A. Specific Aims

When performing a motor task, we need to constantly supply motor commands to the wrist to control its motion whether the wrist stays at a specific location or moves to a desired location. However, it is still unknown about the central mechanism controlling the actions. Previous studies on the oculomotor system or the cervical motor system have illuminated the existence of a leaky neural integrator that plays an important role in its control of actions. The pulses induced by the motoneurons during the move phase are generated and integrated in real time to accumulate into a step output to provide a real-time estimation of the displacement. However, this system is inherently imperfect that requires sensory feedbacks for corrections. Driven by the aforementioned evidence of a leaky neural integrator in the other systems and a current lack of understanding of the control design of the wrist, we want to investigate how the neural controller of the move phase affects that of the hold phase. We start with the hypothesis that the wrist also includes a neural integrator that updates its position information. The aim of this research is to identify if separate control mechanisms exist for the wrist move and the hold phase and to understand, if such distinct paradigms exist, whether the wrist needs additional sensory inputs such as the proprioceptive or visual feedbacks to modulate its motor commands.

Current psychophysical approach to investigate the feedback commands we generate in the wrist movement is conducted in the able-bodied individuals by using a robotic manipulandum to generate error-based reaching activities in response to trial-to-trial force field adaptation or error-clamped task preprogrammed in the manipulandum. Because the study solely focuses on the motor command of the wrist, we ensure that only the joint of the wrist can rotate by fixing the subject's forearm.

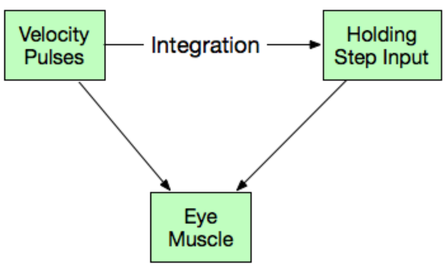


Figure 1. A simplified diagram illustrating the control mechanism in the occulomotor system. In such a system, the holding signals are updated by integrating the velocity signals. Therefore, the move phase can alter the behavior during the hold phase but the hold phase cannot change the inputs from the move phase. Similarly, such idea can be applied in the motor control of the wrist movement where force field adaptations are applied at both holding and moving phases to see how changes in one phase affect the behavior of the other phase.

Specific Aim 1 will be to verify that the force field adaptation in the moving phase does affect the performance of the holding phase and is tested under two conditions (a). during a reaching movement, the subjects learn to generate forces in response to a specific force field (b). at the end of the movement, the subjects hold their positions with error clamped trials where the position of the manipulandum is unaffected by the forces produced by the subjects but the force fields that the subjects exert are recorded.

Objective: These experiments are designed to verify the hypothesis whether the motor control of moving phase affects the holding phase and to measure if the magnitude of the force adapted during the moving phase sums up to the force produced during the holding phase.

Specific Aim 2 will be to ensure that the force tails are dependent on the movement past history, not where it is located in space and is tested under 4 conditions where the subjects adapt to a specific force field but the directions of the movement changes in each condition and these directions start off at the same center point but move towards north, south, west and east then back.

Objective: These experiments are designed to knock out the covariate of the hand's spatial location as an input to the control paradigm of the wrist.

Specific Aim 3 will be to characterize the wrist movement in absence of visual or proprioceptive feedback and are tested under 4 conditions: (a). An error-clamp reaching movement where the subject is able to recognize the hand position (b). Same activities are applied to the subject but a vibrator is placed on the wrist to block the proprioceptive feedback. (c). Same activities in (a) are applied with the exception that the visual cues of the subject' hand position is removed to remove the visual sensory information. (d). An error clamp trial with both the removal of the visual cues and the vibrator applied at the wrist.

Objective: These experiments are design to test if the wrist needs additional sensory feedback such as proprioceptive or visual feedback to control its movement and to test to what extent each sensory feedback plays a role in the modulation of the wrist movement.

