© Jaana Leppala 2022

Follow this and additional works at: <https://ir.lib.uwo.ca/etd>

Recommended Citation

Leppala, Jaana, "Virtual hand actions show behavioural and neural signatures of right handedness" (2022). *Electronic Thesis and Dissertation Repository*. 8907.
<https://ir.lib.uwo.ca/etd/8907>

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlsadmin@uwo.ca.

Abstract

Using functional magnetic resonance imaging (fMRI), I examined whether video games could evoke similar neural signatures as real actions (specifically, activation contralateral to the hand performing an action) and whether brain activation depended on causal control with closed-loop feedback. During Play runs, right-handed participants used their right or left hand on a gamepad to control a virtual right or left hand to move an object. During React runs, participants used the gamepad to follow actions without control of viewed actions. During Watch runs, participants passively viewed actions. Activation in was stronger in the hemisphere contralateral (vs. ipsilateral) to the virtual hand, particularly for the right hemisphere (left hand). Moreover, having control over actions (Play > React) increased sensorimotor activity, whereas, a lack of control (React > Play) increased association cortex activity. These results suggest video games hold potential for neuroimaging research, particularly under active control with closed-loop visual feedback.

Keywords

fMRI

video game

avatar

hands

closed-loop feedback

reach-to-grasp

reach

actions

left hand

right hand

Summary for Lay Audience

Although it is important to study how the human brain controls actions, neuroimaging of real actions in a brain scanner is difficult. I examined whether video games can serve as a better approach for studying actions than existing methods in the scanner. Specifically, this study investigated whether controlling the actions of a human avatar can activate the brain similarly to performing the same actions in real life. Participants could either use their left or right hand on a gamepad to control an avatar's left or right hand in the video game. Moreover, participants engaged with the video game in three ways. First, participants' used the gamepad to control the actions of the avatar. Second, participants used the gamepad to mimic the actions of the avatar. Third, participants did not use the gamepad and simply watched the avatar's actions. The results from this study suggest that whether a hand looks like a left or right hand affects both brain activity and behaviour. As such, when the avatar performed actions with its left hand, there was increased brain activation related to reaching actions. Moreover, participants were less accurate at controlling a left avatar hand than a right avatar hand. Importantly, increased brain activation and poorer game performance associated with avatar left-hand actions were unaffected by the controlling hand used (left vs right hand on the gamepad). Additionally, when participants had control over the avatar's actions, there was increased brain activation relating to actions. When participants did not have control over the actions there was increased brain activation relating to cognition. Overall, the results suggest that video games in which participants have control over a realistic human body, can be used as a new way to study actions at a level more similarly to real actions than other methods.

Co-Authorship Statement

This study was completed with the contributions of Jody Culham, Kevin Stubbs and Karsten Babin. Kevin Stubbs contributed to fMRI and behavioural data analyses and Karsten Babin aided in the design of the video game. Dr. Jody Culham supervised this project, providing guidance during experimental design, analysis planning and thesis writing.

Acknowledgements

I would like to thank my supervisor, Dr. Jody Culham for providing helpful guidance throughout my Masters thesis. I would like to thank Kevin Stubbs and Karsten Babin for their technical support throughout this experience. I would also like to thank Ishrat Mangat and Nishita Sharif for aiding in data collection as well as Guy Rens, Mel Goodale and Joern Diedrichsen for helpful advice. Lastly, I would like to thank New Frontiers in Research Fund (Canada), Natural Sciences and Engineering Research Council (Canada), Canada First Research Excellence Fund and “BrainsCAN” Grant to University of Western Ontario for sponsoring this project.

Table of Contents

ABSTRACT	II
KEYWORDS	III
SUMMARY FOR LAY AUDIENCE	IV
CO-AUTHORSHIP STATEMENT	V
ACKNOWLEDGEMENTS	VI
TABLE OF CONTENTS	VII
LIST OF TABLES	IX
LIST OF FIGURES	X
1 INTRODUCTION	1
CHAPTER 2	6
2 METHODS	6
2.1 PARTICIPANTS.....	6
2.2 SETUP AND EXPERIMENTAL PROCEDURE.....	6
2.3 ANATOMICAL AND FUNCTIONAL SCANS.....	10
2.4 PREPROCESSING & ANALYSIS.....	11
2.5 COMPARISON WITH KNOWN BRAIN REGIONS.....	13
2.6 POST-SCANNING QUESTIONNAIRES.....	14
2.7 QUESTIONNAIRE DATA ANALYSIS.....	14
2.8 EQUIPMENT.....	14
2.9 BEHAVIORAL EXPERIMENT.....	15
CHAPTER 3	17
3 RESULTS	17
3.1 ORGANIZATION OF RESULTS.....	17
3.2 fMRI DATA	17
3.2.1 VIRTUAL HAND EVOKES CONTRALATERAL ACTIVATION, PARTICULARLY FOR THE LEFT VIRTUAL HAND IN THE RIGHT HEMISPHERE.....	17
3.2.2 BRAIN ACTIVATION EVOKED FROM ACTIONS SEEN IN THE LEFT SIDE VERSUS RIGHT SIDE IS ASYMMETRICALLY LATERALIZED.....	20
3.2.3 CONTROLLING HAND EVOKES BILATERAL MOTOR ACTIVITY AS EXPECTED.....	22
3.2.4 HAVING CONTROL OVER VIRTUAL HAND ACTIONS RESULTS IN INCREASED ENGAGEMENT OF THE MOTOR NETWORK... ..	25
3.3 IN-SCANNER BEHAVIOURAL DATA	28
3.3.1 BRAIN ACTIVATION DOES NOT APPEAR TO BE RELATED TO INDIVIDUAL DIFFERENCES.....	28
3.3.2 VIRTUAL LEFT HAND ACTIONS RESULT IN POORER ACCURACY THAN VIRTUAL RIGHT HAND ACTIONS.....	28
3.3.3 NO TASK-RELATED TIMING DIFFERENCES WERE FOUND BETWEEN VIRTUAL HANDS. PARTICIPANTS REPORTED EQUAL TASK DIFFICULTY BETWEEN PLAY AND REACT.	30
3.4 OUT-OF-SCANNER BEHAVIOURAL DATA	31
3.4.1 EYE MOVEMENTS AND GAZE ARE AFFECTED BY STATE BUT NOT VIRTUAL HANDS, CONTROLLING HANDS OR SIDE.....	32
3.4.2 JOYSTICK USE WAS GREATER IN PLAY THAN REACT.....	33
CHAPTER 4	34

4	DISCUSSION.....	34
4.1	SUMMARY OF RESULTS	34
4.2	THE IMPORTANCE OF THE VISUAL APPEARANCE OF THE HAND	35
4.3	HAVING CONTROL OVER ACTIONS IS KEY FOR MOTOR SYSTEM ENGAGEMENT.	36
4.4	LIMITATIONS	38
4.5	FUTURE DIRECTIONS	39
4.6	CONCLUSION.....	40
	REFERENCES	41
	CURRICULUM VITAE	41

List of Tables

TABLE 1: MNI COORDINATES OF BOLD-SIGNAL MAXIMA FROM VARIOUS CONTROLLING AND VIRTUAL HAND CONTRASTS. .	24
TABLE 2: MNI COORDINATES OF BOLD-SIGNAL MAXIMA FROM VARIOUS STATE CONTRASTS.	27

List of Figures

FIGURE 1: 2x2x3 EXPERIMENTAL DESIGN.....	4
FIGURE 2: THE EXPERIMENTAL PROCEDURE.....	9
FIGURE 3: MAIN EFFECT OF VIRTUAL HAND.....	20
FIGURE 4: MAIN EFFECT OF SIDE.....	22
FIGURE 5: MAIN EFFECT OF CONTROLLING HAND.....	23
FIGURE 6: ACTIONS IN PLAY RESULTS IN INCREASED RECRUITMENT OF THE MOTOR SYSTEM THAN REACT AND WATCH.....	26
FIGURE 7: DROP ERROR WAS WORSE FOR VIRTUAL LEFT THAN RIGHT HAND ACTIONS.....	30

Chapter 1

1 Introduction

Understanding the neural basis of human actions is critical for helping those with neurodegenerative and neuromuscular disorders. One predominant way to study actions is using functional magnetic resonance imaging (fMRI). However, current fMRI methods are limited due to space and movement constraints in the scanner. Due to these constraints, fMRI has been used to study only a limited range of real actions, such as grasping (Binkofski et al., 1999; Culham et al., 2003), reaching (Cavina-Pratesi et al., 2010; Connolly et al., 2003) and tool use (Brandi et al., 2014; Gallivan et al., 2013), while other ethological actions like feeding, head movements, and locomotion have been largely neglected (for exceptions see (Castiello et al., 2000; Petit & Beauchamp, 2003; Toyomura et al., 2012)).

Considering the constraints on real movements, many fMRI studies of motor control rely on proxies for actual movements (e.g., action observation, motor imagery, pantomimed actions). Although these proxies have been found to evoke similar brain activation to real actions (Grafton et al., 1996; Rizzolatti et al., 1996), they differ in fundamental ways. Real actions produce consequences, providing sensory feedback that can be used to adjust actions on the fly and make future actions more accurate (Dewey, 1896; Wolpert & Flanagan, 2010). Ongoing interactions between sensory systems, the motor system and the environment make real actions *closed-loop*. Closed-loop actions stand in contrast to *open-loop* actions, in which there is no direct sensory feedback (e.g., motor imagery, action observation), actions do not have physical consequences (e.g., pantomimed actions), or the consequences cannot be used to modify behaviour. Evidence suggests that the difference between closed- and open-loop actions affects neural processing; for example, brain activation differs between real and pantomimed actions (Freud et al., 2018; Króliczak et al., 2007).

Given the limitations of studying real actions and common proxies using fMRI, I sought an approach to incorporate closed-loop actions using fMRI. Specifically, I set out to

examine whether the control of actions performed by an avatar in video games can evoke brain activation similar to that of actions performed by oneself in real life. Crucially, video game play is closed-loop, such that the player's actions have consequences in the virtual environment that are seen through visual feedback and used to update movements and forward models. One benefit to video games is that they enable us to study actions that would not be possible with fMRI. Nevertheless, I chose to study reach-to-grasp movements because past studies have established the neural substrates of real closed-loop actions (Binkofski et al., 1999; Castiello, 2005; Cavina-Pratesi et al., 2010; Culham et al., 2003, 2006) and open-loop proxies (Bencivenga et al., 2021; Króliczak et al., 2007; Monaco et al., 2020; Singhal et al., 2013).

A past study by Frey and colleagues (2015) found that the simulated control of hand actions did not evoke the same activation as the real action; however, numerous factors may have contributed to this null result. In that study, participants performed real reaching and grasping, or they pressed buttons to initiate video clips depicting either a robotic arm reaching or grasping an object (Frey et al., 2015). Although real grasping evoked higher activation than real reaching, no such difference was found for the simulated robotic grasp compared to the robotic reach. The authors concluded that grasp-selective neural responses require naturally occurring actions (e.g., a human hand reaching to grasp versus a button press causing a robotic grasp). However, three factors may have hampered the ability to see similar responses between the simulated and natural hand actions. First, the actions in this study were open-loop, such that participants could not update movements and forward models based on sensory feedback. Second, the effector was unnatural (a mechanical claw versus the participant's own hand) and third, the perspective of the video clip (third-person versus first-person point of view) may have reduced embodiment of the effector.

To address whether simulated actions could evoke similar activation as real actions, this study used a video game with naturalistic reach-to-grasp actions to overcome the limitations found in the study of Frey and colleagues (2015). As such, the video game actions were closed loop: participants had continuous control over virtual hand actions

and were able to modify reach-to-grasp actions on the fly based on visual feedback. Moreover, to enhance embodiment in the virtual environment, the effector was a left or right hand of a human avatar seen from first-person perspective and participants were able to view the scene freely (without maintaining fixation) during trials (Foulsham, 2015; Hofree et al., 2015; Snow & Culham, 2021).

To assess the degree to which simulated actions in a video game evoke responses similar to those of real actions, a key signature of motor system was investigated. Specifically, the motor cortex follows a principle of lateralization, such that actions evoke greater activation in the cortical hemisphere contralateral to the acting hand. Although this signature holds true for real actions, our knowledge of motor system lateralization evoked from *using* our hands versus *seeing* our hands is limited. This gap arises due to real hand actions having congruent visual and motor properties. For example, when one uses their *right* hand to perform an action, visual feedback of using their *right* hand is received. In video games, the acting hand and seen hand are typically congruent; however, they can be decoupled (e.g., when a real right hand controls a virtual left hand). This raises the intriguing possibility to investigate the degree to which lateralized activation follows the controlling hand versus the seen hand. Previous work has shown that viewing hand actions also evokes contralateral motor activity (Shmuelof & Zohary, 2005).

Interestingly, a “hand identity” effect was found such that observing a left or right hand grasp an object evokes activation in the contralateral hemisphere, regardless of the visual field in which the grasp is presented (Shmuelof & Zohary, 2006). Given that both real and seen hand actions evoke contralateral neural activity, a video game in which the controlling and virtual hand can be decoupled may be expected to evoke motor activity contralateral to both the controlling hand, particularly in motor regions, and to the seen hands, particularly in sensory regions.

The first aim of the study was to test how brain activation evoked from simulated hand actions in video games is modulated by controlling versus virtual hands. To test this, motor system lateralization was investigated in the cortex, cerebellum, and other subcortical structures. In a 2x2 design, participants used their left or right hands to control

(CL, CR) a virtual left or right hand (VL, VR) (Figure 1A). I hypothesized the neural contributions of Controlling and Virtual Hand actions in video games would depend on the location of the brain area in the sensory-motor pathway. Although primary motor cortex (M1) should display activation contralateral to the Controlling Hand, one key question was whether other sensorimotor brain regions would show activation contralateral to the Virtual Hand used. Moreover, I predicted there would be an interaction in regions that incorporate both visual and motor information, such that when the Controlling and Virtual Hands are congruent (e.g., CR, VR hands) activation would be greatest in the contralateral (e.g., left) hemisphere.

