UREAP – Final Report

Investigating age-related cognitive decline with fNIRS and peripheral vascular function analysis

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1.1 Introduction

Technological and medical advancements as well as an increased standard of living has resulted in a larger cohort of older adults who are living longer among the population (Cabeza et al., 2018). Blum et al. (2021), predicts that the population of individuals over the age of 65 is expected to double over the next two decades. Age is the leading risk factor in the development of neurodegenerative diseases such as Alzheimer's and Parkinson's Disease, and there is strong evidence that cognitive function declines with age, even in the absence of pathology (Blum et al., 2021; Cabeza et al., 2018). It is important to understand the reasons and mechanisms behind why cognitive decline is occurring faster in certain aging individuals whose brains appear healthy (Cabeza et al., 2018).

Researchers have identified that older adults exhibit reduced lateralization in brain activity (using one hemisphere or the other) when compared to younger adults, who utilize one hemisphere while performing the same task (Cabeza 2002). This reduced hemispheric asymmetry in older adults (HAROLD) is especially apparent in the prefrontal cortex during working memory tasks. Working memory, which is required for short-term storage and processing of information for higher level cognition, is limited by both the capacity and ability of an older individual to activate the required neural regions to accomplish a complex task (Mattay et al., 2006).

A study by Piefke et al. (2012) showed that when subjected to a visual-spatial working memory task, older participants had greater prefrontal cortex activation across both hemispheres, while younger participants primarily activated only the left hemisphere. There are two theories that offer possible explanations for age-related reduction in hemispheric asymmetry. The first

theory is the dedifferentiation hypothesis, and the second is the neural compensation theory. The dedifferentiation theory suggests that brain activity becomes less selective in response to a stimulus, so brain structures have less processing specificity under specific cognitive loads (Carp et al., 2010; McDonough et al., 2022; Piefke et al., 2012). Young adults show distinct patterns of synchronous brain activity within neural networks, whereas these patterns become less distinguishable in older adults (Grady et al., 2016; McDonough et al., 2022). Conversely, neural-compensation refers to the increase in brain activity to enhance cognitive performance through either upregulation, selection, or reorganization (Bunzeck et al., 2023; McDonough et al., 2022). The compensation-related utilization of neural circuits hypothesis (CRUNCH), the primary model used to test compensation, describes a quadratic function in regard to brain activation under increasing cognitive loads. When the task is easy, there is limited brain activation in younger and older adults, but as the task becomes more difficult, brain activity increases until it reaches a threshold where the task is too difficult and brain activity decreases (Lorenz and Cappell 2008). The difference between younger and older adults is that compensatory brain activity in older adults is expected to be at its maximum during lower task demands (Lorenz and Park 2014).

Carp et al. (2010) tested CRUNCH by having younger (18-25yrs) and older (61-82 yrs) adults complete working memory tasks while measuring brain activity patterns using functional magnetic resonance imaging (fMRI). First, they found that during memory encoding and retrieval, older adults had reduced distinctiveness regardless of memory load. Second, during memory maintenance at lower task loads, older adults had higher activation of PFC regions than young adults, but as the memory load increased, the older adults had reduced distinctiveness and increased recruitment of neural resources until they eventually hit a limit and could no longer

perform the task (Carp et al., 2010). Although these results support CRUNCH and thus, compensation, they also provided evidence for dedifferentiation. Additionally, several researchers have provided evidence against CRUNCH, with older adults being able to show compensation even in high cognitive load tasks (Jamadar 2020; Ranchod et al., 2023). During a picture memory encoding task, Duzel et al. (2011), found a subgroup of older adults who, without compensatory activity, had recollection memory performance that was indistinguishable from the young adult cohort. However, there were still older adults in the study who exhibited compensatory activity in the prefrontal and parietal regions to maintain memory performance (Duzel et al., 2011).

