BME 200/300 (Biomedical Engineering Design)
Fall 2008

Project #26: Development of a Device for Neurochemical Sample Collection from Freely Moving Monkeys

FINAL REPORT

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Abstract

The goal of this design project is to develop and construct a device to provide protection for the microdrive unit, an apparatus that is used in microdialysis experiments conducted on nonhuman primates. This would allow the experiments to be conducted without restraining the monkeys in a chair, providing them with a more comfortable and realistic experimental setting. Currently, there are no existing devices in the market specifically catered for this purpose. Building on last semester's prototype, the current design consists of an aluminum casing with a form fitted silicone rubber interior to surround the microdrive unit. In accordance with the client's requirements, the team considered alternatives to make the device more lightweight and secure, and decided to pursue a porous aluminum cylindrical top as well as a zip tie strap configuration to accomplish this aim. The team implemented these improvements and then carried out preliminary testing on live monkeys. Results of the testing importune the need for further modifications to be made, particularly to reduce the weight of the device.

Problem Motivation

Microdialysis allows for real-time *in vivo* measurements of various substances in the body[2]. In particular, direct measurements of neurochemical substances in the brain from free-moving nonhuman primates is significantly important for understanding complex brain function and developing treatment strategies for brain disorders in humans. A modified microdialysis method has been developed for application to Rhesus macaques (*Macaca mulatta*). However, it requires restraining the monkeys in chairs for up to 12 h while samples are collected. Although this is considered a norm and the monkeys have been appropriately conditioned, the situation is less than ideal since the monkeys are subjected to a certain amount of discomfort due to the restricted movement and long period of chairing. The data collected might also not be representative of a monkey in its natural environment, since it is confined to a chair. One way to address this problem is to allow the monkeys to be free from chairing while the experiments are being conducted. Besides alleviating the discomfort experienced by the monkeys, it would also better simulate the monkey's natural environment since it would be free to move around, albeit within the confines of a cage. Additionally, this method would allow the experiments to be conducted without the 12 h limit imposed by chairing. More time would be available for sample collection and safety inspections to be conducted, allowing the experiments to be carried out more smoothly and safely. However, allowing the monkeys to move freely introduces the risk of them tampering with the experimental apparatus (called a microdrive unit), thus compromising the experimental procedure. Hence, a protective device must be constructed to protect the microdrive unit during the experiment. This device must be compatible with the monkeys such that it will not incur greater discomfort than is necessary or encumber the experimental process. There are currently no products in the market that specifically address this issue, so a suitable device must be designed and constructed.

Background

RHESUS MACAQUE

The Rhesus macaque, also known as the Rhesus monkey, is one of the best known species of Old World monkeys. Rhesus macaques have an extensive geographic distribution and are found ubiquitously throughout mainland Asia, ranging from Afghanistan to India and Thailand to southern China. They range in color from brown to gray and have little fur, if any, on their reddish-pink faces[5]. On average, adult males measure approximately 53 cm and weigh 7.7 kg. Females are smaller, measuring 47 cm and weighing 5.3 kg on average. Their tails are of medium length, averaging between 20.7 and 22.9 cm, and are not prehensile (i.e. the tails are not adapted to be able to grasp and/or hold objects). Typically, Rhesus macaques have a lifespan of about 25 years[10].

Because of their anatomical and physiological similarity to humans, as well as the relative ease at which they can be maintained and bred in captivity, Rhesus monkeys have long been an ideal choice to carry out research on nonhuman primates. As a result, they have become the most studied nonhuman primate, both in the field and in laboratory settings. Some examples of research involving Rhesus monkeys include the experiments on maternal deprivation carried out by comparative psychologist Harry Harlow in the 1950s, development of rabies, smallpox, and polio vaccines, and the creation of drugs to manage HIV/AIDS[5]. As with all other macaques, the *Herpesvirus simiae* (B virus) is endemic among Rhesus monkeys, but could be deadly if spread to a human. Thus, extra care must be taken when interacting with them.

CLIENT'S RESEARCH

A faculty member at the University of Wisconsin-Madison Department of Pediatrics, the client is interested in understanding how growth and development are controlled in humans. One particular focus is on the role of the brain in triggering puberty[3, 4]. In order to investigate this, the client studies neuroendocrine function by measuring the release of neuropeptides, neurotransmitters, and neuromodulators from the hypothalamus in the brain. Currently, this research is being carried out on Rhesus monkeys, due to their anatomical and physiological closeness to humans. It is hoped that through these neuroendocrine studies on the monkeys, a better understanding of complex brain function in humans can be achieved. Since the studies revolve around the events occurring during puberty, the monkeys used for the experiments are generally young and pubertal. Unlike adult Rhesus monkeys, these monkeys generally range from 2.5 to 5 kg in weight[1].

MICRODIALYSIS & EXPERIMENTAL PROCEDURE

In order to study the release of substances from the hypothalamus of the Rhesus monkeys, a technique known as microdialysis is employed. Microdialysis is widely used in clinical research in areas such as neuroscience (to study the neurochemical bases of brain disorders) and pharmacology (to study drug metabolism, drug delivery, and the effects and efficacy of drugs) [6]. In general, microdialysis entails inserting a probe into the extracellular fluid of a particular part of the body. The probe contains a semipermeable membrane for substances to diffuse in/out based on a concentration gradient. The inlet of the probe is connected via tubing to a pump, which infuses a physiological salt solution. Exchange of substances occurs at the semipermeable membrane, and the desired samples are collected by a fraction collector connected via tubing to the outlet of the probe[2, 9].

A brief outline of the experimental setup used in the client's research is shown in Figure 1. Before experiments can be conducted on the monkeys, a cranial pedestal (head cap) must be implanted into their skulls and secured using dental cement. This allows the microdrive unit to be fitted onto their heads. The purpose of the microdrive unit is to properly position the microdialysis probe for insertion. On the day of the experiment, the monkey is anesthetized and placed in a stereotaxic apparatus. The microdrive unit with a guide cannula are attached and positioned precisely to the specific area desired for testing. Accurate placement is ensured using radiographic visualization. The monkey is then transferred to a primate chair (Figure 2), which it has been conditioned and well-adapted to prior to the experiment. Apart from moving its hands to feed itself and turning its head a little, this chair restricts all other movements of the monkey. Once the monkey has been put in place, the guide cannula is removed and the microdialysis probe is inserted. The pump is used to perfuse cerebrospinal fluid (CSF) through the probe and the exchange of substances occurs at the semipermeable membrane (which is in the vicinity of the hypothalamus). The perfusate containing the desired substances that have diffused into the probe are collected by a fraction collector and immediately frozen for storage. The entire experimental process takes approximately 12 h, and the monkeys are confined to the chair throughout this time[1].