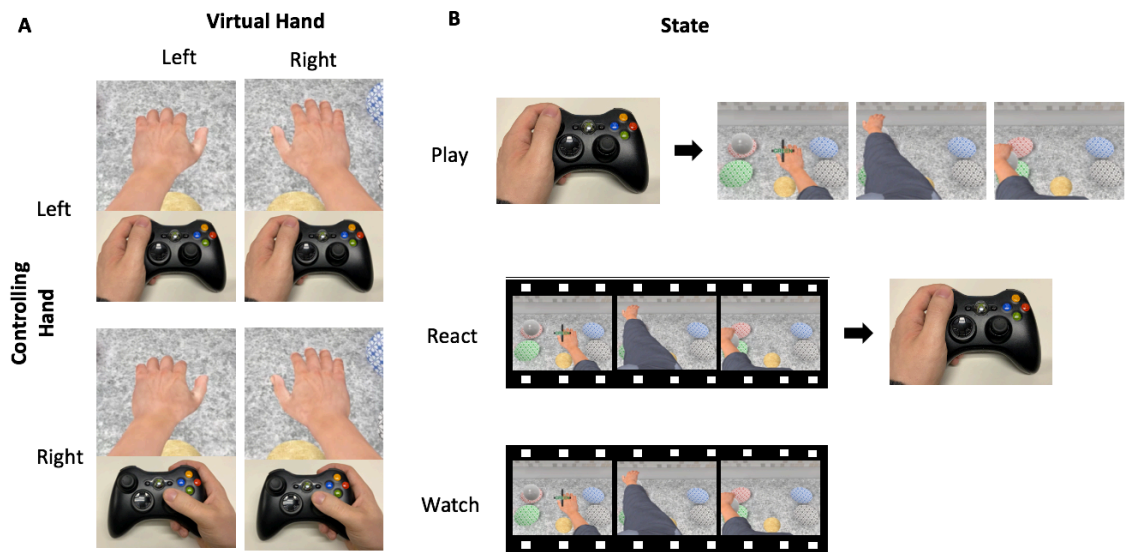


Figure 1: 2x2x3 experimental design. A) Participants used either their real left or right hand to control a virtual left or right hand. B) Participants first controlled the simulated actions in the video game in Play runs, using the joysticks to reach (e.g., push joystick forward to reach forward) and the triggers to grasp (e.g., squeeze index finger to close virtual hand). Participants' task was to guide the avatar hand toward a ball on a colored plate (e.g., red), grasp the ball and move it to a target plate indicated by an instruction (e.g., GREEN). In React runs, participants used the joystick and triggers in response to what they viewed in the video replay of their previous Play run. Namely, participants were instructed to push the joystick in the appropriate direction when they saw reaching and squeeze the trigger when they saw grasping. In Watch runs, the participants were instructed to not use the gamepad and simply watch the video replay of the previous Play run.

A second aim of the study was to determine how having control over Virtual Hand actions would affect neural activation. In addition to runs where participants had control over the avatar's actions (Play), I introduced two additional conditions in which either participants watched a replay of a previous Play run and followed the avatar's hand

actions using the gamepad (React) or passively viewed the actions unfold (Watch) (Figure 1B).

The three game states (Play, React and Watch) differed in aspects of control over the actions and motor activity. Namely, participants first completed a Play run of the video game, such that they controlled the actions of the avatar (e.g., toggle joystick to reach, squeeze trigger to grasp). In React runs, participants had motor activity and visual stimulation similar to Play, but did not have control over the actions; accordingly, participants watched the replay and mimicked the hand actions using the gamepad (e.g., toggled the joystick when they saw a reach, squeezed the trigger when they saw a grasp). Another key distinction between Play and React was the order of action causation. Specifically, in Play runs, the participants' actions caused sensory consequences; whereas in React runs, visual information influenced the participants' actions. Importantly, by comparing Play to React, I could explore the effect of having control over actions, while controlling for visual and motor stimulation, which were closely matched between the two conditions. Lastly, Watch runs were similar to action observation paradigms. That is, participants had neither motor activity or control over the actions and simply watched the replay of the virtual hand actions. It was hypothesized that having control over virtual hand actions (Play) would engage the motor system more similarly to real hand actions than proxies involving more open-loop processing (React, Watch).

Chapter 2

2 Methods

2.1 Participants

25 right-handed participants (14 women, 11 men; ages 20-29) with normal or corrected-to-normal vision were recruited for fMRI. The study was approved by the university's Non-Medical Research Ethics Board and conforms to the 1964 Declaration of Helsinki. Prior to testing, informed consent was obtained from each participant. fMRI participants received financial compensation (\$25/hour) for their time. In a follow-up behavioural study, consent was obtained from 10 participants (5 women, 5 men; ages 20-29) with the same inclusion criteria. Seven of these participants also completed the fMRI study. In the behavioural study, participants received \$15/hour as financial compensation.

I characterized the sample in terms of handedness and video-game experience before testing. The Edinburgh Handedness Inventory was used to ensure participants had at least a 70% right-hand preference (mean = 90%). Participants also completed a video-game experience questionnaire generated by the experimenter using Qualitrics^{XM} software. On an open-ended question about the number of years of gaming experience, the fMRI participants indicated a median of 10 years of video-game experience (mean = 9, minimum = 0, maximum = 16 years). On a categorical question about the number of hours of video games played per week, most participants (17/25) indicated playing <2 hours/week (with 3 indicating 3-4 hours/week, 1 indicating 5-6 hours/week, 1 indicating 7-8 hours/week and 3 indicating 9+ hours/week).

2.2 Setup and Experimental Procedure

Holding an MRI-compatible fibre-optic gamepad (Current Designs, 2019) in their laps, participants lay supine in the scan bore and viewed the game on a back-projection screen through a mirror angled 45 degrees above them. During the anatomical scan, in effort to provide spatial context and enhance the sense of embodiment, participants watched a

video in the first-person perspective of an avatar walking through a house and into a kitchen where the virtual task takes place (Figure 2A).

During functional scanning, a slow-event related design was used to measure the blood oxygenation level-dependent (BOLD) signal. At the start of each run, participants fixated on a cross for 20 s then received either a “right-hand only” or “left-hand only” audiovisual cue (Figure 2C-D). This cue indicated which hand they should use to operate the gamepad for the duration of the run. The aim of each trial was to pick up a ball from one plate and transport it to a different coloured target plate within 5 s. Each trial began with a colour cue “RED”, “GREEN”, “GREY” or “BLUE” appearing on the screen for 1 s with the simultaneous appearance of the ball to be transported (Figure 2E). This colour cue indicated which coloured plate the target would be for that trial. The onset of a “go” audio cue indicated the start of a trial. In each trial, participants could control either a left or right *virtual* hand. To move the virtual hand, participants manipulated the analog joystick (forward/backward, left/right) using their left or right thumb. To perform a whole-hand grasp with the virtual hand, participants squeezed the gamepad’s trigger using their index finger on the back of the gamepad. To release the virtual grasp and/or drop the ball, participants released the trigger using their index finger on the gamepad. Notably, during virtual grasping the virtual hand was closed or opened abruptly as the button was squeezed or released, rather than having hand aperture change gradually as in real grasping (Jeannerod, 1984). After each trial, a left or right virtual hand was reset at the starting position and the ball disappeared in preparation for the next trial. At this time, either a high-pitch chime indicated a successful trial, or a low-pitch chime indicated an unsuccessful trial. For a trial to be considered successful, participants had to pick up and place the object accurately. Namely, participants had three attempts to grasp the object, which required squeezing the trigger when the hand was within 4 cm of the object in Unity space. Moreover, participants had to drop the object within 8 cm of the center of the target plate in Unity space to pass a trial. Additionally, participants received points based on the accuracy of their grasp and ball placement on the target. Grasp Error was measured by the Euclidean distance from the hand to the center of the ball when participants squeezed the trigger. Similarly, Drop Error was measured using the

Euclidean distance from the ball to the center of the target when participants released the trigger, dropping the ball. Inclusion of points and successful trial sounds encouraged participants to complete trials correctly. Additionally, participants were given the chance to practice six trials (three each with their real left and right hands on the gamepad) while in the scanner prior to the experiment (Figure 2B).

Even though the gamepad had an asymmetric design, such that the placement of the joystick was higher on the left side than the right, this was not expected to affect neural processing or behaviour because the movements were comparable for each hand (e.g., push the joystick forward to move hand forward). Moreover, the gamepad was held with the controlling hand in the same posture throughout the run, including baseline periods such that any postural differences would be expected to “subtract out”. Also, because the joystick only enabled two degrees of freedom (x and y positions) but actual avatar hands can move in three directions, the game was programmed such that the apparent height of the hand increased when participants pushed the joystick and lowered when participants stopped pushing the joystick, in a manner appearing similar to real reach-to-grasp actions.

Although many fMRI studies require constant fixation, this is very unnatural (Foulsham, 2015; Johansson et al., 2001) and can affect behaviour and brain activation (Liu et al., 2020; Ryan & Shen, 2020). As such, I chose to prioritize natural hand-eye behaviours over experimental control. In this experiment, a fixation cross only appeared during baseline conditions and at the start of the trial; participants were free to move their eyes during trial execution. Nevertheless, in a separate behavioral experiment, I analysed gaze behaviours to determine whether they could account for differences in brain activation.

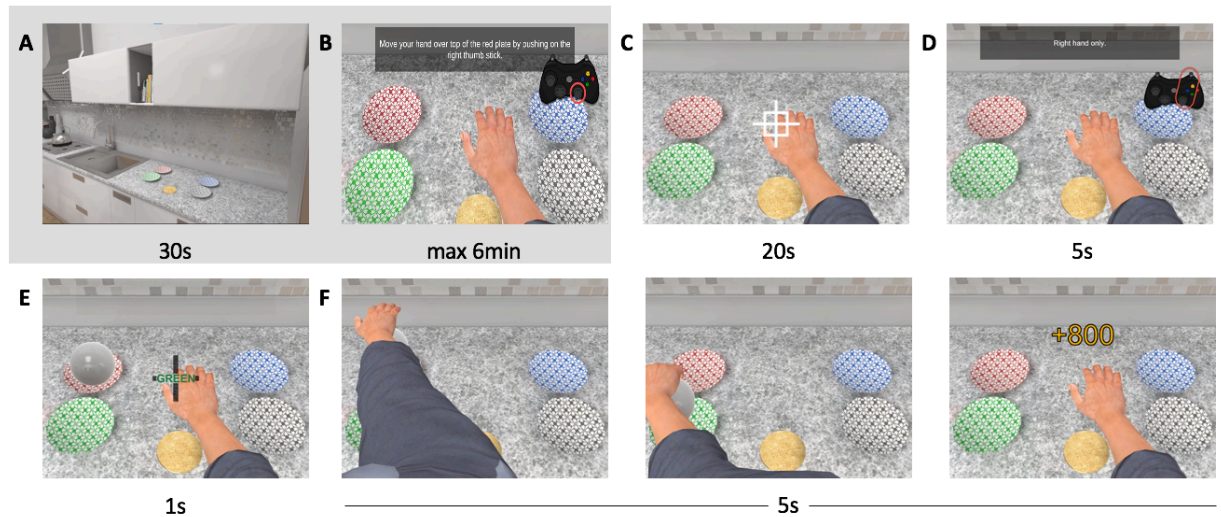


Figure 2: The experimental procedure. A) One frame of the 30-s introduction video. In the first-person perspective, participants watched an avatar walk through a house and into the kitchen where the task takes place. B) Participants engaged in a tutorial teaching them how to play the game and were given six practice trials before the experiment (3 Controlling Left, 3 Controlling Right hand). C) Play, React and Watch runs begun with 20 s of fixation on a cross in the center of the screen to collect baseline activation. D) Participants received a 5-s “right-hand only” or “left-hand only” cue to indicate the controlling hand for that run. E) Participants received a 1-s colour cue to indicate the target plate for that trial. Simultaneously, the ball to be transported appears. F) An example trial of a participant reaching for the ball and transporting it to the appropriate coloured target plate. Participants received points based on the success of their trial. Grey background indicates that the events occurred during the anatomical scan. White background indicates the events occurred during functional scanning.

To explore how having control over virtual hand actions modulates neural activity, three types of runs were used. In Play runs, participants had control over virtual hand actions; as such, participants used the gamepad to complete the virtual reach-to-grasp task (i.e., toggled joystick to reach, squeezed trigger to grasp). In React runs, participants watched a replay of their last Play run and used the gamepad to reproduce the joystick and trigger presses that had been necessary to cause the actions (i.e., toggled joystick to replicate the reach, squeezed trigger to replicate the grasp). Importantly, because participants were watching a replay, they did not have control over the virtual hand actions. In Watch runs, participants watched the Play replay again; however, this time they were instructed not to use the gamepad. Including Watch runs helped determine the neural correlates of observing virtual hand actions (comparable to action observation studies), whereas comparing Play to React runs helped determine the neural correlates specific to having control of virtual hand actions versus matched visual and motor stimulation.

To limit task switching demands, each run utilized the same Task (Play, React, or Watch) and the same Controlling Hand (CL or CR). Within each run participants controlled the VL and VR hands to move the ball in each of the 12 possible trajectories between plates of different colors (e.g., red to blue, red to green, red to grey, blue to red, etc.) for a total of 24 trials/run. Triplets of Play, React and Watch runs were completed in series four times for a total of 12 runs (e.g., Play CL, React CL, Watch CL, Play CR, Watch CR, React CR, Play CL, React CL, Watch CL, Play CR, Watch CR, React CR). Within a Play, React and Watch triplet, the controlling hand used (in Play, React) and presented virtual hand actions were identical because React and Watch runs were replays of each Play run. Controlling hand orders were counter balanced across State triplets both within and across participants; whereas, virtual hand and trajectory orders were counterbalanced within and across State triplets and participants to control for order effects. Between trials there was intertrial interval (ITI) of 10 s (15 per run) or 14 s (8 per run). ITIs were longer than typical to allow partial recovery of the BOLD response between trials and jittered to facilitate fitting of the general linear model. Runs began with 20 s of a fixation baseline and ended with an additional 20 s of a fixation baseline. Given that each run was 7 minutes 32 seconds (452 1-s volumes), about 90 minutes of the experiment was allocated to functional scanning, 10 minutes for anatomical scanning accompanied by the simultaneous completion of a tutorial and practice trials, and 20 minutes of screening and pre- and post-scanning questionnaires made the experiment a 2.5-hour session.