1.2 Using fNIRS to Test CRUNCH and Measure Systemic Vascular Function

Functional near-infrared spectroscopy (fNIRS) is a portable and versatile neuroimaging tool that can be used to measure brain activity by observing the hemodynamic response in the cortical tissue of the brain. Neural activity is associated with an increase in regional arteriolar vasodilation caused by a larger demand in nutrients, such as glucose and oxygen, from local neurons which causes an influx of oxygenated haemoglobin (Pinti et al., 2018). The changes in concentration of oxygenated and deoxygenated haemoglobin can then be detected when looking at the differences in absorption of near-infrared light in the cortical layer of the brain (Pinti et al., 2018). It is imperative that the CRUNCH hypothesis be more robustly tested using our fNIRS equipment, so that we can examine the possibility that the compensation effect is related to the working memory task itself, and not just a general mechanism to increase neurocognitive functionality (Jamadar 2020). Therefore, it is possible to incorporate a Corsi-block tapping task

(rather than a N-back task) that involves a 9 square array where the length of the sequence of the visual stimulus can be modified to vary task difficulty (Brunetti et al., 2014). The hemodynamic observations made in the prefrontal cortex during a Corsi-block tapping task of varying complexity will help give us a better understanding of the brain activity pattern differences between older and younger adults and how neural compensation is involved in cognitive function as we age.

A review by Toth et al. (2017) sates having adequate nutrient and oxygen supply through the cerebromicrovascular network is critical in the maintenance of normal brain function. Age-related dysregulation of the cerebral blood flow (CBF) network is implicated in the advancement of cognitive decline, namely in the form of dementia. Autoregulation of CBF from both larger proximal arteries and the microvasculature of the brain is imperative to prevent both hyperperfusion and hypoperfusion for optimal oxygen and nutrient transport to neurons. As people age, their arteries become less elastic, causing high hemodynamic pulsatility. This hypertensive action may increase blood pressure in the cerebral microcirculation causing cerebral brain capillary damage and, consequently, cognitive impairment (Toth et al., 2017).

Toth et al. (2017) also explain studies on aging concluded that endothelial dysfunction increases because of the accumulation of reactive oxygen species that decrease the bioavailability of nitric oxide (NO): a key local mediator in vasodilation. This general mechanism of endothelial dysfunction is likely to contribute to cerebral hypoperfusion, exacerbating cognitive decline (Toth et al. 2017).

Moreover, there is little research measuring the function of blood vessels in the periphery of the cardiovascular system as a potential explanation for compensatory brain mechanisms (Ransom et al., 2024). Owens et al. (2022) investigated the correlation between microvascular

endothelial dysfunction in the periphery and its effect on neurovascular coupling and thus cognitive performance during a N-back working memory task. Normal brain function is dependent on appropriate adjustments to cerebral oxygenated blood supply, which is in turn dependent on effective microvascular endothelial function.

Owens et. al (2022) enlisted participants with peripheral artery disease as well as healthy participants to use as a control group for the measurements. Participants' brain activity was observed in the prefrontal and motor cortex regions using an fNIRS cap and optode array. Their endothelial function was measured using the flow-mediated dilation (FMD) technique. The study found that individuals with peripheral artery disease had decreased neurovascular coupling and general endothelial microvascular dysfunction, which could be correlated with a decrease in cognitive task performance (Owens et. al 2022). It is therefore important to assess peripheral vascular function in tandem with compensatory hemodynamic mechanisms observed in the brains of aging individuals to better understand the changes in neurocognitive patterns. For the purpose of this report I will be focusing on the methods and preliminary results for measurements pertaining to microvascular function and arterial function.