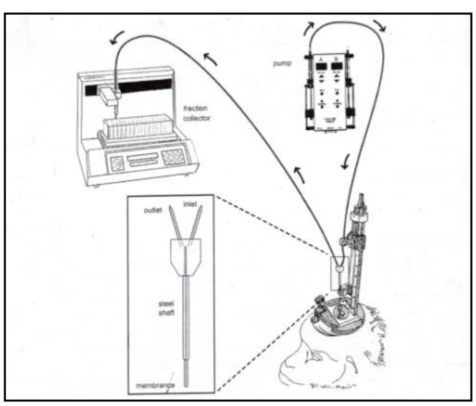


Figure 1: Experimental Setup for Microdialysis

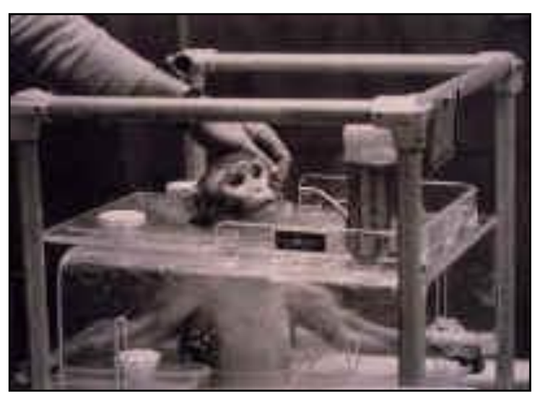


Figure 2: Rhesus Monkey in a Primate Chair[8]

Client's Requirements & Design Constraints

The device must be strong enough to provide protection for the microdrive unit such that the monkeys will not be able to tamper with it during the experimental process. This means that the device must be rigid and cover the entire microdrive unit. Taking into account any forces that the monkey may apply, it should also be able to withstand a force of 100 N. This value was an estimate based on human arm strength[7].

Given that the monkeys are generally smaller in size than the average adult Rhesus monkey, the microdrive unit already imposes a considerable amount of weight on the monkey's head. As such, the materials used to construct the protective device must be lightweight (not more than 0.5 kg as determined by the client) to minimize the additional weight to be imposed.

The design of the device must be simple such that it can be easily integrated with the current experimental apparatus, so as not to interfere with or impede the data collection process. Yet, a certain degree of complexity must be incorporated to prevent the monkeys from dismantling the device. Also, there must not be any sharp edges or protrusions that can possibly harm the monkey or researcher during the experimental setup and process.

The device should be detachable, so that adjustments to the experimental apparatus can be made during the experiment if needed. This will also allow the device to be cleaned and sterilized prior to subsequent use. In addition, the design and construction of the device must comply with USDA regulations and NIH guidelines, subjected to approval by the attending veterinarian.

Last Semester's Design

The design of the protective device created last semester is shown in Figure 3. It evolved from the Cushion & Shell design introduced last semester; the device consists of three distinct, interlocking pieces. To improve on last semester's design, the team decreased the wall thickness of each aluminum component manufactured last semester, thus reducing the overall weight. A left and right aluminum half shell, weighed 69.7 g and 66.9 g respectively, form the base of the device. Using a model of a monkey's skull, a radius was cut from each piece so that the device follows and is in closer proximity to the contour of the monkey's skull and sits lower on the head overall. This proves advantageous when considering increased rigidity of the protective device in its placement onto the monkey's head.

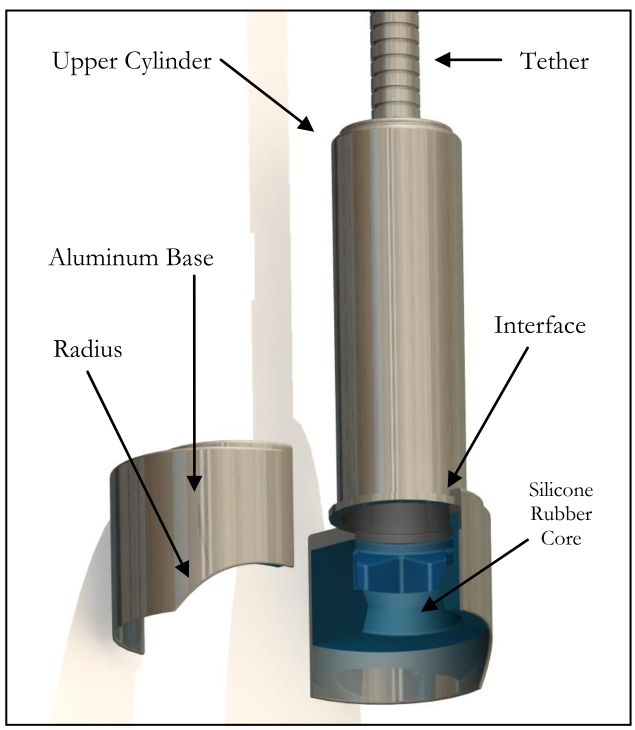


Figure 3: Current Protective Device Design

One improvement from last semester involves the addition of a silicone rubber core to the aluminum base (shown in blue in Figure 3). Using the same model of a monkey's skull, the team poured silicone rubber around an intact microdrive unit. Once solidified, the silicone rubber body was split into two halves to correspond with the two aluminum base pieces and using a scalpel, excess silicone rubber was cut off. Currently, the silicone rubber core (139.9 g) functions to "clasp" the microdrive unit. In doing so, the silicone rubber protects the base of the microdrive unit and the entire protective device remains inflexible on the monkey's head. Also, the impervious property of the silicone rubber allows for cleansing after experimentation.

When the two aluminum base components and silicone rubber core pieces mesh around the microdrive unit, a three-way interface allows the aluminum cylindrical top to interconnect. The cylindrical top functions to protect the upper portion of the microdrive unit, while providing an attachment point for an experimental tether. Last semester's team manufactured the cylindrical top with a lower lip that integrates with the slots of the two aluminum base pieces, which are all secured with an adjustable hose clamp (not shown in Figure 3).