2.3 Anatomical and Functional Scans

All scans were acquired at the Centre for Functional and Metabolic Mapping (CFMM; at the University of Western Ontario) using a 3-Tesla Siemens Prisma^{fit} scanner and a 32-channel head coil. Functional data were collected using a T2*-weighted gradient-echo echo-planar sequence (repetition time [TR] = 1000 ms; voxel size = (2.5 mm)³; echo time [TE] = 33 ms; field of view [FOV] = 210 mm, flip angle = 34 degrees). Whole-brain coverage was obtained using 72 interleaved slices with a multiband factor of 8. T1-weighted anatomical images were collected using a sagittal MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, FOV = 256 mm, flip angle = 9 degrees, voxel size = (1 mm)³).

Anatomical and functional scans were positioned to provide full coverage of participants' eyes (for future analyses with DeepMReye (Nau et al., 2020)) and cerebella.

2.4 Preprocessing & Analysis

Preprocessing was performed using BrainVoyager 22.2 (Brain Innovation, Maastricht, the Netherlands). 3D motion correction (3 translations, 3 rotations) with trilinear-sinc interpolation, and slice scan-time correction with cubic-spline interpolation was applied to functional images. High-pass temporal filtering (modelling 3 cycles/run) corrected for linear drift and spatial smoothing using a 3D Gaussian kernel with full-width, half-maximum (FWHM) of 6 mm was applied to the data. Functional data were co-registered with the T1-weighted anatomical images and transformed into Montreal Neurological Institute (MNI) ICBM152 non-linear asymmetric space.

Data were analyzed with a random-effects (RFX) general linear model (GLM). No trials were excluded from fMRI data analysis. Although participants had up to 5 s to complete trials, on average, they took 2.4 s. As such trial predictors were generated by convolving square-wave functions for 2.4-s events with the Brain Voyager's default double-gamma hemodynamic response function. Although there were 12 predictors of interest (POI) in the 2x2x3 design (VL, VR x CL, CR x Play, React, Watch), each run only contained 2 conditions (1 State, 1 Controlling Hand, 2 Virtual Hands); therefore, the other 10 POIs were modelled as flat predictors when the conditions were not present in the run. I used a variety of predictors of no interest (PONIs) to account for known noise variance in the data. These PONI's included the six motion parameters and their derivatives.

Additionally, six aCompCor and six tCompCor regressors (Behzadi et al., 2007; Esteban et al., 2019) were used to remove physiological noise and two run-specific PONIs modeling the derivative of each POI for a run was used to account for variability of the hemodynamic response across participants (Cignetti et al., 2016). To exclude voxels outside the brain, the RFX GLM was masked with the participant-average 3D anatomical.

Although my primary interest was in factors of Virtual Hand, Controlling Hand, and State, for a control analysis, I was also interested in whether activation was affected by the side on which the actions occurred. As such, in a supplementary RFX GLM, a $2 \times 2 \times 3 \times 4$ design (VL, VR x CL, CR x Play, React, Watch x 4 Trajectories) was used to determine the effect of Side. Specifically, four trajectory conditions were included: actions that started and ended on the left side, started and ended on the right side, started on the left and ended on the right side and started on the right and ended on the left side. This GLM included the same 3D motion correction and CompCor PONIs mentioned above and was also masked with the participant-average 3D anatomical.

Analyses utilized voxelwise statistical maps that were corrected for multiple comparisons using false discovery rate (FDR) correction ($q < 0.05$). For better visualisation in BrainVoyager, volumetric data was displayed on an inflated surface using MNI Colin brain smoothed with 40 iterations. Note, however, that although the data are rendered on the cortical surface, analyses were not performed using cortex-based alignment of individual brains and as such, the accuracy of location of activation with respect to sulcal landmarks is limited.

To assess whether contrasts between Virtual Hands (VL vs. VR), Controlling Hands (CL vs. CR) or Side (Left Side vs. Right Side) evoked significantly different activation magnitudes between the two hemispheres, an additional analysis, inter-hemispheric subtraction, was performed. In a first-level analysis, for each participant, a map contrasting the two conditions was generated (e.g., VL-VR). For each participant, a first-level map of the opposite contrast (e.g., VR-VL) was flipped in the left-right orientation was also generated (e.g., VR-VL flipped in left/right orientation). For each voxel, the activation for the original and flipped maps were subtracted. If activation in the two hemispheres was of equal magnitude but in opposite directions, the sum would be zero. For example, if the right hemisphere showed the same increase in activation for the left hand as the left hemisphere showed for the right hand, the sum would be zero. If the magnitude of the preference were asymmetrically lateralized, however, the sum would not be zero. For example, where the right hemisphere showed a greater preference for the

left hand than the left hemisphere showed for the right hand, this analysis would show activation greater than zero. To assess the significance of such differences in a second-level analysis, I computed a voxelwise one-sample t test on the difference between the original and flipped maps (against a null hypothesis of difference = 0 in light of participant variability). Because I was only interested in whether lateralized areas are significantly greater in one hemisphere than the other, data were masked with regions of interest (ROIs) generated from the group [VL-VR] OR group [VR-VL] contrast with FDR $q < 0.05$ thresholding.

I also compared neural activity between States. To ensure that the analysis showed only differences in activation not deactivation (compared to the resting fixation baseline), only increases in activation were considered. For example, to compare Play to React, the following contrast was used [Play-React AND Play-Baseline].

2.5 Comparison with Known Brain Regions

To pinpoint activation foci with respect to known anatomical and functional brain regions, I utilized several brain atlases (see Tables 1 and 2). Cortical activation foci were compared with a version of the Julich cytoarchitectonic brain atlas (Amunts et al., 2020) in MNI (ICBM152) space. For comparison with the cerebellum, MNI space version of a spatially unbiased atlas template of the cerebellum and brainstem (SUIT) (Diedrichsen et al., 2009; King et al., 2019) and multi-domain task battery (MDTB) atlases were used for anatomical and functional regions, respectively. For comparison with other subcortical regions, MNI-space Atlasing of the basal ganglia (ATAG) (Keuken et al., 2014, 2017) and Scale II Melbourne subcortex atlas (Tian et al., 2020) were imported into Brain Voyager. In some cases, Neurosynth (Yarkoni et al., 2011) search terms were used to compare activation foci with known brain networks. Specifically, Neurosynth performs meta-analyses to generate activation maps using significant voxels reported in articles including a specific search term in their abstract. Notably, these Neurosynth maps are corrected for multiple comparisons (FDR $q < 0.01$). Comparison to Neurosynth search

terms was used for the region LOTChand; that is, search term “hand” revealed a significant cluster of voxels in the LOTC.

2.6 Post-scanning Questionnaires

After scanning was complete, participants completed a post-scanning questionnaire generated by the experimenter using Qualtrics^{XM} software. This questionnaire asked participants to rate how comfortable they felt controlling the gamepad with their left and right hands (1 = very uncomfortable, 5 = very comfortable), and how difficult was to both control the virtual hands as in Play and follow the virtual hands as in React (1 = very easy, 5 = very difficult). Lastly, participants were asked if they noticed the virtual left and right hands changing between trials (yes or no); all participants indicated yes. Due to human error, 1 participant did not complete the post-scanning questionnaire (N=24).

2.7 Questionnaire Data Analysis

To assess questionnaire data (e.g., “How comfortable were you controlling with your left hand?”), behavioural data was compared using paired-sample *t* tests and Spearman correlations. An analysis of covariance (ANCOVA) was used to determine whether video game experience or sex modulated BOLD signal during the experiment.

2.8 Equipment

A back-projection screen was viewed at a distance of 59 cm, such that the display subtended a visual angle of 25.4 degrees horizontally x 19.2 degrees vertically (1024 x 768 resolution). Graphics for this experiment were created on Unity. The scene package used was ArchVizPro Interior Vol. 6 (Unity 2019.4.19f1) and trial and controlling hand orders were counterbalanced and generated using MATLAB (Matlab R2021a). Video replays were generated using Bandicam Screen Recorder (Bandicam Company, 2022). As such, Play runs were recorded and saved as MP4 videos which were played back to participants for React and Watch runs.

2.9 Behavioral Experiment

Because participants were able to gaze freely during trial execution, I wanted to investigate whether gaze patterns could explain activation differences. Future analyses will use an algorithm, DeepMREye (Nau et al., 2020) that can detect eye movements during fMRI based on MRI signals from the eyeballs. In the meantime however, I analyzed gaze data from a follow-up behavioural study in which participants played the same game outside the MRI scanner. Gaze position data were collected from the participants' dominant eye using an SR Research EyeLink 1000 (a pupil-based eye tracker) at a frequency of 1000 Hz. Participants sat in front of a computer holding a gamepad rested on a table. A chin/forehead rest was used to reduce head motion during the experiment. Prior to testing, the EyeLink's built-in 9-point calibration was used. Both the fMRI and behavioural experiments used a display with a horizontal visual angle of 25.4 degrees (however the vertical visual angle was smaller in the behavioral study, 14.2 vs. 19.2 due to a different screen resolution, 1920 x 1080, and a viewing distance of 115 cm). Behavioural data was used to evaluate gaze differences between conditions and not for a direct comparison to the fMRI eye tracking data. For data collection, the Unity application communicated with PsychToolBox (Brainard, 1997) to control the EyeLink recordings. Eye tracking data was collected for each trial. To generate replays for React and Watch, Unity asset AVPro Movie Capture was used. Prior to eye tracking data analysis, blink distortions and drift were manually corrected in Matlab. To assess differences in eye movements between States, two repeated-measures ANOVAs were used to compare the total eye-movement path length over a trial and the number of saccades/trial across Play, React and Watch. Total eye-movement path length was defined as the sum of frame-to-frame eye movements, and the number of saccades was determined by the default EyeLink setting (velocity threshold of 22 degrees per second). 83/2880 trials were excluded due to unsuccessful completion of the task.

To assess differences in eye movements between Side, Virtual Hands, Controlling Hand and State, I quantified the amount of time that participants gaze fell within the left,

middle and right thirds of the display. I then compared the ratio that participants spent looking in the right versus left side of the display across conditions (Virtual Hand, Controlling Hands, State) to test for differences in eye movements. Two participants were excluded from eye tracking analyses due to issues with eye tracking data quality.

Using the gamepad data collected during the eye tracking experiment, I tested whether there were differences in joystick movements (i.e., x, y position data) during Play and React. Three paired-sample *t* tests were used to compare the Joystick X-Movement, Joystick Y-movement and Joystick Time. Joystick X-Movement was defined as the average change in joystick movements in the x direction. That is, I used the absolute value of the first derivative of each value (sampled in 60-Hz frames) in the x direction (min = 0, max = 1). Joystick Y-Movement was defined similar to Joystick X-Movement but using joystick movements in the y direction. Joystick Time was defined as the sum of the number of frames in which joystick pressure was greater than 0.1. Watch data was omitted from this analysis because the gamepad was not used.

Chapter 3

3 Results

3.1 Organization of Results

This study asked two key questions; how Controlling versus Virtual Hands modulate neural activity and how State, namely, having control over actions differs from actions having matched visual and motor stimulation or visual stimulation only. I used a 2x2x3 voxelwise ANOVA (FDR corrected) to evaluate the effect of Virtual Hands, Controlling Hands and State. The ANOVA revealed main effects for Virtual Hands, Controlling Hands and State and an interaction between Controlling Hands and State; however, there were no other two-way interactions nor a three-way interaction. The fMRI results will be presented in five sections: 1) the main effect of Virtual Hand; 2) given that each Virtual Hand is lateralized to the respective side of space, a supplementary analysis includes the Side of the action trajectory as an additional variable; 3) the effects of Controlling Hand and its interaction with State; 4) the effects of Virtual Hand, Controlling Hand and Side on behavioral accuracy during game play; Subsequently, behavioral results on eye tracking and joystick data collected outside the scanner will be presented.

3.2 fMRI Data

3.2.1 Virtual Hand evokes contralateral activation, particularly for the Left Virtual Hand in the Right Hemisphere

The main effect of Virtual Hand reveals seeing a left versus right avatar hand plays a key role in modulating neural activity (See Figure 3). Specifically, contrasting the Virtual Hands [VL-VR] reveals three key results. First, activation is evoked in the hemisphere contralateral to each virtual avatar hand (i.e., seeing an avatar's left hand evokes activation in the right cerebral hemisphere and vice versa) (Figure 3A). Specifically, contralateral cortical activation was found bilaterally in somatosensory (S1), parietal

(superior parietal lobule; SPL) and occipital regions (V1, V2, V6 and cuneus). In agreement with Shmuelof and Zohary (2006), the results suggest the mere appearance of the Virtual Hand (i.e., whether it looks like a left or right avatar hand) evokes contralateral brain activation.

The second key result revealed by the Virtual Hand contrast [VL-VR] is that there is asymmetric recruitment of brain regions, such that there is more brain activation for VL > VR in the right hemisphere than for VR > VL activation in the left hemisphere (Figure 3A). As seen in Panel 3A, right PMd but not left PMd was activated by the contralateral vs. ipsilateral hand. Other regions activated in the right but not left hemisphere include: the ascending band of the cingulate gyrus (AbCing) and an area that overlaps with motion sensitive area, MT+ and the hand processing region of the lateral occipitotemporal cortex (LOTChand). In addition, the statistical significance of the contralateral preference was stronger in the right than left hemisphere for SPL and reach-selective visual area V6 (Figure 3A, Table 1, $q < 0.05$). Moreover, increased brain activity in response to the virtual left than right hand was also identified in foci in the cerebellum. Given that the cerebellum, unlike the cortex, typically shows higher activation for ipsilateral than contralateral actions, I found a preference for the ipsilateral virtual hand in four cerebellar regions: three regions related to motor activity based on King and colleagues (2019) MDTB functional atlas in the left hemisphere and one region related to cognition (King et al., 2019) in the right hemisphere (Figure 3B, Table 1, $q < 0.05$). Taken together, Virtual Hands evoke brain activation in the contralateral cerebral cortex and ipsilateral cerebellum, with some regions appearing to show stronger activation for the virtual left hand than the virtual right hand.