2. Methods: Measuring Endothelial Function Using NIRS and Its Relationship to Flow-Mediated Dilation

2.1 Participants

This completed study will involve 40 total participants consisting of 20 young participants (18-25 years old), and 20 older participants (>65 years old). The younger

participants have been recruited by word of mouth referrals and will be continually recruited through posters placed on bulletin boards around TRU, the TCC, and local restaurants and cafes. The older adults will be recruited by contacting local retirement homes, community centers, and through social media such as Facebook. Participants were given a consent form to read through and sign explaining the experiment, the goals of the experiment, how their information will be used, and what is expected from them. The consent form also contains exclusion criteria to determine participant eligibility, this includes: the aforementioned age restrictions, requiring good vision, English language proficiency, having no known neurological complications (traumatic brain injury, stroke, mild cognitive impairment) or psychological disorders (depression, bipolar disorder), right-handedness, six years of formal education, and no attention enhancing medications or psychoactive drugs. Along with the consent form, Older participants will also be required to complete a Montreal Cognitive Assessment (MoCA) to determine overall cognitive function.

2.2 Procedure and Analysis

Initial phases prior to testing first involved assessing and validating techniques to assess vascular function using muscle NIRS not previously available at TRU. As such, the initial 6 weeks of the UREAP was dedicated to obtaining pilot data and examining the output and optimal procedures using the MOXY muscle oxygenation monitor (Fortiori Design LLC, Minnesota). This device was used to obtain oxygen saturation measurements in the microvasculature of the forearm. The monitor has one emitter that propagates near-infrared light within the range of 630 to 850 nm into the tissue which is then absorbed at different wavelengths by oxygenated and

deoxygenated hemoglobin. Two detectors, one spaced at 12.5 and the other at 25 mm from the emitter, then simultaneously sample the light intensity to calculate oxygen saturation of the underlying microvasculature. Based upon previous studies by McLay et al. (2016) data collection required the device to be set at a sampling rate of 1Hz to enable adequate temporal resolution to determine the 10 second reperfusion slope as recommended by McLay et al. (2016), which will be discussed later. The Moxy monitor unit was connected via Bluetooth to the VO2 Master mobile app (version 0.41.1), so that the data from the unit could be downloaded and exported into excel as a .csv file.

For this pilot phase, participants were asked to refrain from exercise, caffeine, and alcohol for a period of 24 hours prior to testing and to be in a fasted state. The participants were required to rest for 20 minutes in a supine position before three measurements of blood pressure were taken by an automated cuff. Participant height, weight and sex was also accounted for in the MOXY monitor settings. A blood pressure cuff was placed on the upper arm above the elbow. The muscle oxygenation monitor was then placed at a distance one-third of the way down the inner forearm from the elbow to the wrist. The device was also wrapped with a tensor bandage to block any external light from being detected (Rogers et al., 2022; Soares et al. 2020). To test the reproducibility of the NIRS muscle oxygenation experimental design, two vascular occlusion tests were administered on four individuals on two separate days. The coefficient of variation was 25.94% ± 16.02% (n=4). High variation could be partially because after 5 minutes of occlusion, the sensor would stop collecting data if the oxygen saturation percentage dropped to 0%. This was followed by a horizontal lag-phase in the reperfusion slope analysis. During these pilot tests the device was only sampling every 2 seconds, so this is why we increased the sampling rate to 1Hz (McLay et al., 2016).

Since future tests in the young and older adult populations were to be performed non-simultaneously, the vascular occlusion test (VOT) using NIRS and FMD described by Soares et al. (2020) was used. However, this was modified so that the NIRS-VOT was done on the right arm and the FMD-VOT was done on the left arm. The MOXY monitor recorded a baseline hemodynamic response at rest for at least 10 minutes. The blood pressure cuff was inflated past 200 mmHg, which is beyond systolic blood pressure to occlude the brachial artery and induce ischemia. Occlusion lasted for 3 minutes, during which the oxygen saturation in the muscle tissue dropped. A 3-minute occlusion period was used instead of a 5-minute occlusion period because the sensor would stop recording data if oxygen saturation dropped to 0.0% (Bezemer et al., 2009). After 3-minutes the pressure cuff was released and recording continued until the percent oxygen saturation values returned to baseline. The data was then used to calculate the 10s reperfusion slope, to evaluate microvascular endothelial function (Soares et al., 2020).