Reviewing the current design in accordance with the client's requirements, the team determined that further modifications were necessary in order to reduce the weight of the device and to make it more secure. The team identified two areas for improvement: modification of the cylindrical top to make it more lightweight, and the incorporation of a strap configuration to make the protective device more secure.

Design Alternatives for Cylindrical Top

The cylindrical top is the upper portion of the helmet design and protects the upper extension of the microdrive unit. It is simply a 152.3 mm cylindrical shell that has a 3.175 mm thick lip on the lower end and an attachment for the tether at the top. The lip fits flawlessly within the slots that are machined into the top of the two half disks of the lower helmet and a lip-groove relationship secures the upper cylindrical shell to the other two half disks. A hose clamp finally fastens this configuration together around the monkey's skull. The tether, on the other hand, attaches to the cylindrical shell directly using multiple screws. The materials used and other various specifications for the cylindrical top are examined below.

ALUMINUM

The current (last semester's construction) is also the first possible cylindrical top design. It is composed of approximately 2.38 mm aluminum and has holes threaded through the top for the tether attachment (Figure 4).

The advantages of this design include strength, durability and ease of manufacture. Aluminum is one of the most lightweight metals available with a density of 2.685 g/cm^3 (specific to the alloy used; determined from McMaster-Carr catalog[11]). Due to the metallic properties of the material used, there is a very low chance that the monkey could break this design, making it a safe and reliable option. In addition, as stated earlier, this design has already been manufactured and would require no additional work.

The disadvantages of this design are its weight and potential for anaerobic bacteria growth. Weight is a critical issue with this design because the monkey needs to be able to withstand the weight of the protective device; the weight for each part should therefore be minimized as much as possible. The weight of the aluminum cylindrical top was estimated to be 117.60 g using the density of aluminum (2.685 g/cm^3) and an estimated volume (calculated using SolidWorks). This estimated weight is very similar to the measured weight of 110.91 g. Also, this design has the potential for harmful anaerobic bacteria growth on the sensitive tissue surrounding the dental cement on the monkey's head; no airways exist to allow oxygen to access this region.

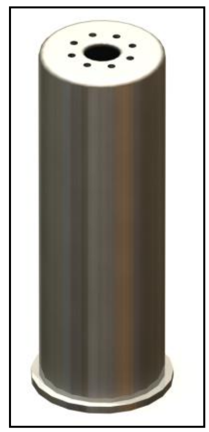


Figure 4: Aluminum Design

POROUS ALUMINUM

The second design alternative for the cylindrical top involves a porous aluminum cylinder. This design is much like the first aluminum alternative in that it is composed of approximately 2.38 mm aluminum and has threaded holes on the top for the tether attachment. However, unlike the first aluminum alternative, it has 3.175 mm diameter holes drilled in a linear pattern along the sides (Figure 5).

This device, like the first aluminum alternative, is composed of aluminum. The advantages of this design are therefore its strength, durability, ease of manufacture and overall safety. The linear pattern of holes only minimally affects the overall strength of the aluminum, making it safe from the monkey. In addition, this design would only require drilling holes in the already manufactured aluminum cylindrical top making it relatively easy to manufacture. Lastly, the holes in the aluminum would allow the monkey's head to breathe, preventing anaerobic bacteria from potentially growing. Also, it may allow the client the ability to see the condition of the microdrive unit.

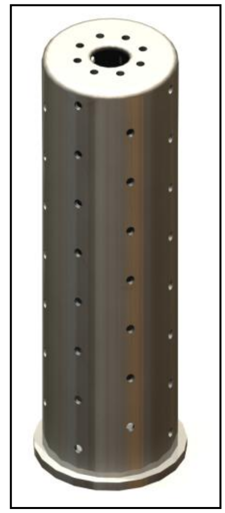


Figure 5: Porous Aluminum Design

The disadvantage of this design is that it is still relatively heavy. As stated earlier, weight is a critical issue with this design because the monkey needs to withstand the weight of the protective device for up to 12 h. The holes in the aluminum minimally reduce the weight; with 60 holes drilled into the cylinder, the weight is estimated to be 115.57 g using the density of aluminum (2.685 g/cm^3) and an estimated volume calculated using SolidWorks. This is only a 2.03 g difference from the estimated weight of the first aluminum alternative. In doubling the number of holes to 120 holes, there is only a 4.06 g difference in the estimated weight from the first aluminum alternative. Therefore, drilling holes into the aluminum does not have a drastic effect on the overall weight of the cylindrical top.

PLASTIC

The third design alternative for the cylindrical top utilizes a plastic cylinder composed of high-density polyethylene (HDPE). This design uses the cylindrical shape of the previously mentioned alternatives and, like the first two alternatives, the plastic cylindrical top would also have threaded holes for the tether attachment on top and a 3.175 mm lip at the lower end (Figure 6). However, because of the flexibility of the plastic, it would need a thickness greater than the 2.38 mm aluminum cylindrical alternatives. For all practical purposes, it is estimated that a plastic cylinder would require twice the thickness of the aluminum cylinder to maintain strength and durability.

The advantages of this design are its weight and strength. HDPE is a strong, lightweight plastic making it an ideal material for this purpose. Once again, creating a part that minimizes weight is important for the comfort of the monkey. The weight is estimated to be 84.38 g using 0.936 g/cm^3 as the density[12] and estimating the volume using SolidWorks. This 34.42 g difference from the estimated weight of the first aluminum alternative, coupled with a similar strength (due to doubling the thickness of the material relative to the aluminum alternatives) proves valuable.

The disadvantages of this design relate to safety and ease of manufacturing. Despite doubling the thickness of the plastic (relative to the aluminum) making it just as strong, a potential for failure exists at the lip of the cylinder. The strength of the plastic relies on the cylindrical shape of the top, but the base of the helmet is designed for a 3.175 mm thick lip. Therefore, a great amount of stress is placed on the lip of the cylindrical top and must be able to withstand any forces applied to it. Creating a plastic cylindrical top, with a plastic lip, greatly increases the chances of failure at this interface (Figure 7). In addition, drilling holes in the plastic may weaken the cylinder too much, creating another risk for failure. Therefore, holes should not be drilled into the plastic; as in the case of the first aluminum alternative, anaerobic bacteria could then proliferate. Lastly, this design requires molding plastic to the desired shape, adding an additional cost and a difficult manner of manufacture to the qualities associated with this design.