The third key result uses an inter-hemispheric subtraction to examine whether activation in one hemisphere is *significantly* greater than the other hemisphere (i.e., whether the magnitude of activation in the right-hemisphere evoked from VL-VR is greater than the magnitude of activation in the left-hemisphere evoked from VR-VL, and vice versa).

Indeed, all of the cortical regions that showed apparent asymmetries in activation—PMd, SPL, AbCing, V6, LOTC_{hand}/MT+—had significantly greater contralateral activation in the right hemisphere than the left hemisphere (Figure 3C, $q < 0.05$). Additionally, one motor-related focus in the cerebellum (King et al., 2019) for VL>VR (Figure 3C, Table 1) was significantly greater in the left than right hemisphere, and the region involved in cognition (King et al., 2019) for VR>VL (Figure 3C, Table 1) was significantly in the right than left hemisphere.

Altogether, the results show that a host of sensorimotor cortical and cerebellar areas are strongly affected by which virtual hand is shown, often with activation that is stronger for the left virtual hand. Moreover, the absence of an interaction between Virtual Hand x Controlling Hand or Virtual Hand x State suggests the main effect of Virtual Hand is a visual response and does not depend on the use of a left or right hand on the gamepad or whether gameplay is active (Play), reactive (React) or passive (Watch).

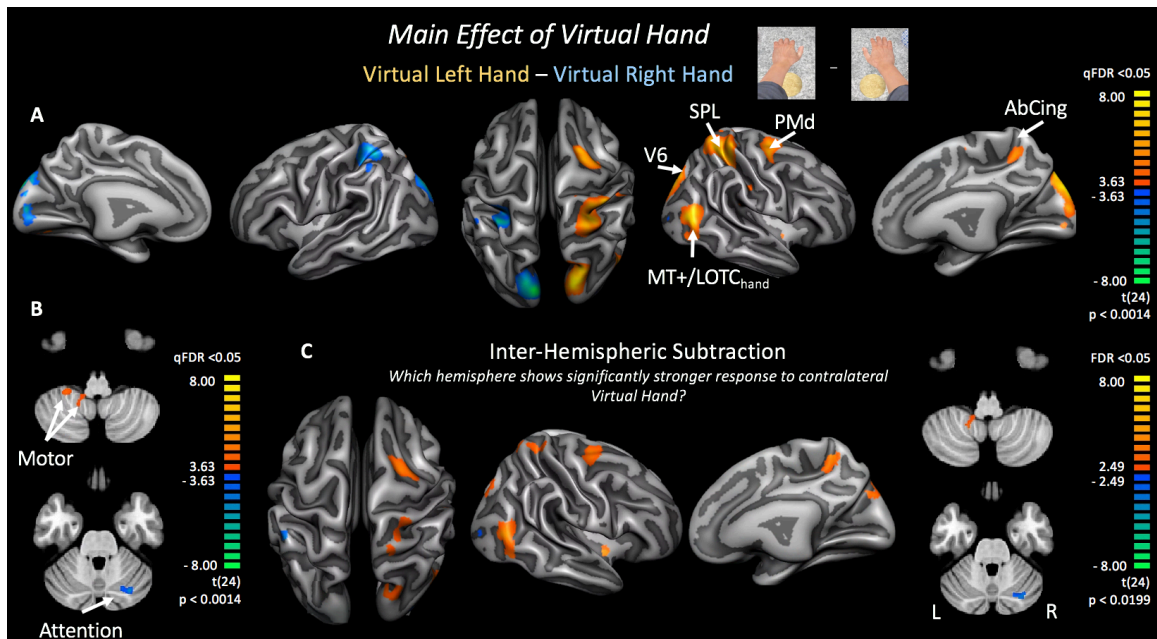


Figure 3: Main effect of Virtual Hand. A) Contrasting virtual hands [Virtual Left – Virtual Right] reveals significant activation in response to the contralateral virtual hand. More regions of the right-hemisphere show increased activation for the contralateral virtual hand than in the left-hemisphere. Images from left to right: left-hemisphere medial view, left-hemisphere lateral view, arial view, right-hemisphere lateral view, right-hemisphere medial view. Volumetric data was FDR corrected to $q < 0.05$ and displayed on an inflated surface. B) Contrasting the virtual hands [Virtual Left – Virtual Right] reveals increased motor-related activity in response to the virtual left hand and increased cognitive-related activity in response to the virtual right hand. Slices depicted in coronal view (top slice $z = -50$, bottom slice $z = -30$). C) Inter-hemispheric subtraction of [Virtual Left – Virtual Right] reveals the regions in which the magnitude of virtual hand differences in one hemisphere is significantly greater than the other hemisphere. Orange/yellow = VL > VR, Blue/green = VR > VL. Images from left to right: arial view, right-hemisphere lateral view, right-hemisphere medial view with volumetric was displayed on an inflated surface. Slices depicted in coronal view (top slice $z = -50$, bottom slice $z = -30$). All data FDR corrected ($q < 0.05$). $N = 25$.

3.2.2 Brain activation evoked from actions seen in the Left Side versus Right Side is asymmetrically lateralized

One key difference between the two virtual hands is that each arm extends from the ipsilateral side of the body and thus is more visible on the ipsilateral side of space. As such, I was interested in whether there were also differences for virtual hand actions executed in the left versus right side of space (Gallivan et al., 2011; Gonzalez et al., 2007; Monaco et al., 2015; Perenin & Vighetto, 1988; Shmuelof & Zohary, 2006). Recall that participants could freely view the display during actions, such that data cannot be analyzed in terms of visual fields (as in Shmuelof and Zohary, 2006); however, by

examining the different trajectories for the ball movements separately, I can see whether there are differences between actions in the left side vs. the right side of space.

In a supplemental analysis, I performed a 2x2x3x4 ANOVA including four action trajectory conditions (actions that start and end on the right side [Right Side], actions that start and end on the left side [Left Side], or cross over from the left-to-right or right-to-left side). This analysis revealed a main effect of Side that did not appear to be modulated by other variables including Virtual Hand. In the contrast of [Left Side – Right Side], I found Side differences asymmetrically lateralized in the right hemisphere. That is, there was increased recruitment of right-hemisphere regions—PMd, SPL, V6 and LOTC_{hand}/MT+—in response to the actions performed on the Left vs. Right Side of space (Figure 4A, $q < 0.05$). In addition, early visual cortex (medial occipital cortex) showed higher responses when trajectories were on the ipsilateral side. Though this may initially seem counterintuitive, it can be explained by the fact that if participants were gazing on the side of the trajectory (as behavioral data, presented later, indicates), most of the scene would be falling in the opposite visual field (e.g., when gazing at left trajectories, the scene would largely fall in the right visual field) stimulating left early visual cortex. Additionally, one motor-related region of the left cerebellum (King et al., 2019) showed increased neural activity when actions were in the Left versus Right Side (Figure 4B, $q < 0.05$). An inter-hemispheric subtraction of Side contrasts revealed the effect of Side was significantly greater in the right than left hemisphere for PMd and SPL and in the left than right hemisphere for the cerebellar focus (Figure 4C, $q < 0.05$).

Although regions showing a main effect of Side partially overlapped with those revealed from the main effect of Virtual Hand (e.g., PMd, SPL), activation differences evoked from Side are lateralized in the right hemisphere only, and appear to be weaker than activation differences evoked from Virtual Hand (e.g., main effect of Virtual Hand is revealed in MT+/LOTChand and V6 but not for the main effect of Side). Importantly, given that there is no Side x Virtual Hand interaction, the main effect of Side is independent of the Virtual Hand used, suggesting that the activation depends on the Virtual Hand regardless whether actions are performed in the Left or Right Side of space.

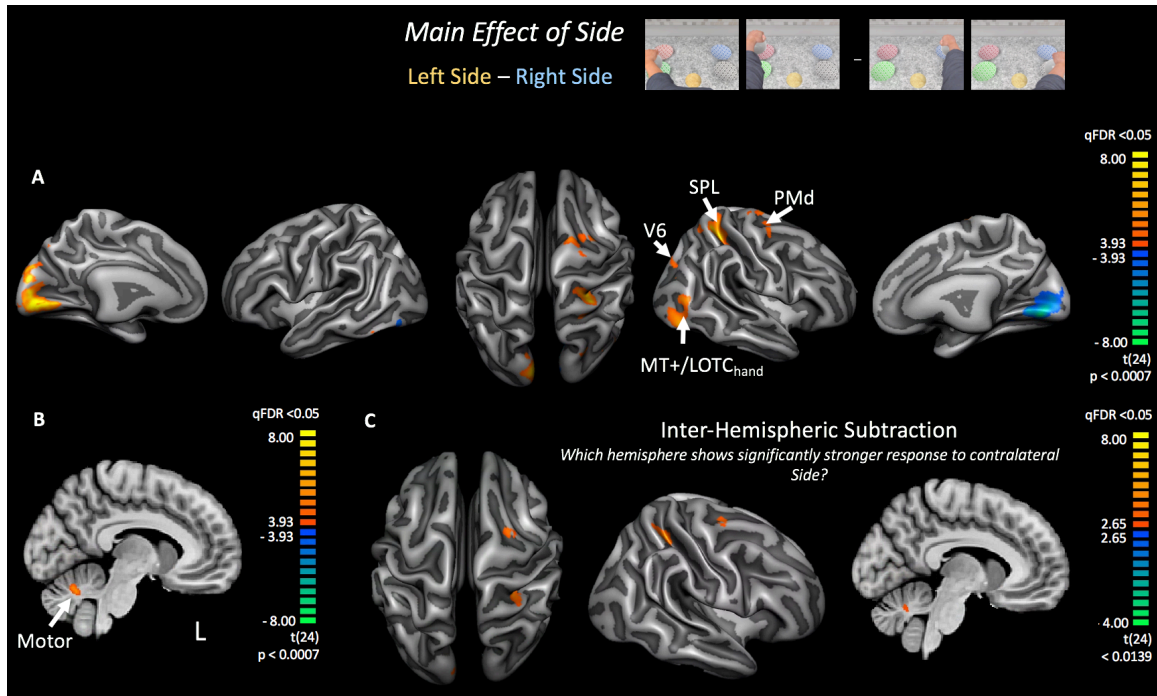


Figure 4: Main effect of Side. A) Contrasting the side that the action occurred in [Left Side – Right Side] reveals significant activation in response to actions performed in the Left Side. Actions in the Left Side evoke bilateral activation in occipital regions and unilateral activation in the right parietal cortex. Images from left to right: left-hemisphere medial view, left-hemisphere lateral view, arial view, right-hemisphere lateral view, right-hemisphere medial view. Volumetric data was FDR corrected to $q < 0.05$ and displayed on an inflated surface. B) Contrasting actions in the two sides [Left Side – Right Side] reveals unilateral cerebellar activation in response to actions in the Left Side. Slice depicted in sagittal view ($x = -7$). Only significant voxels in the cerebellum were depicted. C) Inter-hemispheric subtraction of [Left Side – Right Side] reveals the magnitude of Side differences are significantly greater in the right-hemisphere than the left-hemisphere. Orange/yellow = LS > RS, Blue/green = RS > LS. Images from left to right: arial view, right-hemisphere lateral view, right-hemisphere medial view. Volumetric data displayed on an inflated surface. Slice depicted in sagittal view ($x = -7$). All data was FDR corrected to $q < 0.05$. $N = 25$.

3.2.3 Controlling Hand evokes bilateral motor activity as expected

The $2 \times 2 \times 3$ ANOVA revealed an interaction between State and Controlling Hands ($q < 0.05$). The interaction was localized in motor and somatosensory areas (e.g., M1 and S1), which was expected given that in Watch there was no gamepad use. Nevertheless, the main effect of Controlling Hands was used as a “sanity check” to assess differences in gamepad use between the two hands. As expected, a contrast of Controlling Hands [CL-CR] revealed significant contralateral activation bilaterally in M1, somatosensory cortex (S1) and other sensorimotor regions (Figure 5A, Table 1, $q < 0.05$). Similarly, cerebellar and other subcortical structures also revealed motor system lateralization as expected

from using ones left versus right hand. Namely, activation was higher for the ipsilateral than contralateral Controlling Hand in the cerebellum, and higher for the contralateral than ipsilateral Controlling Hand in the thalamus and striatum (Figure 5B-C, Table 2, $q < 0.05$). An inter-hemispheric subtraction of the Controlling Hand contrasts revealed no differences, suggesting the preference for the contralateral Controlling Hand in each cortical hemisphere is comparable, and likewise for the ipsilateral Controlling Hand in each cerebellar hemisphere.