B. Background and Significance

Overview

In order to generate a point to point movement, the nervous system needs to produce not only the transient command to move the body to its destination but also the sustained command to hold the body part at its destination. In order words, we produce not only moving command to change the spatial location of our body but also holding command to maintain the current position of our body. In this project, we want to characterize the organization and interaction of the wrist's move and hold phase motor commands.

Background

In the oculomotor system, it is now understood that these two phases (moving and holding) are controlled by two distinct circuits, the premotor circuit that is responsible for generating the transient response to move the eye from one location to another and the neural integrator that acts as an operator to convert the transient input to sustained output that holds the eye. These two modalities for controlling movement can be mapped into specific anatomical regions in the cerebellum, where the oculomotor vermis processes the transient neural signals that move the eye via efference copy and the flocculus is responsible for controlling the sustained neural signals that hold the eye, monitoring the activities in the neural integrator[1]. Several experiments that are done in neural recording of animals making saccades confirmed that there are distinct sets of motor control mechanisms during the moving and holding phase. Firstly, it is known that the neuronal firing of the motor nucleus abducens (eye muscle) happens both in the moving and the holding phase, implying that the eye muscle receives both the transient response signal to move the eye from one location to another and the sustained response to hold the eye[2]. The neural recording of the premotor neuron (specifically, the EBN (excitatory burst neuron)) showed that the premotor neuron only bursted during the moving phase, showing that EBN encoded the moving phase velocity signal to abducens neurons[3].

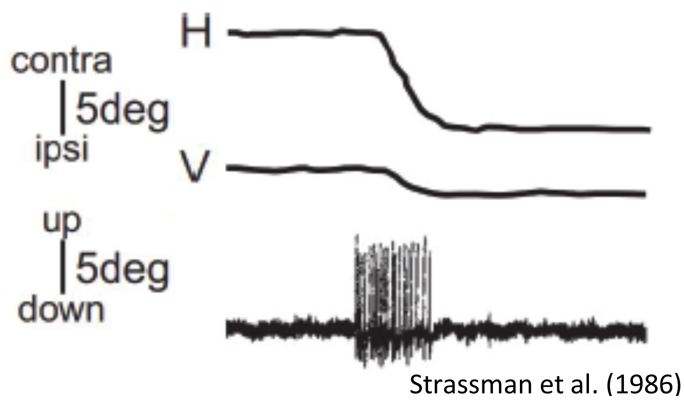


Figure 2. The recording of an excitatory burst neuron (EBN) in the left brain stem during saccadic movements. X-axis shows the time scale. The result shows that the EBN cells fires only during the movement phase but has no activity during the holding phase.

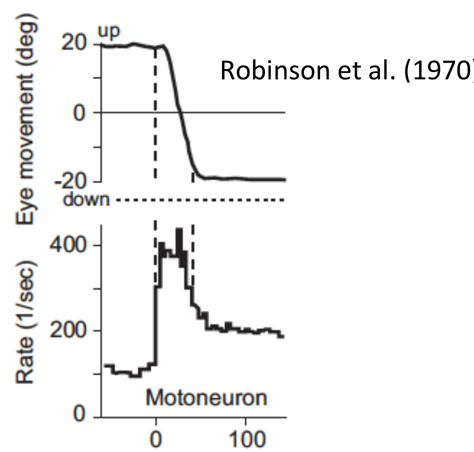


Figure 3. The recording of the motoneuron during the eye movement. The result shows that the motoneuron fires both at the move and hold phase. It might imply that the motoneurons receive inputs both from the move phase but also from the hold phase.