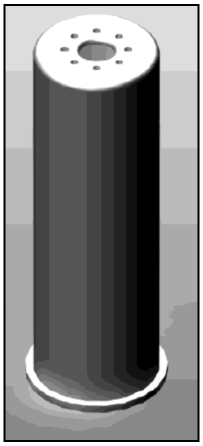


Figure 6: Plastic Design

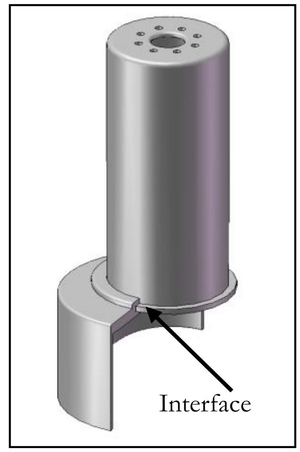


Figure 7: Interface between Cylindrical Top and Aluminum Base

Design Matrix for Cylindrical Top

In order to evaluate the three design alternatives for the cylindrical top, a design matrix was created with several weighted criteria and the designs were ranked in each category (Table 1).

The first criterion is the weight of the cylindrical top. The entire protective device requires placement on the monkey's head for the duration of the experiment (approximately 12 h). Therefore, it has to be light enough so as not to cause harm or discomfort. Since the cylindrical top was found to contribute the most weight to the entire device, lightening the cylindrical top would result in a significant reduction in the weight of the device. Aluminum, being denser than plastic, proved heavier for a given volume. Hence, both aluminum designs would be heavier than the plastic design. However, since the porous aluminum design contains additional holes drilled into it, it incorporates less material when compared to the solid aluminum design, and hence weighs less.

The ability of the cylindrical top to withstand force is another key aspect of the design. Rhesus monkeys are strong and capable of hitting the cylindrical top with their hands or on the sides of the cage. As a result, the cylindrical top must be able to withstand these forces without breaking. Aluminum is a strong metal, and able to absorb a very large amount of force; it is unlikely that Rhesus monkeys would be able to generate a force great enough to penetrate the current aluminum's thickness. Hence, the aluminum design would be the strongest. The porous aluminum design would be slightly weaker, due to holes drilled into it, which might weaken the overall strength of the cylinder relative to the aluminum design. The plastic design would be the weakest, since it is made of high-density polyethylene (HDPE), which is not as rigid and strong as aluminum.

Safety is also an important component of the design. The protective device must be safe for the monkey. With respect to the cylindrical top, this entails preventing the possibility of the growth of anaerobic bacteria, which can harm the monkey. The porous aluminum design thus proves safest; its multiple holes allow for ventilation within the cylinder, preventing anaerobic bacteria growth. On the other hand, both the aluminum and plastic designs do not allow ventilation, so the risk of anaerobic bacteria growth persists.

The last criterion is the ease of construction. The chosen design for the cylindrical top must be relatively easy to construct so that it can be used by the client and possibly reproduced. The aluminum design would be the easiest to construct, since a prototype is already currently available, and can be easily reproduced if more are required. The porous aluminum would require a little more work, although it would still be very easy to construct, since it simply involves drilling additional holes into an existing aluminum cylinder. The plastic design would be the hardest to construct, given that it entails molding the HDPE to the required cylindrical shape, and adding a lip at the bottom to allow the cylindrical top to fit snugly with the base.

CRITERIA	WEIGHT	ALUMINUM	POROUS ALUMINUM	PLASTIC
Weight	30	20	22	25
Ability to Withstand Force	30	30	28	26
Safety	30	25	28	26
Ease of Construction	10	10	9	4
TOTAL	**100**	**85**	**87**	**81**

Table 1: Design Matrix for Cylindrical Top

Design Alternatives for Strap Configuration

The base of the protective device needs to securely fit onto the heads of multiple test subjects. In order for this to occur, the team designed a single strap configuration, involving a collar, connected to the base on either side (point b in Figure 8). Nylon fabric will be used; different fashions of securing this configuration at points b and c in Figure 8 are considered below.

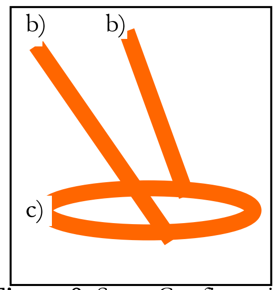


Figure 8: Strap Configuration

LOCK & KEY

The first option considered involves the use of a system of grommets inserted into the sides of the nylon straps in increments to allow for multiple monkeys' skulls to fit securely into the base of the device. Through the desired loop, a tiny lock, secured by a key, fastens the straps to the base of the apparatus in this design (Figure 9).

The advantages of this configuration include the fact that that the device stays fastened on top of the monkeys' head regardless of tampering by the monkey, or anyone not holding the necessary key. Since the team can simply purchase the locks and keys, the construction of this design seems simple.

The disadvantages of this configuration involve the idea that although the grommet design allows for adjustability at increments, the fact that a monkey's head size may be between the set increments detract from this quality. Due to the fact that a lock requires a key and this tiny lock requires a comparably sized key, keeping track of the key(s) could prove hassling to the staff of the laboratory. Measuring increments and inserting grommets into the nylon seem to present difficulties such as errors in measurement, tearing of the fabric, and determination of increments based on a limited data set of monkey head sizes.

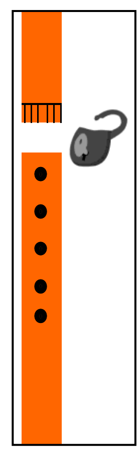


Figure 9: Lock & Key Design

ZIP TIE

The second option makes use of a zip tie (also known as a cable cord) to fasten the straps to the base; an internally threaded collar zip tie (as opposed to an interface configuration) serves to close that gap. Although the monkey's hands could deform the plastic a tiny bit (using a lot of force), ultimate escape from the apparatus seems unlikely (Figure 10). Once fastened, a scissors is required to disengage a zip tie.