The FMD-VOT was also assessed for reproducibility since operator error can add to variability in the measure. This technique involves imaging vascular ultrasound that requires substantial practice to gain expertise. The UREAP period was also used to acquire this training. An EPIQ 5 ultrasound machine (Philips, Professional Healthcare, The Netherlands) with an L12-3 probe was used to measure the left brachial artery at rest in participants on two occasions separated by at least several days. The participants were connected to an electrocardiograph (ECG), so that heart rate could be used to average the arterial diameter data over three heart cycles and smooth the data. A 30s video clip was acquired for a baseline measurement of the artery. A blood pressure cuff was positioned around the forearm and inflated to a pressure of 200mmHg (far above systolic blood pressure). After an ischemia period of 5 minutes, the probe was placed on the arm in the same position that the baseline brachial artery image was acquired,

and a new video clip was acquired while the cuff was rapidly deflated. Thirty second clips were then acquired over the next 2.5 minutes to enable the peak diameter of the artery to be obtained. The percent difference between the baseline and peak artery diameter is typically used as an indicator of peripheral macrovascular endothelial function. An ultrasound image analysis software (CAROLAB, IEEE Ultrasonic Symposium, Glasgow, Scotland, version 5.0) was used to measure the artery diameter for each frame (23fps) of the image. The data was exported to excel along with the pulse, blood velocity, and ultrasound audio signals for further analysis.

3. Results

Initially, ultrasound imaging accuracy was evaluated using participant FMD samples and calculating the percent difference between day one and day two measurements. Refer to Table 1 to see coefficient of variation measurements.

Table 1. Comparing percent difference between day one and day two trials to verify the precision of FMD measurements over two days (n=4).

Participant	Trial 1 % change	Trial 2 % change	Coefficient of Variation (%)
1	4.73	6.07	17.51
2	9.71	5.22	42.44
3	10.72	10.59	0.87
4	7.99	6.51	14.37
		Mean	18.80
		Standard Deviation	±17.34

The day to day variation in FMD measurements had a mean percent coefficient of 18.80% (±17.34%) which is marginally high. The day-to-day variation indicates poor precision. However, the day-to-day measurements for participant 3 were very precise indicating good precision for that sample. Using another analysis technique, we could calculate the sum of the

absolute minimum arterial diameter and the absolute maximum arterial diameter to present a complete vascular response. Table 2 shows the coefficient of variation results using this different analysis technique.

Table 2. Comparing percent difference between day one and day two trials to verify the precision of measurements using the total vascular response (n=4).

Participant	Trial 1 % change	Trial 2 % change	Coefficient of Variation (%)
1	6.68	6.44	2.62
2	8.45	16.50	45.67
3	10.72	11.66	5.95
4	14.47	11.85	14.07
		Mean	17.08
		Standard Deviation	±19.66

The mean total vascular response coefficient of variation is 17.08% (±19.66%) which is more precise than the mean FMD variation values. The improved precision can indicate that the period of rest prior to collecting a baseline clip was insufficient, so moving forward we increased the rest period to at least 30 minutes. After testing the precision of our testing method, we started to collect FMD data in the brachial artery to measure the peripheral vascular function of our participants. Table 3 features the percent change calculated for each participant's baseline and peak brachial artery diameters before and after the 5 minute occlusion.

Table 3. Percent change in each participant's brachial artery diameter (mm) pre and post cuff occlusion (n=5).

	Diameter (mm)		
Participant	Baseline	Peak	% change
1	4595	4796	4.37
2	3796	4053	6.77
3	4031	4297	6.60
4	3584	3781	5.50
5	3323	3452	3.88
		Mean	5.42
		Standard Deviation	±1.29

The mean percent change in brachial arterial diameter was 5.42% with a standard deviation of ±1.29%. These FMD percent change values will be compared to literature FMD values for young, healthy adults in the discussion. Figure 1 shows a boxplot comparison of the baseline values for brachial artery diameter (mm) to the peak values for brachial artery diameter in response to cuff release after a 5 minute period of ischemia.