As shown in figure 4, it is found that a short stimulation of the premotor neuron in the paramedian pontine reticular formation (PPRF) not only moves the eye but also holds the eye after the end of the stimulation.[4] These experiments together demonstrate that the premotor neuron only response to the eye movement, but the signals encoded from the premotor neurons further translate into another circuit that give command to the holding phase. The Necleus Prepositus Hypoglossi (NPH) in rostral medulla was the region where the brain encodes sustained activities to hold the eyes. This region fires only during the holding phase, providing the position signal to abducens neurons.[5] However, as it is shown in figure 2, when this region temporally deactivated, the eye was able to make a movement but was unable to hold its position.[6] These evidence suggest that there are separate neural circuits controlling moving and holding of the eye and they are serially influencing each other. Collectively, we are able to characterize the neural encoding for moving and holding in figure 5.

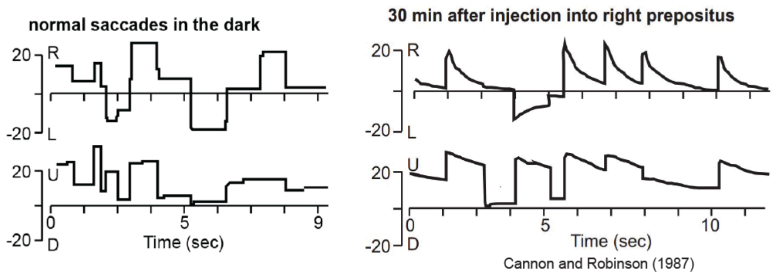


Figure 3. The recording of eye position of saccadic movement performed by a monkey in the dark. A temporary neural inhibitor was injected into the right prepostius which is most commonly known as the neural integrator of the eye. The comparison of these graphs shows that the lesion of the neural integrator only disrupts the hold phase but has no effect on the move phase.

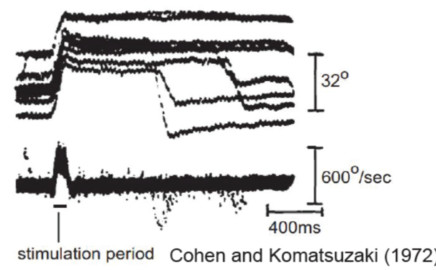


Figure 4. The recording of the eye movement as a result of the premotor burst neurons in the PPRF region of the brain. Data were collected in darkness. The plot shows that the burst neuron firing results in a change both the eye's velocity and position.