Other advantages to this configuration center on the concept that this option proves to be the most adjustable of all options considered; it is manufactured to fit in very tiny increments (in some cases millimeters). Also, a zip tie's simple design allows for ultimate ease of use by the scientists executing the experiment and its availability allows for multiple sizes and quantities for use as desired. Simple looping of the nylon to provide for a place to fasten the zip ties presents the easiest option in terms of construction on the part of the engineers. A metal loop would serve as a position to fasten the nylon to the aluminum base (a rivet would secure this loop), and looping of the nylon at its ends would work to create a zip tie-metal interface.

The only disadvantage associated with zip tie employment involves wastefulness; due to the fact that it takes three zip ties to secure the straps and that they only function for one use, they waste material and require subsequent re-purchasing by the lab staff.

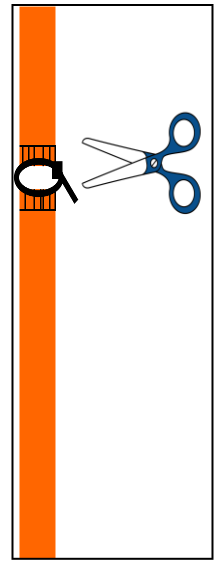


Figure 10: Zip Tie Design

BELT

The final option involves a simple belt loop configuration; grommets would serve as a means to increment the length of the strap (Figure 11).

Disadvantages to this configuration are more apparent than its advantages. After considering this option further and following communication with the client, the team found that the monkey's dexterous hands could easily figure out how to undo the clasp on a belt buckle (given the duration of the experiment). This option also presents the same level of adjustability as the lock and key arrangement as it utilizes the same method of defining increments, without the security of the lock.

Advantages to this design relate to its simplicity and ease of construction; a belt loop, used by many in everyday life, seems to be an easy way to fasten the device's straps. Constructing this mechanism seems comparable to the construction of the lock and key configuration in that, by inserting grommets at increments and then using a belt buckle to hold the strap in place, the experimenters could secure the base of the device to the monkeys' skulls.

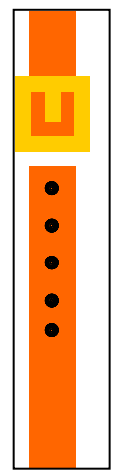


Figure 11: Belt Loop Design

Design Matrix for Strap Configuration

In order to evaluate the three alternatives for the strap design, a separate design matrix was created with different weighted criteria and the designs were ranked in each category (Table 2).

Security from monkey is a very important criterion for the design; the method of fastening the straps must be secure and complex enough such that the monkey would not be able to dismantle it. If the monkey is able to figure out how to undo the straps, it would greatly compromise the stability of the entire device. The lock & key design would be the most secure, since it requires a key in order to undo the straps. Hence, the monkey would not be able to undo the straps as long as the key is kept out of its reach. The zip tie design is also secure, since it is virtually impossible to undo a locked zip tie without the use of scissors. The belt design is the least secure, since the monkey might be able to figure out how to undo the belt buckle given enough time.

An equally important criterion is the adjustability of the strap design; the straps must be adjustable so that they can fit monkeys of different head shapes and sizes. The zip tie design would be the most adjustable, since the zip tie can be fastened in very small size increments, so it would be able to fit most, if not all, of the monkeys. Both the lock & key and belt designs are less adjustable, since their adjustability is similar to that of a belt, with fixed distances between holes. As a result, if a monkey has an intermediate size, between the holes, the straps would not fit tightly.

The strap design must also be easy to use by the experimenters, so that time will not be wasted trying to figure out how to secure the straps. The zip tie design seems straightforward and simple, because it only involves looping the zip tie around the straps and pulling to fasten it. The belt design is also relatively easy to use, since it is similar to buckling a normal belt. The lock & key design appears the most complicated of all due to the fact that it requires a separately housed key to unlock the padlock that secures the straps. Additionally, there is a risk of misplacing the key, which would lead to further complications and delays.

The last criterion is the ease of construction. Similar to the cylindrical top, the chosen strap design must be relatively easy to construct so that it can be used by the client and possibly reproduced. The zip tie design would be the most reproducible and easiest to construct, since zip ties can be bought and looped through the existing straps without a need to further modify the straps. On the other hand, both the lock & key and belt designs require punching holes into the straps to serve as sites for either the padlock or belt buckle to attach, which make them harder to construct.

CRITERIA	WEIGHT	LOCK & KEY	ZIP TIE	BELT
Security from Monkey	30	28	25	20
Adjustability	30	25	30	25
Ease of Use	25	17	25	22
Ease of Construction	15	13	15	13
TOTAL	**100**	**83**	**95**	**80**

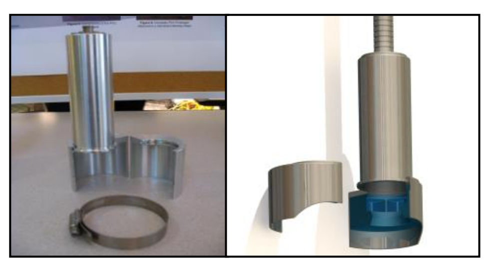
Table 2: Design Matrix for Strap Configuration

Proposed Solution

After careful consideration and evaluation of the two separate design matrices, the porous aluminum design and zip tie design were determined to be the most effective among the cylindrical top alternatives and strap alternatives respectively. The porous aluminum design provides a good balance of strength and safety, although it might still be possible to reduce its weight. The zip tie design is both secure and adjustable, and also seems simple to use and construct; it proves the most practical method for securing the straps to the monkey's head. Hence, the team incorporated these two designs into the current prototype, which already included an aluminum base that is shaped to the contour of a monkey's head, with a silicone rubber core to provide cushioning for the microdrive unit.

Final Design

The final design is a culmination of 2 semesters work; it builds on the aluminum Cushion & Shell Design finalized in the spring of 2008 (Figures 12 & 13). The design still utilizes the three original aluminum pieces that fit together at an interface to protect the microdrive unit, but holes drilled in the cylindrical top and the shortening of the top reduced the overall weight of the apparatus. Layers of aluminum, shaved from the thickness of the base and the cylindrical top, also reduced the weight and increased the functionality of



Figures 12 &13: Design as of Spring 2008 the device with respect to the client's need for it to fit on multiple monkeys' heads.