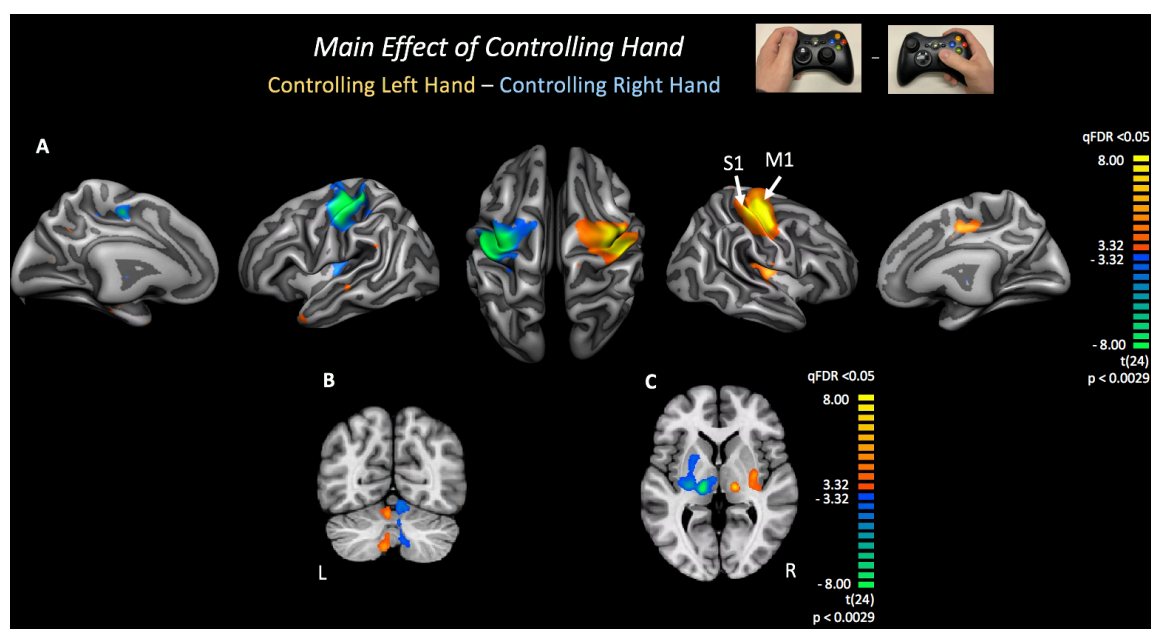


Figure 5: Main effect of Controlling Hand. A) Contrasting the hands used on the gamepad [Controlling Left – Controlling Right] reveals significant motor and somatosensory activity in response to the contralateral hand. Images from left to right: left-hemisphere medial view, left-hemisphere lateral view, arial view, right-hemisphere lateral view, right-hemisphere medial view. Volumetric data was FDR corrected to $q < 0.05$ displayed on an inflated surface. B) Contrasting the hands used on the gamepad [Controlling Left – Controlling Right] reveals bilateral motor-related activity in response to the ipsilateral controlling hand used. Cerebellar slice in coronal view ($y = -66$). C) Contrasting the hands used on the gamepad [Controlling Left – Controlling Right] reveals bilateral activation in response to the contralateral controlling hand used. Slice in axial view ($z=3$). B-C) Only significant voxels in the cerebellum and other subcortical structures were depicted. All data was FDR corrected to $q < 0.05$. $N = 25$.

Table 1: MNI coordinates of BOLD-signal maxima from various controlling and virtual hand contrasts. Cortical regions were defined using the Julich atlas (Amunts et al., 2020). Hotspots in the cortex were evoked by the contralateral virtual or controlling hand. Cerebellar regions were defined using the MNI SUI anatomical atlas (Diedrichsen, 2009) and the MDTB functional atlas (King et al., 2019). Hotspots in the cerebellum were evoked by the ipsilateral virtual or controlling hand. Subcortical regions were defined using known anatomical landmarks, the ATAG atlas (Keuken et al., 2017) and the Scale II Melbourne subcortex atlas (Tian, 2020). Hotspots in other subcortical structures were evoked by the contralateral virtual or controlling hand. Asterisks indicate regions evoked by the non-conventional controlling or virtual hand (e.g., for cerebellum, activation evoked by the contralateral hand). Acronyms for MDTB functional atlas: LH = Left Hand, RH = Right Hand, AO = Action Observation, WC = Word Comprehension, DA = Divided Attention. Data was FDR corrected to $q < 0.05$. $N = 25$. Acronyms for anatomical regions: SPOC = Superior Parietal Occipital Cortex, SMA = Supplementary Motor Area, IPL = Inferior Parietal Lobule, GP = Globus Pallidus.

<u>Cortical</u>	<u>Left-Hemisphere</u>			<u>Right-Hemisphere</u>		
	MNI	anatomical	Julich	MNI	anatomical	Julich
<i>Virtual Hand Effect</i> [VL-VR]	-33, -40, 52	S1	Area 2	29, 41, 52	S1	Area 2
	-28, -46, 60	SPL	7PC	24, -52, 60	SPL	7PC, 7A, 5M
	-8, -87, 42	V6	hPO1	15, -85, 42	V6	hPO1
	-8, -88, 28	Cuneus	hOc3d, hOc4d	16, -88, 32	Cuneus	hOc3d, hOc4d
	-7, -87, 11	V2, V1	hOc2, hOc1	10, -89, 16	V2, V1	hOc2, hOc1
				22, -8, 60	PMd	6d1
				13, -82, 60	SPOC	Posterior 7P
				51, -69, 7	LOTChand/MT+	hOc5
			51, -25, 34	IPL	PFt	
			7, -47, 57	AbCing		
<i>Controlling Hand Effect</i> [CL-CR]	-41, -22, 60	M1	4a, 4p	36, -21, 60	M1	4a, 4p
	-45, -29, 62	S1	1, 3a, 3b	43, -32, 62	S1	1, 3a, 3b
	-6, -14, 50	SMA	6mp	8, -10, 48	SMA	6mp
	-43, -22, 14	IPL	OP1, OP2, OP3	48, -16, 12	IPL	OP1, OP2, OP3
	-34, -20, 9	Insula	Ig1, Ig2	35, -20, 9	Insula	Ig1, Ig2
<u>Cerebellar</u>	MNI	Anatomical	MDTB King	MNI	Anatomical	SUIT
<i>Virtual Hand Effect</i> [VL-VR]	-24, -41, -48	VIIIa	LH Presses	31, -73, -29	Crus I	DA
	-5, -65, -41	Vermis VIIIb	LH Presses			
	-14, -48, -49	IX	AO			
<i>Controlling Hand Effect</i> [CL-CR]	-17, -52, 21	V, VI	LH Presses	17, 52, -21	V, VI	RH Presses
	-16, -58, -49	VIIIa, VIIIb	LH Presses	20, -57, -49	VIIIa, VIIIb	RH Presses
	-3, -67, -40	Vermis IIIb	LH Presses	5, -63, 40	Vermis IIIb	RH Presses
				28, -83, -36	Right Crus II*	WC
<u>Subcortical</u>	MNI	Anatomical	Contrast	MNI	Anatomical	Contrast
<i>Virtual Hand Effect</i>	-21, 5, 2	Putamen	VR > VL	19, -24, 11	Thalamus	VL > VR
	-20, 0, -12	Amygdala	VR > VL	15, 4, 19	Caudate	VR > VL
				18, -4, 2	GP interna	VR > VL
<i>Controlling Hand Effect</i>	-14, -19, 3	Thalamus	CR > CL	15, -20, 3	Thalamus	CL > CR
	-28, -18, 3	Putamen	CR > CL	31, -11, 0	Putamen	CL > CR
	-20, -9, -5	GP externa	CR > CL			

3.2.4 *Having control over virtual hand actions results in increased engagement of the motor network*

Given that participants had control over avatar hand actions in Play, whereas in React, participants had matched visual stimulation and motor output (watched a replay and used the gamepad), comparing Play to React reveals the effect of having control over Virtual Hand actions (see [Figure 6](#)). A conjunction of two contrasts—([Play – React] AND [Play – Baseline])—revealed Play-selective recruitment of the sensorimotor network ([Figure 6A](#), Table 2, $q < 0.05$). Similarly, activation in motor-related cerebellar foci (King et al., 2019) and other subcortical structures were also greater for Play than React ([Figure 6B](#), Table 2) Specifically, activation in the thalamus, subthalamic nuclei, putamen and superior colliculi among other regions were significantly greater for Play than React.

Conversely, a conjunction ([React – Play] AND [React – Baseline]) revealed React-selective recruitment of association cortex (supramarginal gyrus, SMG; posterior superior temporal sulcus/middle temporal gyrus, pSTS/MTG and several small foci in prefrontal cortex) as well as reach-related (V6A = Julich 7P) and grasp-related (aIPS = Julich hIP2) visuomotor areas ([Figure 6A](#), Table 2, $q < 0.05$). There was also increased activation in cerebellar foci related to attention (King et al., 2019) for React than Play ([Figure 6C](#), Table 2, $q < 0.05$).

In sum, active Play engages the core motor system more than React, perhaps because of the closed-loop nature of the task; whereas, React engages more cognitive and visuomotor systems, perhaps because its artificial nature requires more cognitive control to perform actions after the outcomes rather than before.

Given that Watch conditions only involved visual stimulation, activation during Watch closely resembled that of an action observation paradigm. As expected, Play and React evoked more motor-related cortical, subcortical and cerebellar activity than Watch (Table 2, $q < 0.05$). Surprisingly, even without motor stimulation, Watch > Play ([Watch – Play] AND [Watch – Baseline]) revealed significantly more activity in association cortex and

cognitive foci (King et al., 2019) of the cerebellum (Figures 6A, 6D, Table 2, $q < 0.05$). Indeed, both Watch > Play and React > Play involved increased recruitment of association cortex suggesting activation differences between open- vs. closed-loop actions do not depend on the absence (Watch) or presence (React) of motor responses.

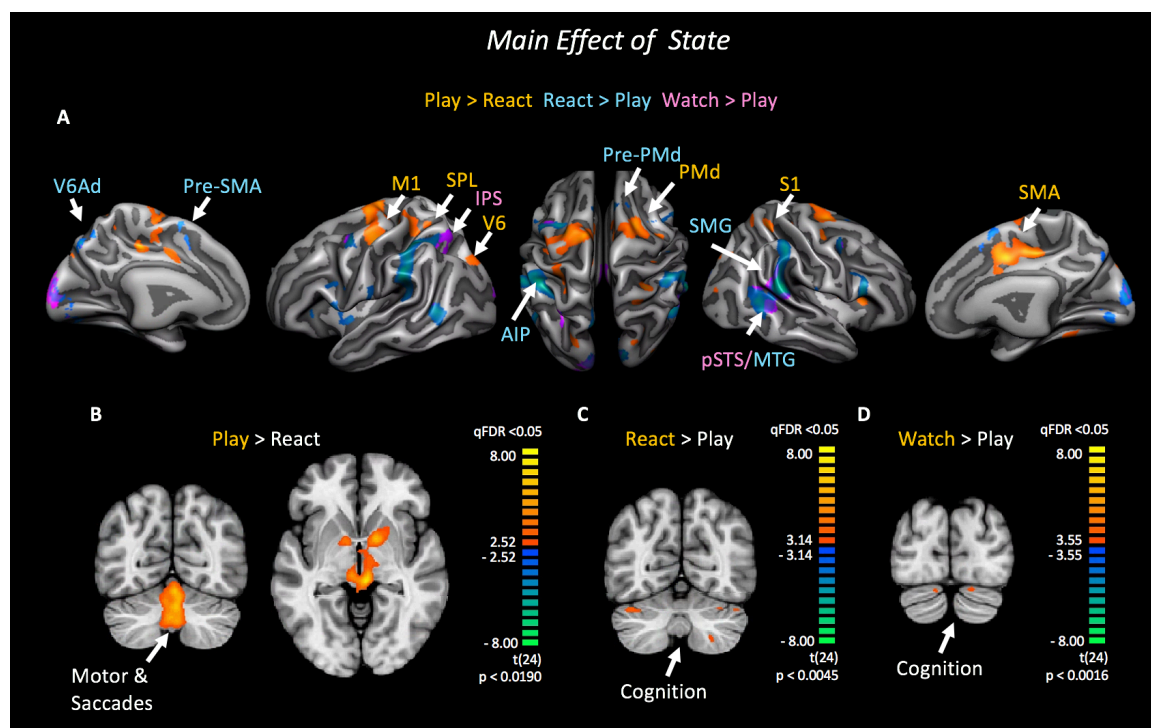


Figure 6: Actions in Play results in increased recruitment of the motor system than React and Watch. A) Having control over virtual hand actions in Play recruits relatively more motor system activity. In React, there was relatively more activation in association cortex and grasp-related visuomotor areas. In Watch, there was also relatively increased association cortex, but to a lesser extent than React. Orange/yellow = Play > React. Blue/green = React > Play, Pink/purple = Watch > Play. Volumetric data for was FDR corrected to $q < 0.05$ and displayed on an inflated surface. B) Areas greater for Play than React [Play-React AND Play-Baseline] in the cerebellum and other subcortical structures. Coronal slice ($y = -66$). Axial slice ($z = -4$). C) Areas greater for React than Play [React-Play AND React-Baseline] in the cerebellum. Coronal slice ($y = -66$). D) Areas greater for Watch than Play [Watch-Play AND Watch-Baseline] in the cerebellum. Coronal slice ($y = -84$). B-D) Only significant voxels in the cerebellum and other subcortical structures were depicted. All data was FDR corrected to $q < 0.05$. $N = 25$.

Table 2: MNI coordinates of BOLD-signal maxima from various state contrasts. Cortical regions were defined using the Julich atlas (Amunts et al., 2020). Cerebellar regions were defined using the MNI SUIT anatomical atlas (Diedrichsen, 2009) and the MDBT functional atlas (King et al., 2019). Subcortical regions were defined using known anatomical landmarks, the ATAG atlas (Keuken et al., 2017) and the Scale II Melbourne subcortex atlas (Tian, 2020). Data was FDR corrected to $q < 0.05$. $N = 25$. Acronyms for anatomical brain regions: LOC = Lateral Occipital Cortex, IFG = Inferior Frontal Gyrus, aIPS = Anterior Intraparietal Sulcus, PreCS = Precentral Sulcus, FO = Frontal Operculum, IPS = Intraparietal Sulcus.