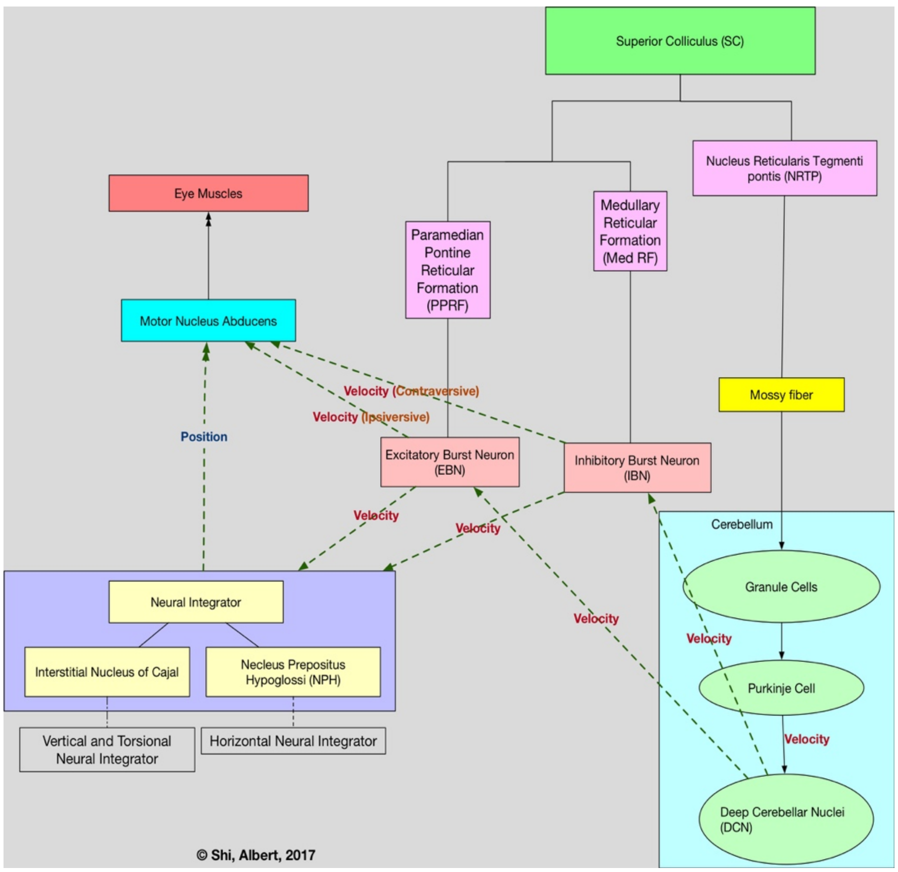


Figure 5. A schematic diagram showing how the motoneurons of the eye innervate the eye muscle **to move and hold the position.** The superior colliculus houses the EBN (excitatory burst neurons) and IBN (inhibitory burst neurons) to send velocity signals to modulate the saccade (fast eye movement) in real-time to drive the eye to move. These velocity signals are subsequently integrated as the position information of the eyes in the neural integrators to sustain the eye to a fixed location. The integrated position information provides an estimation of the current position of the eye and will later be feedforward to the motor nucleus abducens. When the eye gets to its desired location, the integrator's output matches the desired position and ends the pulse to move.

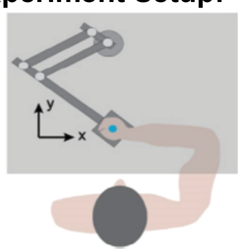
Previous investigators have investigated if the central mechanism of the control system in the occulomotor system also applies to the head[7]. By distorting the proprioceptive and the visual feedback, they were able to find a neural integrator that is inherently imperfect and needs sensory feedback for error correction, an analogous property similar to that of the eye. These results have driven us to test if the wrist movement possesses the two distinct modalities in moving and holding like the eye and the head. The aim of this research is to identify what is the design of the control mechanism of the wrist and to test whether this control system is leaky or not.

Significance and Innovation

Understanding about how these different neural circuits relate with each other has great value. First of all, from a cellular perspective, if there are different circuitries contributing to holding and moving, the neuron that fires during the move phase would be unaffected if there is a disruption during the hold phase, and vice versa. Answering the question about the separation of control in the wrist could be one of the sub-questions to test if such a distinct design shares globally across different motor system. This has great evolutionary value because it implies that our nervous system design itself to adapt to the different modalities of actions. Furthermore, understanding about whether there are two distinct circuits for moving and holding phase of the wrist can be crucial in a clinical perspective. Diseases such as dystonia, ataxia, cerebral palsy, and Parkinson's and Alzheimer's diseases result in serious motor control problems in which people either spasm uncontrollably or lose control of their muscles completely. If this distinct control paradigm also applies to the wrist control system, we propose that this information can be used to develop treatments targeting these neurological impairments based on symptoms directly linked to the affected anatomical site enabling rehabilitation of the patient's wrist and hand movement and restoration of sufficient strength to hold objects for a sustainable period of time. We expect that this study will also benefit the athletes who suffer from neurological wrist injury and are unable to perform a task at a specific position or angle. With the understanding of the distinctness of the holding and moving control mechanism, we can make a better decision to develop better treatment plan. This study opens door to the current understanding about the motor control of the wrist and it could imply important information about the motor control in the joints of the limbs. Finally, this study could also benefit the use of neuroprosthetics because this separation of the motor control could refine the rehabilitation paradigm where the stimulation parameters of device could stimulate the muscle or nerve more locally and accurately.