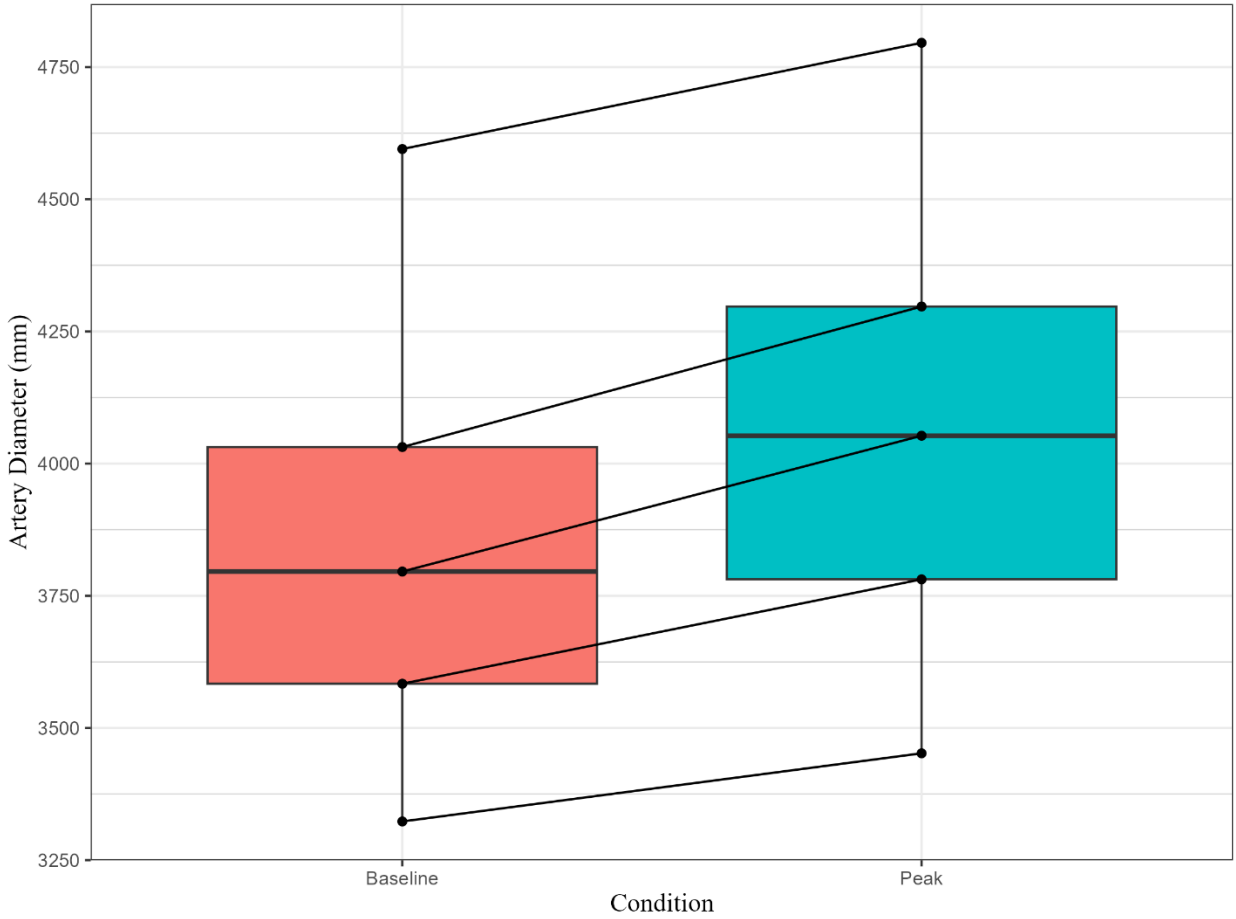

Figure 1. Comparing the mean baseline brachial artery diameter (mm) before cuff release to the mean peak brachial artery diameter (mm) after a 5 minute occlusion (n=5). The diagonal lines connect individual participant data.