Cortical	Left-Hemisphere			Right-Hemisphere		
	MNI	anatomical	Julich	MNI	anatomical	Julich
<i>Effect of Play</i>	-29, -39, 54	S1	2	34, -36, 55	S1	2
[Play – React]	-17, -16, 67	PMd	6d1	20, -11, 71	PMd	6d1
AND	-3, -14, 53	SMA	6mp	12, -12, 51	SMA	6mp
[Play –	-20, -52, 60	SPL	7A	19, -55, 60	SPL	7A, 7PC
Baseline]	-21, -78, 38	V6	hPO1	20, -77, 35	V6	hPO1
	-38, -16, 52	M1	4p	36, -85, 14	LOC	hOc41p
[Play – Watch]	-29, -39, 54	S1	1, 2, 3a, 3b	29, -39, 54	S1	1, 2, 3a, 3b
AND	-17, -16, 67	PMd	6d1, 6d2	17, -16, 67	PMd	6d1, 6d2
[Play –	-3, -14, 53	(pre)SMA	6mp, 6ma	3, -14, 53	(pre)SMA	6mp, 6ma
Baseline]	-20, -52, 60	SPL	7A	20, -52, 60	SPL	7A
	-21, -78, 38	V6	hPO1	21, -78, 38	V6	hPO1
	-38, -16, 52	M1	4p	38, -16, 52	M1	4p
	-61, -25, 37	IPL	PFt, PFcm	57, -21, 37	IPL	PFt, PFcm
	-58, 5, 29	IFG	44	55, 5, 29	IFG	44
<i>Effect of React</i>	-50, -10, 47	S1	3b	53, -14, 45	S1	1, 3b
[React – Play]	-7, 7, 68	Pre-PMd	6d2	17, 9, 63	Pre-PMd	6d2
AND	-5, 5, 59	Pre-SMA	6ma	3, 8, 62	Pre-SMA	6ma
[React –	-42, -42, 45	aIPS	hIP2, hIP1	44, -41, 45	aIPS	hIP2
Baseline]	-53, -41, 38	SMG	PF, PFcm, PFt	58, -42, 22	SMG	PFm, PFcm
	-50, -56, 6	pSTS/MTG		54, -58, 8	pSTS/pMTG	
	-50, 10, 24	PreCS		50, 15, 22	PreCS	
	-7, -95, 12	V2	hOc2	10, -89, 11	V2	hOc2
	-54, -7, 2	FO	OP6	49, 14, 21	IFG	44
	-4, -63, 56	V6Ad	7P			
[React-Watch]	-29, -39, 54	S1	1, 2, 3a, 3b	29, -39, 54	S1	1, 2, 3a, 3b
AND [React –	-17, -16, 67	PMd	6d1, 6d2	17, -16, 67	PMd	6d1, 6d2
Baseline]	-3, -14, 53	(pre)SMA	6mp, 6ma	3, -14, 53	(pre)SMA	6mp, 6ma
	-20, -52, 60	SPL	7A	20, -52, 60	SPL	7A
	-38, -16, 52	M1	4p	38, -16, 52	M1	4p
	-61, -25, 37	IPL	PFm, PFcm, PFt	57, -21, 37	IPL	PFm, PFcm, PFt
	-58, 5, 29	IFG	44	55, 5, 29	IFG	44
<i>Effect of Watch</i>	-60, -53, 5	pSTS		56, -45, 6	pSTS	
[Watch-Play]	-38, -2, 52	PreCS		45, 4, 45	PreCS	
AND [Watch-	-3, -95, 9	V2	hOc2	10, -89, 18	V2	hOc2
Baseline]	-31, -53, 38	IPS	hIP1, hIP6	66, -38, 11	IPL	PGa, PF
Cerebellar	Anatomical	Left Hemisphere MNI	Right Hemisphere MNI	MDTB King		
<i>Effect of Play</i>	V	-5, -63, -22	5, -63, -21	Hand Presses		
[Play – React]	VI	-29, -40, -27	31, -40, -27	Hand Presses		
AND	Vermis IV	-3, -67, 21	3, -67, -21	Hand Presses		
[Play –	Vermis IIIa	-3, -68, -39	3, -68, -39	Hand Presses		
Baseline]	Vermis VIIb	-2, -70, -30	2, -70, -30	Saccades		
	Vermis IX	-1, -53, -35	1, -53, -35	Saccades		

<i>Effect of React</i> [React – Play] AND [React – Baseline]	Crus I, VI	-40, -61, -30	30, -57, -30	Divided Attention
	VIIb, VIIIa	-28, -62, -49	22, -68, -49	Divided Attention
	Crus II	-13, -76, -43		Narrative
<i>Effect of Watch</i> [Watch-Play] AND [Watch- Baseline]	Crus I	-13, -82, -23	12, -81, -23	Divided Attention
	Crus II	-11, -72, -42		Narrative
<u>Subcortical</u>	<u>Anatomical</u>	<u>Left Hemisphere MNI</u>	<u>Right Hemisphere MNI</u>	
<i>Effect of Play</i> [Play – React] AND [Play – Baseline]	Thalamus	-5, -23, 4	5, -23, 7	
	Nucleus Accumbens	-8, 1, -1	10, 5, -1	
	Substantia Nigra	-10, -17, -12	9, -15, -14	
	Red Nucleus	-4, -19, -8	7, -19, -7	
	Superior Colliculus		3, -31, -4	
	Putamen		20, 9, -4	
	Subthalamic Nuclei		11, -11, 4	
	GP externa		18, 4, -5	
	GP interna		14, -1, -5	

3.3 In-Scanner Behavioural Data

3.3.1 Brain activation does not appear to be related to individual differences

I wondered whether the fMRI effects of Virtual Hand and State depended on individual differences such as video game experience. I found that video game experience in years was correlated with left- ($p < 0.05$) and right- ($p < 0.01$) hand comfortability using the gamepad, however, this did not appear to affect brain activation. An ANCOVA revealed no significant correlations between voxelwise brain activation (FDR-corrected) and years of experience playing video games (N=25), hours per week of video-game play (N=25), comfortability with using the gamepad (N=24) or sex (N=25). Note, however, that these analyses have relatively low statistical power given the small sample size and the approach (voxelwise analyses corrected for multiple comparisons).

3.3.2 Virtual left hand actions result in poorer accuracy than virtual right hand actions

Given that brain activation depended on the Virtual Hand, I also examined whether behavioral performance differed across conditions. As such, I investigated whether in-

scanner game performance was modulated by Virtual Hands, Controlling Hands or Side (See Figure 7).

To quantify accuracy in the game, Drop Error was defined by the Euclidean distance between the bottom of the ball and the center of the plate when participants dropped the ball on the target in Play runs. Using a 2x2x4 ANOVA (Virtual Hands x Controlling Hands x Trajectory), an interaction between Virtual Hand and Trajectory ($p < 0.01$) was found. In general, actions were the least accurate when starting on one side and ending on the other. However, the more interesting effect is that there was an interaction between Virtual Hand and Trajectory for the actions performed entirely on one side of space. Actions performed using the Virtual Left hand were more accurate in the ipsilateral (left) than contralateral (right) side ($p < 0.001$); whereas, actions performed using the Virtual Right hand showed no significant difference between sides. Actions in the Right Side (red line in Fig. 7) were more accurate using the virtual right than left hand ($p < 0.01$) but actions on the Left Side (blue line in Fig. 7) were comparable between virtual hands. Importantly, there was no main effect for Controlling Hand, which suggests that accuracy was modulated by *seeing* either a left or right hand in the left or right side. In addition, the Drop Error results for actions entirely on one side are consistent with the frequency with which those actions are performed in daily life. Specifically, Gonzalez and colleagues (Gonzalez et al., 2007) found that right-handers frequently used each hand to perform actions on its ipsilateral side—these were the conditions that showed the lowest Drop Error—and very rarely used the left hand to perform actions on the right—this was the condition with the highest Drop Error.

Overall, the results show that the Virtual Hand has a greater effect on Drop Error than the Controlling Hand. Furthermore, the results supports that seeing less-common actions (e.g., virtual left hand) not only results in increased right-hemispheric activation, but also impacts behaviour in the video game.

Another measure of game performance was Grasp Error, which was defined by Euclidean distance between the hand and ball at the time participants squeezed the trigger; however,

there were no interactions or main effects of Controlling Hand, Virtual Hand, or Side for Grasp Error. This null result might be explained by the binary nature of the trigger squeeze (i.e., squeeze to close hand, release to open hand), such that it is a poor representation of real grasping (Jeannerod, 1984).

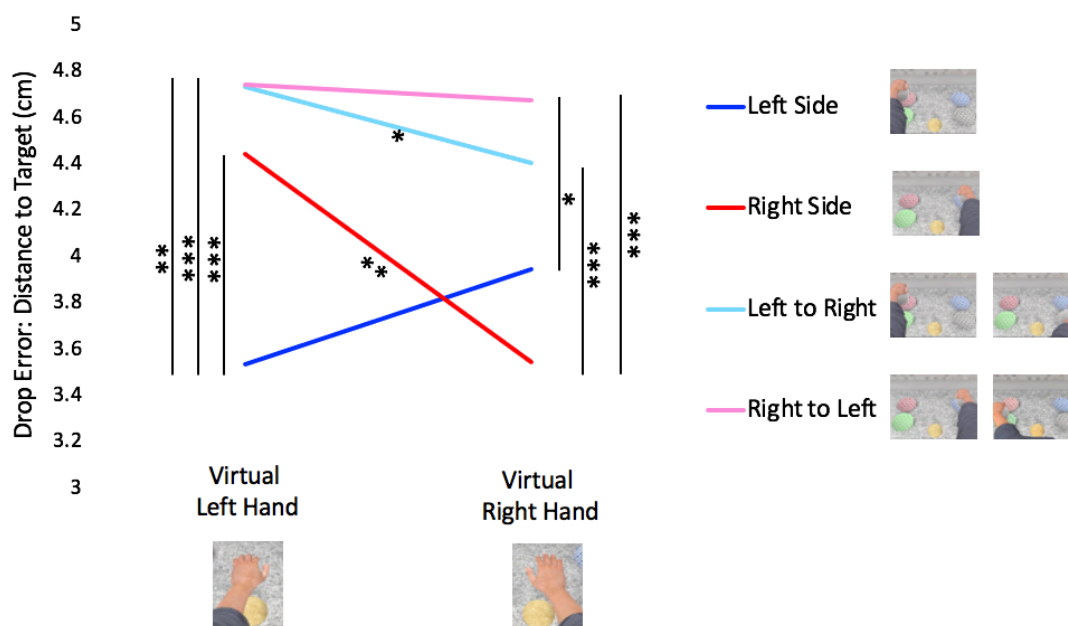


Figure 7: Drop Error was worse for virtual left than right hand actions. Drop Error was defined as the Euclidean distance from where participants dropped the ball to the center of the target plate. Although there was no main effect of Controlling Hand, an interaction between Virtual Hand and Trajectory was identified ($p < 0.01$). As such, actions starting and ending on different sides were generally the least accurate. Virtual left-hand actions were more accurate in the left than right side ($p < 0.001$). Actions in the right side were more accurate using the virtual right hand ($p < 0.01$). $N = 25$.

3.3.3 No task-related timing differences were found between Virtual Hands. Participants reported equal task difficulty between Play and React.

To address potential confounding variables in both the fMRI and in-scanner behavioural data, task-timing and task-difficulty ratings were considered. I examined whether there were differences in the time it took for participants to drop the ball on the target across Controlling and Virtual Hand conditions. Although the controlling left hand dropped the ball on average 100 ms faster than the controlling right hand (CL = 2300 ms, CR = 2400 ms, $p < 0.01$), no significant difference in Drop Time was found between the Virtual

Hands ($p = 0.27$). This suggests the differences in brain activation and Drop Error between virtual hands are not confounded by differences in task timing.

Participants also indicated how comfortable they felt using their left or right hand on the gamepad on a scale of 1-5. Even though the gamepad had an asymmetric design (i.e., left and right joysticks had different placements), no significant difference was found between controlling right- and left-hand comfortability (CL = 4.4/5, CR = 4.4/5, $p = 0.79$).

Furthermore, when participants rated on a scale of 1-5 how difficult it was to control the avatar hands (i.e., Play) versus follow the hands with the gamepad (i.e., React), no significant difference was found between task-difficulty ratings (Play = 2.6/5, React = 2.7/5, $p = 0.77$). Importantly, ruling out task difficulty as a confounding variable strengthens that differences between Play and React can be attributed to having control over actions.

3.4 Out-of-Scanner Behavioural Data

Because participants were able to view freely in the scanner, it was important to determine whether brain activation differences could be explained by different patterns of eye movements across condition types (e.g., VL vs. VR, Play vs. React vs. Watch). In addition, due to technical problems during fMRI scanning, data about joystick use was not collected for all conditions.

To address whether differences in eye and hand movements might explain the fMRI results, I also conducted behavioural experiment in which participants played the same video game as in the scanner while eye position and gamepad data, including joystick movements, was recorded.

Inspection of eye tracking data suggested that, as expected, participants' gaze preceded the movements of the avatar hand (as it does in actual hand movements, Johansson et al., 2001).

3.4.1 Eye movements and gaze are affected by State but not Virtual Hands, Controlling Hands or Side

To assess differences in eye movements (for the behavioral sample, $n = 8$) across the three states, two repeated-measures ANOVAs were used to compare the total path length over which eye position shifted during a trial and the number of saccades per trial. The first ANOVA revealed that the total eye-movement path length differed between conditions ($p < 0.001$). This difference was explained by a longer path length for Play than Watch ($p < 0.001$) and for Play than React ($p < 0.05$) but the difference between React vs. Watch did not reach significance ($p = 0.09$). The second ANOVA revealed that the number of saccades/trial differed between conditions ($p < 0.001$), all of which had approximately 8 saccades/trial (Play = 8.8, React = 8.5, Watch = 8.0). There was a significantly larger number of saccades for Play than Watch ($p < 0.001$) and React than Watch ($p < 0.01$) but with no significant difference between Play vs. React ($p = 0.20$). Together, these results might indicate differences in hand-eye coordination strategies that occur even for virtual hands depend on the goals of the task.