A silicone rubber interior secures the device around the head cap and microdrive unit on the monkey's skull. A hose clamp is still utilized to secure the two halves of the base around the silicone rubber interior; a nylon strap-system further secures the apparatus vertically upon the monkey's skull. The tether, utilized by the client for sample connection, attaches to the cylindrical top via a custom interface.

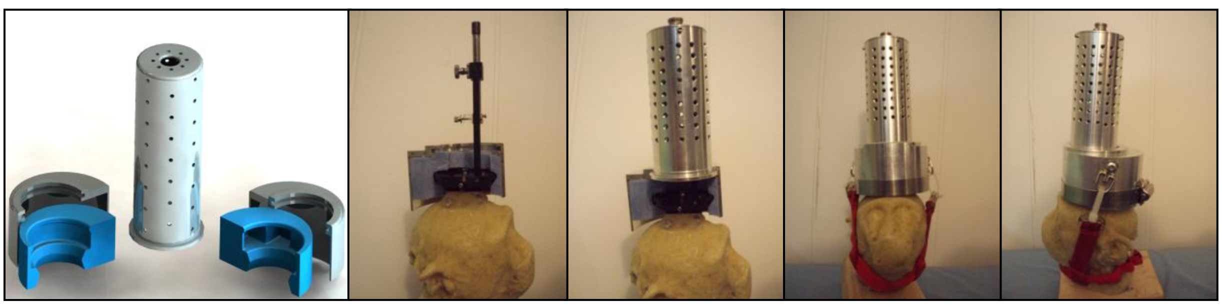
The weights for each component of the final prototype are as follows.

Weights (g):

Microdrive Unit (MU) – 72.3
Silicone Rubber(S) –139.9
Bottom of tether (BT) (part that screws to the top of the upper cylinder) – 15.7
Cylindrical Top (CT) – 104.3
Left Base (LB) – 60.6
Right Base (RB) – 63.7

Total Weight (MU, S, BT, CT, LB, & RB) = **456.5 g** or 1.006 lbs

The weight of the device meets the design specification of under 0.5 grams. Also, the weight of the final prototype was reduced by 18.9 grams from the beginning of the semester by the implementation of a porous cylindrical top and reducing the overall height of the cylindrical top.



Figures 14, 15, 16, 17, & 18: Final Design and Prototype

Testing

The prototype was tested on two different living Rhesus monkeys on two separate occasions. During each live testing, the monkey was first anesthetized to allow placement of the microdrive unit on its head. The prototype was then secured on the monkey's head as per protocol determined by the team (Appendix I). Assembly of the prototype proved to be expedient and was accomplished before the effects of the anesthesia wore off. Subsequently, the monkey was transferred to a cage where it was allowed to gradually awaken. Once the monkey was fully awake, its actions and reactions to the prototype were observed and analyzed to examine the effects of the device on the monkey's behavior. Each monkey was observed for not more than one hour, after which it was anesthetized to allow removal of the prototype.

FIRST LIVE TESTING

Before the first live testing could be carried out, the base of the prototype had to be shortened and some of the silicone rubber interior had to be removed to allow the prototype to fit properly on the monkey's head. This suggests that the prototype is not customized to fit all sizes of monkeys' heads. The team based the dimensions of the prototype on the mold of a monkey's head, but ostensibly this could not suitably accommodate different monkeys. Hence, improvements in the customizability of the device will have to be made.

During testing, the monkey seemed to be irritated with the device when it awoke initially. It tried to tamper with the straps along the sides of its face, which connect the device to the bottom collar strap. One plausible reason for this behavior is that the straps are actually irritating the monkey's ears, since they pass directly over its ears. These straps have to be designed differently such that they would bypass the monkey's ears to prevent irritation. One possible design could be similar to that of a bicycle helmet, where the straps descend in a "Y" shaped configuration.

The straps were also not fastened very tightly because the veterinarians did not want them to cause discomfort to the monkey. As a result, the straps did not seem to serve their intended purpose of securing the device to the monkey. Instead, most of the security seemed to be derived from the silicone rubber interior, which fit tightly around the base of the microdrive unit, thus holding the entire prototype stable on the monkey's head. Although not initially intended by the team, the silicone rubber interior appeared to provide sufficient stability without the need for straps, since the device remained stable on the monkey's head throughout the observation, even though the monkey tried to shake it several times.

The most significant observation was that the device was too heavy for the monkey's comfort. Although the monkey was still able to move its head appreciably, it frequently hung its head low, an action not normally observed. Furthermore, the monkey tested was a large adult; the weight of the device would be even more significant when placing it on smaller, adolescent monkeys. One specific way in which the weight could be reduced was to shorten the cylindrical top of the device. The cylindrical top used at the time was too tall, such that it prevented the monkey from standing up fully inside the cage (without hitting the top of the cage). Thus, shortening the cylindrical top would allow a greater range of motion for the monkey, as well as reduce the weight of the device.

In all, the monkey appeared to be slightly negatively affected by the device when it initially awoke. However, it grew accustomed to the presence of the device after a relatively short period of time, and was able to engage in some "normal" behaviors such as climbing and eating.

SECOND LIVE TESTING

Certain modifications were made to the prototype before the second live testing. First, the cylindrical top was made shorter in view of the observations from the previous live testing. Second, twice as many holes were drilled into the cylindrical top. Third, the tether was removed from the top of the prototype. The net effect of these changes was to reduce the weight of the device. One additional change involved removing some of the silicone rubber interior to allow for a proper fit of the prototype on the monkey's head. Once again, this showed that the device had to be manually customized to fit different monkeys, and this issue must be addressed in the future.

Similar to the observations from the previous testing, the monkey was irritated with the straps along the sides of its face. The monkey attempted more furiously to remove the straps, but they remained secured. Midway through the testing, the straps were removed since they did not seem to be fulfilling their role of securing the device to the monkey. Once the straps were removed, the monkey stopped trying to tamper with the device, which suggests that it was only trying to tamper with the device because of the discomfort caused by the straps. In addition, the device appeared to remain stable with the straps removed and could withstand head shaking from the monkey. However, depending solely on the silicone rubber interior to hold the entire device stable might place too much pressure on the cranial pedestal implanted on the monkey's skull. Further characterization of this pressure must be carried out to determine if it might pose an injury risk to the monkey.