We can then needed to calculate the 10 second reperfusion slope, in percent oxygen saturation per second (%O2/sec) from the NIRS-VOT, so that we could compare these values to

participants' FMD responses. Table 4 reports the 10 second reperfusion slopes for our participants combined with the previously shown FMD responses (% change).

Table 4. The 10 second reperfusion slope (%O2/sec) recorded from the forearm of each participant after a 3 minute ischemia compared to their FMD response (n=5).

Participant	Slope (%O2/sec)	FMD Response (% change)
1	3.0	4.37
2	1.7	6.77
3	1.5	6.60
4	3.0	5.50
5	5.6	3.88
Mean	2.96	

The mean 10 second reperfusion slope was 2.96 %O2/sec. Each participants' slope value was then graphed in relationship with their FMD response value to observe the correlative relationship. Figure 2 examines how the 10 second reperfusion slope and FMD response are correlated.

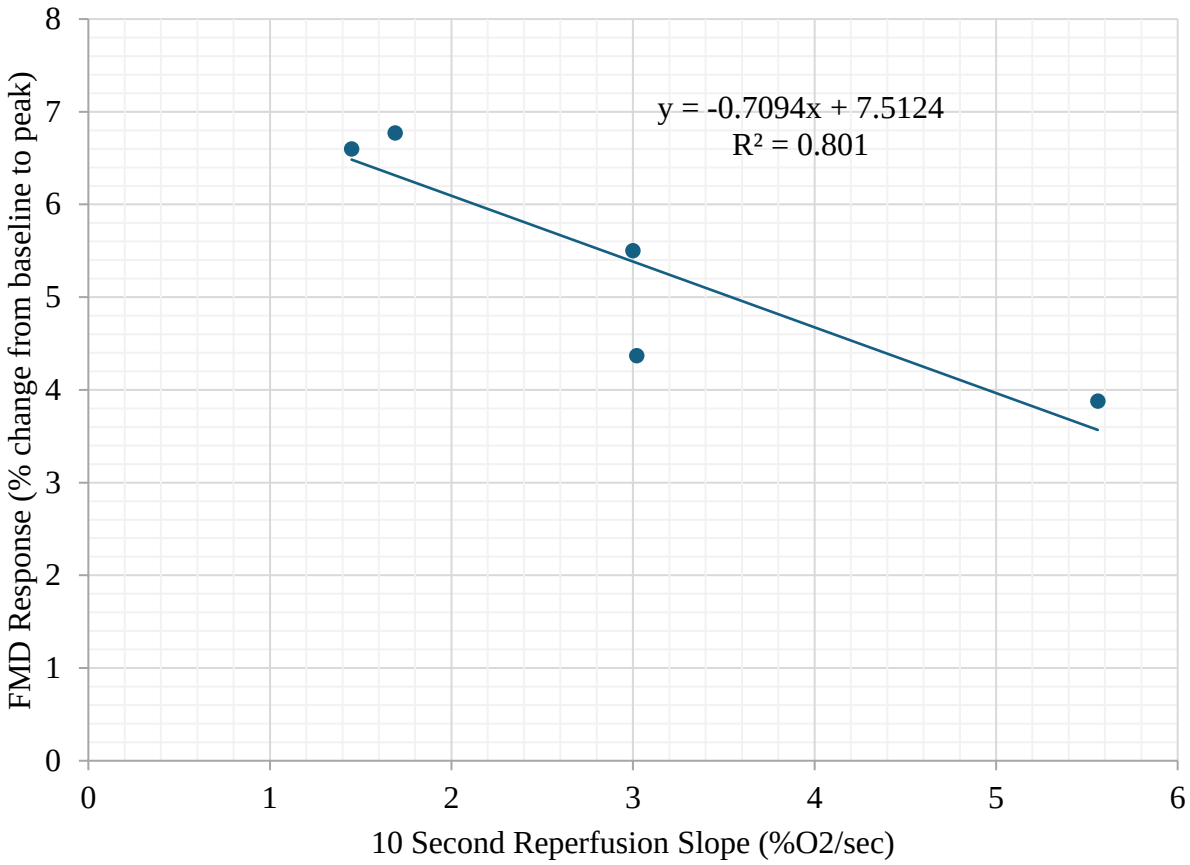

Figure 2. The relationship between the FMD response (% change of arterial diameter from baseline to peak) and the 10 second reperfusion slope (%O2/sec) after vascular occlusion (n=5). The slope is negative and the correlation is 0.8.

The participants' FMD responses and the 10 second reperfusion slopes are highly correlated (R^2 of 0.8). The slope is negative indicating that as the reperfusion slope gets steeper the FMD response should be weaker.

4. Discussion

The preliminary FMD results are promising. They reveal that arterial dilation is occurring and being measured during the vascular occlusion test. As expected participant's brachial arteries are responding to the 5 minute occlusion period and subsequent release by increasing in diameter

to accommodate the increased pressure experienced along the endothelial lining. A meta-analysis incorporating 88 clinical trials by Heiss et al. (2022) found that the FMD values in healthy individuals was 6.4% (95% CI 6.2-6.7%). Our mean FMD value was 5.4% which seems reasonable given that it is within the range of Heiss et al.'s 6.4% mean from a revision of clinical trials, and we can't assume all of our participants have equivalent arterial health. Heiss et al. also suggest that baseline brachial artery diameter does have a significant impact (-0.44%/mm) in FMD values. Furthermore, the FMD values for participants 2 and 3 do align with what is expected for healthy individuals, and participant 4 is approaching the expected range for healthy individuals. Participant 5's FMD value can potentially be explained by the effect of having a smaller brachial artery diameter at rest compared to other participants. Participant 1's FMD value is surprising, however statistical outliers are expected to appear within the data.