To assess differences in eye movements between the two Sides, I compared the percentage of time that participant's gaze fell within the left, middle and right regions of the display. Averaged across all trials, the distribution of gaze in the three regions were: 41.3% in the left, 20.5% in the middle and 38.2% in the right. For actions on one side of space (e.g., starting and ending on left side), on average, participants spent 95.5% of the time looking at that side of space. To determine whether this ipsilateral gaze strategy was modulated by other factors (Controlling Hands, Virtual Hands, State and Side), I performed a $2 \times 2 \times 3 \times 2$ ANOVA. The ANOVA revealed no main effects for Controlling Hands, Virtual Hands or Side, nor any interactions. This suggests that the fMRI activation differences between Virtual Hands are not likely to be explained by differences

in gaze strategies. However, there was a main effect of State ($p < 0.001$), which differed between Play (97.4%), React (95.9%), and Watch (93.2%), with all comparisons reaching statistical significance ($p < 0.05$). Together with differences in eye-movement path length and number of saccades, this result suggests that gaze strategies are modulated by State, which might also be reflected in fMRI differences between States.

3.4.2 Joystick use was greater in Play than React

To determine whether differences in brain activation between Play and React could be explained by differences in gamepad use (for the behavioral sample, $n = 10$), I compared joystick data collected from Play and React conditions outside the scanner. I performed three paired-samples t tests to compare Joystick X-Movement (i.e., changes in joystick movement in the x direction), Joystick Y-Movement (i.e., changes in joystick movement in the y direction) and Joystick Time (i.e., what percentage of the time the joystick was pressed during trials). I found in Play there was greater Joystick X-Movement ($p < 0.01$) and Joystick Y-Movement ($p < 0.05$) than in React. However, Joystick Time was significantly greater in React than Play ($p < 0.05$). These results suggest that although participants spent more time using the joystick in React, in Play, participants made more directional changes with the joystick.

Chapter 4

4 Discussion

4.1 Summary of results

The results from this study suggest that brain activation is affected by both the appearance of a virtual hand (e.g., whether it looks like a virtual left or right hand) and having control over virtual hand actions. First, I found that the Virtual Hand and the Side on which actions were performed evoked activation in visuomotor regions within the contralateral hemisphere. Moreover, the contralateral response for Virtual Hand and Side was significantly greater in the right- than left-cortical hemisphere. Second, I found that Virtual Hand and Side affected accuracy of the actions performed (Drop Accuracy). Specifically, accuracy was worst for the Left Virtual hand acting in the Right Side and best when either Virtual Hand was ipsilateral to the Side of the trajectory. Third, I found that the Controlling Hand predominantly affects only somatosensory and motor regions. These results show that while Controlling Hands affect motor processing, the Virtual Hand (as well as the Side of the action) affects earlier stages of visuomotor networks, as well as behavioral accuracy.

I found that having control over closed-loop actions (i.e., in Play) results in increased recruitment of the motor system compared to more reactive or passive open-loop tasks (i.e., in React or Watch). Moreover, the out-of-scanner behavioural data suggests that increased motor system activity in Play is unlikely to be a confound of the number of saccades; however, it could be related to differences in fine joystick movements, a result that requires further analyses.

Together, the findings that both the appearance of a virtual effector and the active nature of game play affect brain activation suggests that video games are a promising approach for studying sensorimotor systems.

4.2 The importance of the visual appearance of the hand

Classic neuropsychological research by Perenin and Vighetto (1988) on patients with hand reaching deficits (optic ataxia) found a “field effect” – worse performance in the visual field contralateral to a lesion. In addition, they also found a “hand effect” – worse performance with the contralateral hand – but only when the left hemisphere is lesioned (Perenin & Vighetto, 1988). Perenin and Vighetto (1988) suggested that each hemisphere has a specialized function, such that the left hemisphere is specialized for motor functions, while the right hemisphere is specialized for visuospatial abilities and spatial attention.

While previous findings of a hand effect did not decouple the hand that was acting from the hand that was visualized (Perenin & Vighetto, 1988), my results show that both behavioral performance and brain activation along the visuomotor pathway depend more upon the visual appearance of a hand, in this case a virtual avatar hand, than on which hand is actually controlling the movement. Other researchers have also found that the visual presentation of a left or right hand is important for modulating brain activation (Shmuelof & Zohary, 2005, 2006). Unlike those studies, which used images of human hands cut off at the wrist, my stimuli included the avatar arm (especially for far reaches; [Figure 2](#)). Nevertheless, the similarity of my results and theirs suggests the hand itself is the crucial aspect.

In the virtual hand effect, multiple brain regions show higher activation for the contralateral virtual hand, regardless of which hand is actually controlling it. Activation included brain regions involved in functions related to body, arm (reaching) and hand processing—V6 (an area implicated in optic ataxia, (Karnath & Perenin, 2005), the superior parietal lobule and medial parietal cortex (which are implicated in body representations), premotor cortex, and a region of the lateral occipitotemporal cortex that overlapped with motion- (MT+) and hand-selective (LOTChand) regions. Notably, the virtual hand effect did not interact with State, suggesting that it was driven by the visual stimulation from seeing a hand and did not require the active execution of actions.

In addition, my results show that the virtual hand effect is asymmetrically lateralized in right-handed participants, with stronger activation in the right hemisphere for virtual left-hand actions than vice versa (see also Shmuelof & Zohary, 2006). I also found an asymmetric “Side effect” in that the right hemisphere showed stronger activation for actions performed on the left side of space than vice versa. Note that this effect is distinct from previously reported (visual) field effects (Perenin & Vighetto, 1988; Shmuelof & Zohary, 2006) because my participants could freely view the stimuli. These hemispheric asymmetries may be related to the frequency with which right-handers perform various actions in daily life (Gonzalez et al., 2007). For example, right-handers have a strong preference to use their right hand on the right side of space. While right-handers often reach with the right hand across to the left side of space, they almost never use the left hand to reach across to the right. My results indicate the actions that are least common in daily life (left hand in right side) result in the poorest behavioral accuracy. Moreover, they may indicate that observing these uncommon actions also evoke the strongest brain activation in the contralateral hemisphere, consistent with the hand effect reported by Shmeulof and Zohary (2006). An interesting avenue for future research would be to study whether the virtual hand effect also occurs in left-handers and whether it depends upon the frequency of hand use in daily life (Gallivan et al., 2011; Gonzalez et al., 2007).

4.3 Having control over actions is key for motor system engagement.

The key difference between Play and React conditions was that participants had active control of virtual hand movements in Play, which provided visual feedback that enabled them to modify actions on the fly in a closed-loop fashion. In contrast, during React, even though participants could see actions, their response (i.e., gamepad use) had no consequence on the viewed actions. The differences between these two conditions could be related to any of these factors (agency, visual feedback, closed-loop processing).

Comparisons between Play and React revealed Play-selective recruitment of motor areas including M1, PMd, SPL and SMA. The most appealing explanation would be that these

key regions of the motor system are engaged more by closed-loop processing (involving agency and/or the implementation of feedback to modify actions). Another less interesting explanation is that increased motor activity during Play is confounded by differences a larger number of changes in joystick movements than for React. Note, however, that the differences in joystick strategies are likely related to the differences between closed- and open-loop processing. For example, when participants had control over virtual hand actions they could update their actions of the fly by changing the direction of the joystick; whereas, in React, participants did not have causal control, which resulted in fewer joystick movements perhaps because their actions did not have consequences. Ideally, I had intended to utilize joystick data as a covariate in the fMRI analyses. Unfortunately, however, due to technical problems during fMRI, left hand joystick data was not collected during React runs. Future analyses could utilize the in-scanner data from right-hand joystick movements as covariates. If differences between Play and React remain after joystick-specific factors are modelled out, this would suggest that the condition differences are not merely an artifact of low-level motor factors. Another potential confound is that Play conditions always preceded React and Watch conditions, such that differences could be due to adaptation or memory effects. This could be addressed by future studies in which order is counterbalanced by making React runs based on a different participant's actions. Note, however, that the main benefit of the current design choice is that Play and React runs were yoked in terms of visual and motor stimulation.

Another key finding was increased recruitment of association cortex in React vs. Play (Figure 6). React-selective areas included regions of association cortex related to the performance of highly skilled motor actions (i.e., praxis; SMG and pSTS/MTG), including reaching and grasping (V6A and aIPS, respectively).

My results are similar to previous studies that have compared other artificial open-loop tasks like pantomiming (pretending to do an action without actually acting on an object) to real actions. Pantomimed actions differentially engage cognitive networks, particularly those implicated in praxis (Króliczak et al., 2007; Paciocco, 2012; Rossit et al., 2011),

similar to what I found for React > Play. In contrast, real actions better engage later stages of motor processing than pantomimed actions. Together, the similarity of activation for React (vs. Play) and pantomimed (vs. real) actions support the importance of having active control over actions with consequences and on-the-fly corrections in a closed loop. Importantly, subtractions between React and Play are more tightly controlled (involving both motor and visual stimulation) than between pantomimed vs. real actions, providing stronger evidence that closed-loop processing may be the crucial factor.

4.4 Limitations

Although video games offer a visually closed-loop paradigm, haptic feedback was unavailable in this experiment. For instance, even though a participant could *see* if they had grasped the ball in their virtual hand, they could not *feel* if they had grasped the ball (although they did receive tactile sensations from moving the joystick). Given the limitations of current haptic technology, particularly MR-compatible technology, providing haptic feedback in video games would be difficult if not impossible. Previous research has suggested that removing haptic feedback can make real actions more like pantomimed actions (Whitwell et al., 2014). Nevertheless, even though inclusion of haptic feedback would be the gold standard, the present results suggest that even just incorporating visual feedback into a closed-loop task provides a beneficial approach for studying actions with fMRI.

Another limitation of this study, and perhaps video games more generally, is that the range of actions in the game may not naturally map on to the actions afforded by the gamepad. Here, joysticks enabled control of reach trajectories in two dimensions, but changes in the third dimension (the height of the hand) were constrained by the software. In addition, the grip component of the task was binary in nature, such that squeezing the trigger caused all five fingers to shut. This stands in contrast to real grasping in which hand pre-shaping occurs during the reach towards the object (Jeannerod, 1984). Note, however, that this experiment focussed on examining one signature of motor actions—a neural response to the contralateral arm/hand—for which the mapping between the

controller and the game outcome was well suited. Future experiments on action video games, perhaps including ones aimed toward studying grasping per se, might benefit from considerations of more natural ways to control game outcomes (e.g., through kinematic tracking).

Given that this fMRI study did not involve a localizer experiment, some functional brain regions were difficult to decipher. For example, the hand-selective area of the LOTC resides in close proximity to MT+ (Bracci et al., 2012; Weiner & Grill-Spector, 2011). Therefore, it is difficult to determine whether activation evoked from Virtual Hand and Side differences were in the hand- and/or motion-selective regions. Despite this, both regions remain theoretically interesting because they are activated selectively according to the virtual hand used or the side the action is performed in. Moreover, regions of the PMd and FEF are also close together (Amiez & Petrides, 2017). However, the hotspots revealed by the Play > React contrast reveal greater PMd activation as defined by the Julich atlas.

4.5 Future Directions

The results suggest video games are a promising approach to study actions with fMRI. The virtual hand effect suggests that the visual appearance of bodily stimuli does indeed evoke brain signatures consistent with real actions, in this case a preference for movements of the contralateral virtual body. This opens the possibility that video games could be used in fMRI to study a much broader range of actions than would otherwise be possible (e.g., locomotion, defensive movements, etc.). Clinically, virtual displays of realistic human bodies could be used in virtual rehabilitation strategies for phantom limb pain or stroke (e.g., similar to mirror box therapy, Ossmy & Mukamel, 2016).

Intriguingly, the results also suggest that by enabling closed-loop actions, active video game play could serve as a valuable addition to fMRI approaches. My study focussed on sensorimotor control, where the importance of closed-loop processing was first proposed (Wolpert & Flanagan, 2010). Here, I found that the nature of the task affects motor and

praxis networks. Arguably, however, cognition in general typically relies on closed-loop mechanisms (Sokolov et al., 2017) such that cognitive neuroscience more generally may benefit from a move toward closed-loop paradigms through video games. Indeed, my results, based on activation differences between Play, React and Watch in a visuomotor task, are corroborated by another fMRI study from my lab that used the same three conditions during a much more complex task, playing Pac-man (Davidson, 2022). That study found that functional connectivity patterns differed considerably between Play compared to both React and Watch, which were not that dissimilar to one another. Taken together, these studies suggest that video game paradigms offer an exciting new direction for cognitive neuroscience.

4.6 Conclusion

In conclusion, having control over realistic depictions of the human body are important elements for studying actions using video games. Crucially, whether one sees their avatar-self perform a common (e.g., right hand in right side) or uncommon (e.g., left hand in right side) action, it results in distinct patterns of brain activation (e.g., increased right-hemispheric activation for the virtual left hand) and behaviour (e.g., less accurate actions using the virtual left hand), regardless of the controlling hand used. In addition, when participants have control over their actions—as opposed to having matched visual and motor stimulation—there is increased recruitment of the motor system. Moreover, this study highlights that having control over actions results in less recruitment of association cortex typically associated with open-loop methods of studying actions. Overall, this study sheds light on a new paradigm for studying actions with fMRI. Naturalistic video games not only allow us to revisit previously studied actions (e.g., grasping) at a level more similarly to that of real actions than existing proxies, but also to study other ethological actions (e.g., feeding, locomotion) that have been previously neglected given the constraints of studying actions in the scanner.