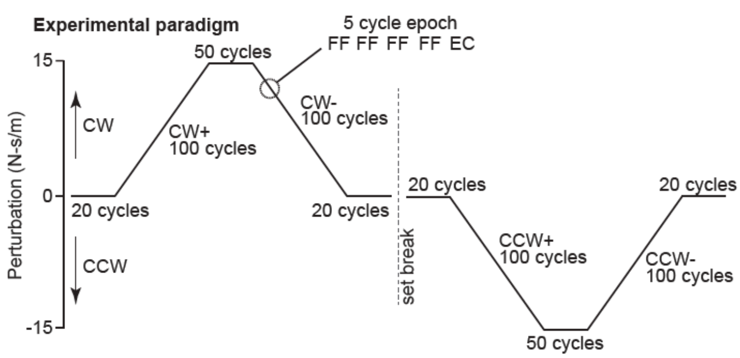
<u>C. Approach</u>

Experiment Setup:

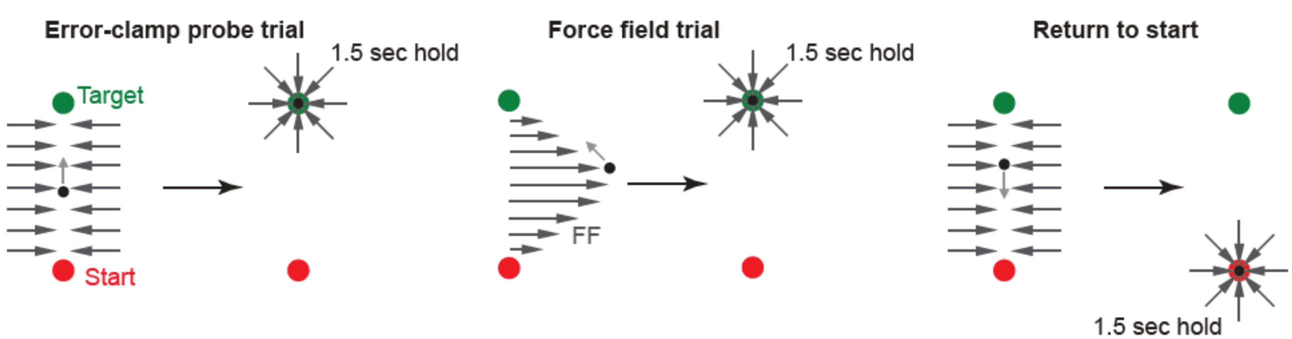


To set up the experiment, we ask the subject to sit in an upright position with the arm fixed with a clamp. The subject is able to move a handle programmed with forces produced by the computer program (C++). The handle is also capable of recording the force response exerted by the subject. A screen is above the handle which makes the subject unable to directly observe the arm position. However, the screen can display the handle's position. During the experiment, the subject is instructed to follow a dot displayed on the screen by moving the handle.

<u>Specific Aim 1. The force field adaptation in the moving phase does affect the performance of the holding phase</u>



(Albert et al., 2017)



Research Design: Using the reaching movements of the wrist, we adapted the subject with a certain force field during the arm movement and examine the force tail (the end of movement) when the arm position is fixed in order to test how do changes in the move neural controller affect the hold neural controller. This idea is built on the premise that if the adaptation learnt during the move phase is transferable to the force response during the hold phase the two circuits would be interrelated. In the experiment, the subject is asked to perform reaching movement where the subject will be gradually adapted and de-adapted to clockwise and counterclockwise force fields[9]. When the subject reaches the target, the handle produces a counteractive force that fix the hand's position. Firstly, the subject performs twenty cycles of free mode trial where no effect is imposed on the subject, then a hundred cycles of CW trials with twenty groups of four force field adaptation and one error clamp trial. Then the subject repeats fifty trials of free mode. Then the subject performs a hundred cycles of CCW trials with twenty groups of four force field adaptation and 1 error clamp trial. Then the subject performs twenty free mode trials. Later, the subject repeats the same activities but the force perturbation is on the opposite direction. By introducing some force field adaptation during the move phase, we were able to capture the force tail behavior to learn about the force response during the hold phase. We can analyze the response using MATLAB to evaluate the if the force tail responses in the 4 experiments are different from each other.