The device once again seemed to be too heavy for the monkey's comfort. The test monkey was actually slightly (approximately 100 g) lighter than the first test monkey, but it appeared to tolerate the weight of the device to a greater extent. Its head was held at a more normal position most of the time, although it still exhibited a low-hung head occasionally. In view of this, the device would have to be made even lighter, although alternative ways to reduce its weight should be explored, such as incorporating a counterweight system to reduce the effective weight of the device on the monkey's head.

In sum, the monkey was initially irritated with the device on its head, but soon got used to its presence (quicker than the monkey from the first live testing). This monkey was much more active and engaged in more "normal" behaviors such as climbing and eating.

TESTING CONCLUSIONS

The observations from the two live testing sessions carried out provide similar implications for the team's design. First, the device is too heavy and weight reduction is of utmost importance to allow the device to be placed on adolescent monkeys (which are the test subjects for microdialysis). Second, the strap design must be modified to provide greater comfort and security for the monkey. Third, the design of the device must be made customizable to fit a range of monkey head sizes. In spite of the need for these modifications, the results from the preliminary live testing are promising in that the monkeys did not react as negatively as expected and became accustomed to the presence of the device relatively quickly. Considering the fact that the test monkeys would be given an acclimatization period to the device before officially using it during microdialysis experiments, there is a concrete possibility of implementing the device in the future. Furthermore, testing carried out on two different monkeys provide evidence that the observations apply across monkeys and are not simply due to the particular idiosyncrasies of one monkey. Further testing to better examine the ability to generalize observations across monkeys is warranted.

Future Work

In the future, it would be desirable to make the current prototype more lightweight and better fitting. Following the live animal testing, it was obvious that the prototype was too heavy for the comfort of the monkey despite meeting the 0.5 gram weight design specification. To reduce the effective load that the monkey would feel on its head, other materials, such as plastic, titanium, and carbon fiber will be considered. Ultimately, a material practical for the upper cylinder and lower base shell that is as rigid as the current aluminum but much lighter is a major goal as this project progresses. In addition to alternative shell materials, the silicone rubber interior will be reconsidered. The majority of the prototype's weight is due to the silicone rubber. Finding a material, such as lightweight foam, that still maintains the current rigidity of the silicone rubber would advance the practicality of the prototype.

Another possibility to help decrease the amount of weight that the monkey felt during experimentation is to implement a counterweight pulley system (Figure 19). This would involve connecting the system to the experimental tether so that the effective weight that the monkey feels would be reduced. The system will need to be designed in a manner so sudden "jerking" due to gravity is minimized. In addition, the system will need to accommodate a swivel system between the tether and upper cylinder to allow rotation by the monkey. Currently, the swivel was intended for blood sampling and as a result, the tubing used is too big for the necessary microdialysis tubing. A swivel system that functions with microdialysis tubing and a linear pulley system will need to be considered.

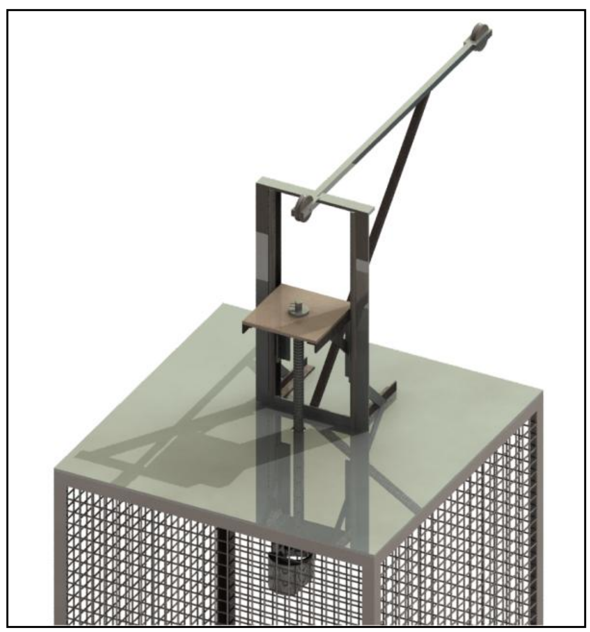


Figure 19: Counter Weight System

To make a better fitting prototype, the current strap system will need to be revised. Currently, the strap and the collar are sewn into one unit so that the monkey cannot reposition the strap locations and jeopardize the secure attachment of the aluminum housing unit. The strap system is successful in that it does not come unattached with ease. However, it doesn't make a large contribution to securing the prototype. Virtually all of the stabilization is due to the silicone rubber interior; the strap system will need to be designed in a manner so that it adds extra support.

Another area of future work is the idea of non-specific use. The current design has been exclusively based of off a foam model of one monkey's skull. However, the client will be using the device on multiple monkeys with slightly different skull conformations. Once testing begins on actual monkeys, alterations may need to be made to the base so that it can accommodate various skull sizes. To account for this ahead of time, a biometric analysis of test monkeys' skulls could be performed to determine a range in head sizes.

Finally, the idea of creating a better fitting prototype could be achieved by altering the shape of the device itself. A helmet design (one that extends further down the head) has been considered. Also, incorporating a memory foam interior that conforms to the monkey's skull will be considered in the future. With future work, a device that improves microdialysis experimental procedure and the overall experience of the monkey will hopefully be developed. Further testing will be carried out to ensure that the prototype satisfies all design requirements.