References

- Amiez, C., & Petrides, M. (2017). Functional rostro-caudal gradient in the human posterior lateral frontal cortex. *Brain Structure and Function*.
<https://doi.org/10.1007/s00429-017-1567-z>
- Amunts, K., Mohlberg, H., Bludau, S., & Zilles, K. (2020). Julich-Brain: A 3D probabilistic atlas of the human brain's cytoarchitecture. *Science*, *369*(6506), 988–992. <https://doi.org/10.1126/science.abb4588>
- Behzadi, Y., Restom, K., Liao, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. <https://doi.org/10.1016/j.neuroimage.2007.04.042>
- Bencivenga, F., Sulpizio, V., Tullo, M. G., & Galati, G. (2021). Assessing the effective connectivity of premotor areas during real vs imagined grasping: a DCM-PEB approach. *NeuroImage*, *230*, 117806.
<https://doi.org/10.1016/j.neuroimage.2021.117806>
- Binkofski, F., Buccino, G., Posse, S., Seitz, R. J., Rizzolatti, G., & Freund, H. J. (1999). A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *European Journal of Neuroscience*, *11*(9), 3276–3286.
<https://doi.org/10.1046/j.1460-9568.1999.00753.x>
- Bracci, S., Cavina-Pratesi, C., Ietswaart, M., Caramazza, A., & Peelen, M. v. (2012). Closely overlapping responses to tools and hands in left lateral occipitotemporal cortex. *Journal of Neurophysiology*, *107*(5), 1443–1456.
<https://doi.org/10.1152/jn.00619.2011>
- Brainard, D. H. (1997). The psychophysics toolbox. *Spatial Vision*, *10*(4), 433–436.
- Brandi, M.-L., Wohlschlager, A., Sorg, C., & Hermsdorfer, J. (2014). The neural correlates of planning and executing actual tool use. *Journal of Neuroscience*, *34*(39), 13183–13194. <https://doi.org/10.1523/JNEUROSCI.0597-14.2014>
- Castiello, U. (2005). The neuroscience of grasping. In *Nature Reviews Neuroscience*. <https://doi.org/10.1038/nrn1744>
- Castiello, U., Bennett, K. M., Egan, G. F., Tochon-Danguy, H. J., Kritikos, A., & Dunai, J. (2000). Human inferior parietal cortex “programs” the action class of grasping. *Cognitive Systems Research*. [https://doi.org/10.1016/S1389-0417\(99\)00011-X](https://doi.org/10.1016/S1389-0417(99)00011-X)
- Cavina-Pratesi, C., Monaco, S., Fattori, P., Galletti, C., McAdam, T. D., Quinlan, D. J., Goodale, M. A., & Culham, J. C. (2010). Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. *Journal of Neuroscience*, *30*(31), 10306–10323. <https://doi.org/10.1523/JNEUROSCI.2023-10.2010>
- Cignetti, F., Salvia, E., Anton, J. L., Grosbras, M. H., & Assaiante, C. (2016). Pros and cons of using the informed basis set to account for hemodynamic response variability with developmental data. *Frontiers in Neuroscience*.
<https://doi.org/10.3389/fnins.2016.00322>
- Connolly, J. D., Andersen, R. A., & Goodale, M. A. (2003). FMRI evidence for a “parietal reach region” in the human brain. *Experimental Brain Research*, *153*(2), 140–145. <https://doi.org/10.1007/s00221-003-1587-1>

- Culham, J. C. (2016). The left hand doesn't know what the right hand is doing—or does it? *Cell Reports*, *17*(11), 2809–2810.
<https://doi.org/10.1016/j.celrep.2016.11.078>
- Culham, J. C., Cavina-Pratesi, C., & Singhal, A. (2006). The role of parietal cortex in visuomotor control: What have we learned from neuroimaging? *Neuropsychologia*, *44*(13), 2668–2684.
<https://doi.org/10.1016/j.neuropsychologia.2005.11.003>
- Culham, J. C., Danckert, S. L., DeSouza, J. F. X., Gati, J. S., Menon, R. S., & Goodale, M. A. (2003). Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. *Experimental Brain Research*, *153*(2), 180–189. <https://doi.org/10.1007/s00221-003-1591-5>
- Current Designs (2019). Gamepad. [Apparatus]
<https://www.curdes.com/mainforp/responsedevices/variabledevices/gamepad.html>
- Davidson, Emily, "Human neuroimaging reveals that agency in a video game boosts functional connectivity within and between networks" (2022). *Master's thesis in Neuroscience University of Western Ontario*
- Dewey, J. (1896). The reflex arc concept in psychology. *Psychological Review*, *3*(4), 357–370. <https://doi.org/10.1037/h0070405>
- Diedrichsen, J., Balsters, J. H., Flavell, J., Cussans, E., & Ramnani, N. (2009). A probabilistic MR atlas of the human cerebellum. *NeuroImage*, *46*(1), 39–46.
<https://doi.org/10.1016/j.neuroimage.2009.01.045>
- Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski, K. J. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111–116. <https://doi.org/10.1038/s41592-018-0235-4>
- Foulsham, T. (2015). Eye movements and their functions in everyday tasks. *Eye*, *29*(2), 196–199. <https://doi.org/10.1038/eye.2014.275>
- Freud, E., Macdonald, S. N., Chen, J., Quinlan, D. J., Goodale, M. A., & Culham, J. C. (2018). Getting a grip on reality: Grasping movements directed to real objects and images rely on dissociable neural representations. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *98*, 34–48.
<https://doi.org/10.1016/j.cortex.2017.02.020>
- Frey, S. H., Hansen, M., & Marchal, N. (2015). Grasping with the press of a button: grasp-selective responses in the human anterior intraparietal sulcus depend on nonarbitrary causal relationships between hand movements and end-effector actions. *Journal of Cognitive Neuroscience*, *27*(6), 1146–1160.
https://doi.org/10.1162/jocn_a_00766
- Gallivan, J. P., McLean, A., & Culham, J. C. (2011). Neuroimaging reveals enhanced activation in a reach-selective brain area for objects located within participants' typical hand workspaces. *Neuropsychologia*, *49*(13), 3710–3721.
<https://doi.org/10.1016/j.neuropsychologia.2011.09.027>
- Gallivan, J. P., McLean, D. A., Valyear, K. F., & Culham, J. C. (2013). Decoding the neural mechanisms of human tool use. *ELife*, *2*.
<https://doi.org/10.7554/eLife.00425>

- Gonzalez, C. L. R., Whitwell, R. L., Morrissey, B., Ganel, T., & Goodale, M. A. (2007). Left handedness does not extend to visually guided precision grasping. *Experimental Brain Research*. <https://doi.org/10.1007/s00221-007-1090-1>
- Grafton, S. T., Arbib, M. A., Fadiga, L., & Rizzolatti, G. (1996). Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. *Experimental Brain Research*. <https://doi.org/10.1007/BF00227183>
- Hofree, G., Urgen, B. A., Winkielman, P., & Saygin, A. P. (2015). Observation and imitation of actions performed by humans, androids, and robots: An EMG study. *Frontiers in Human Neuroscience*. <https://doi.org/10.3389/fnhum.2015.00364>
- Jeannerod, M. (1984). The timing of natural prehension movements. *Journal of Motor Behavior*. <https://doi.org/10.1080/00222895.1984.10735319>
- Johansson, R. S., Westling, G., Bäckström, A., & Flanagan, J. R. (2001). Eye–hand coordination in object manipulation. *The Journal of Neuroscience*, *21*(17), 6917–6932. <https://doi.org/10.1523/JNEUROSCI.21-17-06917.2001>
- Karnath, H.-O., & Perenin, M.-T. (2005). Cortical control of visually guided reaching: evidence from patients with optic ataxia. *Cerebral Cortex*, *15*(10), 1561–1569. <https://doi.org/10.1093/cercor/bhi034>
- Keuken, M. C., Bazin, P. L., Backhouse, K., Beekhuizen, S., Himmer, L., Kandola, A., Lafeber, J. J., Prochazkova, L., Trutti, A., Schäfer, A., Turner, R., & Forstmann, B. U. (2017). Effects of aging on T1, T2*, and QSM MRI values in the subcortex. *Brain Structure and Function*, *222*(6), 2487–2505. <https://doi.org/10.1007/s00429-016-1352-4>
- Keuken, M. C., Bazin, P.-L., Crown, L., Hootsmans, J., Laufer, A., Müller-Axt, C., Sier, R., van der Putten, E. J., Schäfer, A., Turner, R., & Forstmann, B. U. (2014). Quantifying inter-individual anatomical variability in the subcortex using 7 T structural MRI. *NeuroImage*, *94*, 40–46. <https://doi.org/10.1016/j.neuroimage.2014.03.032>
- King, M., Hernandez-Castillo, C. R., Poldrack, R. A., Ivry, R. B., & Diedrichsen, J. (2019). Functional boundaries in the human cerebellum revealed by a multi-domain task battery. *Nature Neuroscience*. <https://doi.org/10.1038/s41593-019-0436-x>
- Króliczak, G., Cavina-Pratesi, C., Goodman, D. A., & Culham, J. C. (2007). What does the brain do when you fake it? An fMRI study of pantomimed and real grasping. *Journal of Neurophysiology*, *97*(3), 2410–2422. <https://doi.org/10.1152/jn.00778.2006>
- Liu, Z.-X., Rosenbaum, R. S., & Ryan, J. D. (2020). Restricting visual exploration directly impedes neural activity, functional connectivity, and memory. *Cerebral Cortex Communications*, *1*(1). <https://doi.org/10.1093/texcom/tgaa054>
- Merleau-Ponty, M. (1964). The primacy of perception and its philosophical consequences. In *The Primacy of Perception*.
- Monaco, S., Malfatti, G., Culham, J. C., Cattaneo, L., & Turella, L. (2020). Decoding motor imagery and action planning in the early visual cortex:

- Overlapping but distinct neural mechanisms. *NeuroImage*.
<https://doi.org/10.1016/j.neuroimage.2020.116981>
- Monaco, S., Sedda, A., Cavina-Pratesi, C., & Culham, J. C. (2015). Neural correlates of object size and object location during grasping actions. *European Journal of Neuroscience*, *41*(4), 454–465. <https://doi.org/10.1111/ejn.12786>
- Nau, M., Frey, M., & Doeller, C. F. (2020). DeepMReye: MR-based eye tracking without eye tracking. *Journal of Vision*, *20*(11), 1014.
<https://doi.org/10.1167/jov.20.11.1014>
- Ossmy, O., & Mukamel, R. (2016). Neural network underlying intermanual skill transfer in humans. *Cell Reports*, *17*(11), 2891–2900.
<https://doi.org/10.1016/j.celrep.2016.11.009>
- Perenin, M. T., & Vighetto, A. (1988). Optic ataxia: A specific disruption in visuomotor mechanisms: I. Different aspects of the deficit in reaching for objects. *Brain*. <https://doi.org/10.1093/brain/111.3.643>
- Petit, L., & Beauchamp, M. S. (2003). Neural basis of visually guided head movements studied with fMRI. *Journal of Neurophysiology*.
<https://doi.org/10.1152/jn.00988.2002>
- Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., & Fazio, F. (1996). Localization of grasp representations in humans by PET: 1. Observation versus execution. *Experimental Brain Research*.
<https://doi.org/10.1007/BF00227301>
- Rossit, S., Malhotra, P., Muir, K., Reeves, I., Duncan, G., & Harvey, M. (2011). The role of right temporal lobe structures in off-line action: evidence from lesion-behavior mapping in stroke patients. *Cerebral Cortex*, *21*(12), 2751–2761.
<https://doi.org/10.1093/cercor/bhr073>
- Ryan, J. D., & Shen, K. (2020). The eyes are a window into memory. *Current Opinion in Behavioral Sciences*, *32*, 1–6.
<https://doi.org/10.1016/j.cobeha.2019.12.014>
- Shmuelof, L., & Zohary, E. (2005). Dissociation between ventral and dorsal fmri activation during object and action recognition. *Neuron*.
<https://doi.org/10.1016/j.neuron.2005.06.034>
- Shmuelof, L., & Zohary, E. (2006). A mirror representation of others' actions in the human anterior parietal cortex. *Journal of Neuroscience*, *26*(38), 9736–9742.
<https://doi.org/10.1523/JNEUROSCI.1836-06.2006>
- Singhal, A., Monaco, S., Kaufman, L. D., & Culham, J. C. (2013). Human fMRI reveals that delayed action re-recruits visual perception. *PLoS ONE*.
<https://doi.org/10.1371/journal.pone.0073629>
- Snow, J. C., & Culham, J. C. (2021). The treachery of images: how realism influences brain and behavior. *Trends in Cognitive Sciences*, *25*(6), 506–519.
<https://doi.org/10.1016/j.tics.2021.02.008>
- Sokolov, A. A., Miall, R. C., & Ivry, R. B. (2017). The cerebellum: adaptive prediction for movement and cognition. *Trends in Cognitive Sciences*, *21*(5), 313–332. <https://doi.org/10.1016/j.tics.2017.02.005>
- SR Research (2009). EyeLink 1000 User Manual Tower. SR Research.
<http://sr-research.jp/support/EyeLink>. 1.5.0 edition.

- Tian, Y., Margulies, D. S., Breakspear, M., & Zalesky, A. (2020). Topographic organization of the human subcortex unveiled with functional connectivity gradients. *Nature Neuroscience*, *23*(11), 1421–1432. <https://doi.org/10.1038/s41593-020-00711-6>
- Toyomura, A., Shibata, M., & Kuriki, S. (2012). Self-paced and externally triggered rhythmical lower limb movements: A functional MRI study. *Neuroscience Letters*. <https://doi.org/10.1016/j.neulet.2012.03.049>
- Weiner, K. S., & Grill-Spector, K. (2011). Not one extrastriate body area: Using anatomical landmarks, hMT+, and visual field maps to parcellate limb-selective activations in human lateral occipitotemporal cortex. *NeuroImage*, *56*(4), 2183–2199. <https://doi.org/10.1016/j.neuroimage.2011.03.041>
- Whitwell, R. L., Milner, A. D., & Goodale, M. A. (2014). The two visual systems hypothesis: new challenges and insights from visual form agnostic patient DF. *Frontiers in Neurology*, *5*. <https://doi.org/10.3389/fneur.2014.00255>
- Wolpert, D. M., & Flanagan, J. R. (2010). Motor learning. *Current Biology*, *20*(11), R467–R472. <https://doi.org/10.1016/j.cub.2010.04.035>
- Yarkoni, T., Poldrack, R. A., Nichols, T. E., van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*(8), 665–670. <https://doi.org/10.1038/nmeth.1635>

Curriculum Vitae

Name: Jaana Leppala

Post-secondary Education and Degrees: University of Western Ontario
London, Ontario, Canada
2016-2020 BSc.

Honours and Awards: Travel Award
2022

Related Work Experience Teaching Assistant
The University of Western Ontario
2021-2022