Expected result: We expect that the force field adaption at the force tail will be influenced by the force adaptation during the move phase.

Pitfall and alternative strategy: The subject might be nervous and intentionally exert a lot of force during the end of the experiment. To prevent this, we could add interactive elements to the experiments by adding sounds when the reach target and reward points when successfully reach the target within a certain time frame.

Specific Aim 2. Force tails are dependent on the wrist's precedent movement, not its spatial location.

Research Design: Under this research goal, we want to eliminate the covariate of the spatial location as a factor that influence the force tail response. To this end, the subject is adapted to the force field with same magnitude but the orientation of the force field is different. In order to magnify the range of the subject's wrist movement, we scale the target dot with respect to the actual position of the subject's hand. At the beginning, the subject rests the hand at the center point position. In the first experiment, the subject performs fifty trials force field adaption to the left and back to the center point. In the second experiment, the subject performs the same force field adaption (fifty trials) to the right and then back to the center point. In the third experiment, the subject performs fifty trials of force field adaption to the up and then back to the center point. In the fourth experiment, the subject performs fifty trials force field adaption to the down and then back to the center point. In the end, we will analyze the force tails from these four experiments using MATLAB.

Expected result: we expect that the spatial location of the subject hand would not vary the force tail response across the four experiments.

Pitfall and alternative strategy: Since the range of the movement of the wrist is so small, it might not produce significance in the end result of the experiment. Therefore, we might consider to do slicing movement inside of the reaching movement to increase the range of movement.

Specific Aim 3. The wrist neural integrator is leaky and needs additional sensory feedbacks for correction

Research Design: Our first working hypothesis is that the wrist is unable to hold its position in the absence of visual feedback. To test this, we propose experiment where each subject was evaluated under conditions with or without visual feedback. In the first condition, the subject sit in a room where the hand grab a robotic arm underneath a projector screen. A visual cue of the hand position is projected on the screen. The subject was instructed to aim his or her hand through the robotic arm toward a target illuminated at the projector, then rapidly move the wrist when the center target was turned off and a newly illuminated target appeared to the right or left. In the first condition, a target was positioned in front of the subject, with targets appearing at the center, or to the right or left at 10°, 20°, and 30°. The subject was instructed to aim the wrist toward a visual cue that was illuminated, then rapidly move the wrist towards the new target on either the right or the left after the previous center target was turned off. In the second scenario, the subject was asked to move the hand towards a target without the visual cue projected on the screen. The condition was designed to remove visual feedback regarding the accuracy of hand position with respect to the target. In the absence of visual feedback, the subject was asked to aim the head toward an eccentrically placed target, head stabilization primarily relies on proprioceptive signals from hand muscles. Our second working hypothesis is that the deficit of feedback from proprioception would impede the recognition of the wrist position and holding of the wrist. To test this, the subjects were asked to aim their wrists at a target with a vibrator disrupting their proprioception with or without visual cue of their hand positions. The vibration with a sinusoidal waveform at 50 Hz frequency and 0.5°amplitude was applied at the same time over the peripheral part of the wrist to take away the proprioception of the hand.[8] Lastly, we want to test the combinatorial effects under the absence of visual and proprioceptive feedbacks.

Expected result: In our first experiment with the removal of visual feedback, we expect that the subject would hold their position when a visual cue is present but having a drifting in their hand positions when the visual cue is absent. In our second experiment with the removal of the proprioceptive feedback, we expect that the subject with the vibrator on their wrist incapable of holding the hand position. We expected the experiment under the subject experience the strongest drift in their hand position with the removal of both visual and proprioceptive feedback.

Potential pitfalls and alternative strategy include the subject is naturally unable to hold the stationary position, being deficit of muscle force or perception of their hand positions or the difficulty concentrating on the task. Alternatively, we could develop some pre-experimental trials as a criterion to include only the subjects with stable reaching movements.

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