Ethical Considerations

Since this project involves creating a device for monkeys used in research, there are some ethical issues surrounding the project. Prior to embarking on this project, the team has been assured that all research carried out with these animals follows all governmental regulations and that the animals are treated in a humane manner. There are limitations placed on the amount of experimentation that can be carried out with the monkeys and they are under the constant care of the Wisconsin National Primate Center veterinarians. The goal of this project is to construct a device that ultimately allows the monkeys to be more comfortable and natural while research is being conducted. Hopefully this will improve their quality of life. In addition, when creating the device, the team kept the comfort of the monkey in mind. The team tried to design a device that would be as light and comfortable as possible while still providing the necessary protection. Throughout this process, there has been constant contact with the veterinarians to ensure that the device satisfies all safety requirements and will impact the monkeys in a positive manner

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APPENDIX I: DEVICE ASSEMBLY PROTOCOL

STEPS FOR ATTACHMENT OF DEVICE TO MONKEY'S HEAD

1. Attach microdrive unit onto cranial pedestal on monkey's head and make necessary adjustments.
2. Clamp silicone rubber interior halves around the base of the microdrive unit (Figures A-1 and A-2).
3. Attach both halves of the aluminum base and the cylindrical top, ensuring that the lip of the cylindrical top fits into the grooves in the aluminum base halves (Figures A-1 and A-2).
4. Clamp the halves of the aluminum base together using a hose clamp (tightened using a screwdriver).
5. Fasten the nylon collar around the monkey's neck using an internally threaded cable tie and tighten. Cut off excess cable tie with a pair of scissors to minimize clutter (Figure A-3).
6. Fasten the side straps to both sides of the aluminum base using cable ties and tighten. Cut off excess cable tie with a pair of scissors to minimize clutter (Figure A-4).
7. Attach the tether to the top of the cylindrical top.

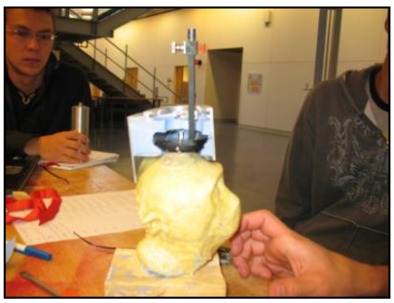

Figure A-1: Clamping half of the silicone rubber interior and aluminum base to the base of the microdrive unit

Figure A-2: Clamping half of the silicone rubber interior and aluminum base to the base of the microdrive unit and attaching cylindrical top

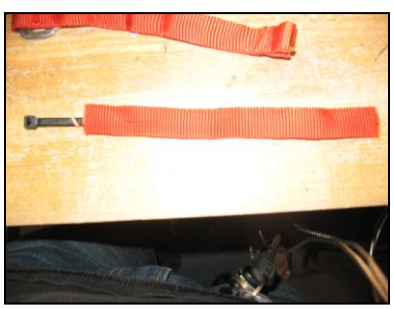

Figure A-3: Nylon collar with internally threaded cable tie

Figure A-4: Completely assembled device

APPENDIX II: PRODUCT DESIGN SPECIFICATIONS

PROJECT TITLE:

Development of a Device for Neurochemical Sample Collection from Freely Moving Monkeys
(Project Number: 26 / Project Code: neurochemical_sampling)

INITIAL PROBLEM STATEMENT:

The purpose of the project is to develop a device allowing monkeys to be free from chairing while experiments are conducted. Direct measurements of neurochemical substances in the brain from free moving nonhuman primates is significantly important for understanding complex brain function and developing treatment strategies for brain disorders in humans. During the last semester four BME students worked hard to design and built a device. However, this device still needs further refinement for actual application. The development of the device for microdialysis experiments may require creativity and intellectual exercise.

REVISED PROBLEM STATEMENT:

To improve on the device created last semester that protects the microdialysis apparatus used during cranial experiments on non-human primates. This involves making the device lighter, more secure around the monkey's head, and better able to cushion the microdrive unit.

CLIENT REQUIREMENTS:

- Material must be lightweight so as not to impose too much weight on the monkey's head.
- Material must be strong enough to withstand forces that the monkey may apply.
- The device must not interfere with the data collection process.
- The device must be able to be easily integrated with the current microdialysis apparatus being used.
- The monkey must be able to move freely with the device attached to it.
- There should be limited space between the device and the microdialysis apparatus.
- The device must be detachable from the apparatus after use.
- The device should be sterile and reusable.

DESIGN REQUIREMENTS:

1. Physical & Operational Characteristics

a. **Performance Requirements:** The device must be strong enough to withstand 100 N (based on human arm strength estimate) to protect the microdrive unit from any forces that the monkey may apply.

b. **Safety:** The device must not contain sharp edges or other protrusions that may injure the monkey or researcher. The materials that are used must not be toxic.

c. **Accuracy & Reliability:** The device must provide reliable protection for the microdrive unit by being able to withstand a force of 100 N for 10 consecutive hits within a time period of 10 s.

d. **Life in Service:** The device must be able to withstand at least 12 h of use at a time, and must be sterile so that it can be reused.

e. **Shelf Life:** At least 5 years.

f. **Operating Environment:** Normal laboratory environment for nonhuman primate research.

g. **Ergonomics:** The device must not restrict the monkey's motion except for the head and neck.

h. **Size:** The base of the device should have a diameter of 82.55 mm and a maximum height of 73.025 mm (height differs due to the shaping of the base to provide a custom fit for the Rhesus monkey's head). The cylindrical top should have a diameter of 50.8 mm (with a 3.175 mm lip around the bottom), a height of 152.4 mm, and a thickness of 2.38 mm.

i. **Weight:** Not more than 0.5 kg so as not to impose too much weight on the monkey's head (as determined by client). The current weight of the device is 0.46 kg, but results from the live testing showed that this might still be too heavy.

j. **Materials:** Aluminum alloy 5052 for the outer casing and RTV silicone rubber for the form-fitted interior.

k. **Aesthetics, Appearance & Finish:** The device must be aesthetically pleasing and look "humane" so as not to create a public outcry.

2. Production Characteristics

a. **Quantity:** 1 reproducible device.

b. **Target Product Cost:** Not more than USD1000.

3. Miscellaneous

a. **Standards & Specifications:** The design and construction of the device must comply with USDA regulations and NIH guidelines, subject to approval from the attending veterinarian.

b. **Customers:** Primarily the client, but can be potentially extended to any research institution that is involved with cranial microdialysis studies on non-human primates.

c. **Patient-Related Concerns:** The device must be sterilized before use with a different primate. It should not cause more discomfort to the monkey than the current experimental apparatus (i.e. the primate chair) does.

d. **Competition:** No currently known products specifically address the need to protect the microdrive unit during cranial microdialysis studies on nonhuman primates.

APPENDIX III: PROJECT EXPENDITURE

SOURCE	ITEM	QUANTITY	TOTAL COST (USD)
The Home Depot	Box of Rivets Box of Riveting Washers Box of Ring Hangers Bag of Cable Ties	1 1 1 1	11.77
McMaster-Carr	1lb of RTV Silicone	1	39.08
		TOTAL:	**50.85**