Our precision measurements obtained before continuing with the experiment were not very consistent or precise, but this is not critical because in our study we are only taking one FMD measurement for each participant on the same day. The important part is that the post-cuff release ultrasound image is taken in the same area as the baseline ultrasound image so that the analysis is accurate. It is also crucial to collect clear ultrasound images with defined boarders, so the CAROLAB ultrasound image software can accurately trace the borders of the artery.

The strong correlational relationship between the FMD response and the 10 second reperfusion slope analysis does align with Soares et al. (2019), however the direction of the relationship in our study is negative. It is expected that as one variable increases as should the other in tandem. It is not possible to claim whether these preliminary results are significant because of the small sample size. Therefore increasing the sample size will help us further examine this relationship's magnitude and direction.

5. Future Directions

This project will be continued as an honours project, so more data will be collected in the Fall 2024 and Winter 2024 semester. It is imperative to collect enough quality data from young, healthy participants to be able to observe the correlation between healthy endothelial function and good cognitive function. It is expected that older adults will have lower FMD values because endothelial function declines with age. The same observations between young and old adults is expected to be reflected in NIRS-VOT 10 second reperfusion slope analyses, where older adults are predicted to have smaller slopes as a result of age-related decline in endothelial function.

The fNIRS testing will examine brain activity in both young and old adults. We hypothesize that the older adults will generally show increased bilateral brain activity during the working memory task when compared to young adults. Older adults with lower cognitive function (identified by low MoCA scores) are predicted to increase bilateral compensation during lower complexity tasks. Altering task complexity will also allow us to investigate CRUNCH, which predicts that older adults will exhibit compensatory brain activity up until the task becomes too difficult at which point brain activity is expected to decrease. Lastly, the Corsi-block tapping task enables us to verify that the neural compensation effect is not simply task specific but a general method for older individuals to increase cognitive function. Lastly, the fNIRS data can be analyzed with the data from the two vascular occlusion tests to see if there are correlations between poor systemic endothelial function and decreased brain efficiency and lateralization.

6. References

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