SENSORIMOTOR NEUROPROSTHETICS

FOCUSED ULTRASOUND TO TREAT NICOTINE ADDICTION

GROUP 3

Joël Daout, Jan Frogg, Salar Rahimi, Philipp Spiess

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Abstract

With over 1.1 billion smokers worldwide today and tobbacco causing more than 8 million death per year[1], cigarette and tobacco consumption is one of the biggest public health threats the world has ever faced. Despite those dramatic figures, people yet continue to smoke. This is due to one key element: addiction to cigarette, more specifically to nicotine, present in cigarettes. It is the main reason why smokers, even when trying hard, are unable to give up smoking. There has been, of course, some methods which have risen to treat nicotine addiction over the years, such as patches for instance, which unfortunately have never proved very efficient. In this work, we present a novel device that aims at reducing nicotine addiction through neuromodulation. The proposed device presented forth uses a combination of activation of the PFC and suppression of the insular cortex, using Low-Intensity Focused Ultrasound (LIFU) integrated in a minimaly-invasive device.

Contents

1 Introduction

Smoking has been around for decades, and, more specifically, the use of nicotine has been around for even longer. Today, more than 1.1 billion smokers are found worldwide and tobacco kills more than 8 million people each year[1]. While the number of smokers appears to be decreasing with time, the real problem at hand is the unsuccessful attempts by smokers to quit. Indeed, a majority of smokers want to quit, but without assistance, only about 4% of those trying to quit succeed[1]. Current approaches used for smoking cessation are numerous [2]. Those all come in the form of a drug or medicine, which not only have proven low effectiveness overall, but have also shown negative side effects. The most common medication for smoking cessation is known as *Nicotine Replacement Therapy* (NRT), in which the main mechanism of action is to partially replace the nicotine formerly obtained from tobacco smoking. This helps reduce the withdrawal effect of nicotine in cigarettes. However, NRT does not completely eliminate those symptoms because the available systems do not deliver reliably the rapid and high levels of nicotine achieved through inhalation of cigarette smoke [3], [4], [5]. Overall, this and similar treatments, as well as treatments like nicotine patches show rapid relapse time and seem to be ineffective. Lastly, economic regulations like higher taxes on tobacco products have been put in place so that people are discouraged to purchase and consume such products, which show to have very little effect as well.

In this report, we present a novel method that approaches the treatment of nicotine addiction directly through the brain, in the form of neuromodulation of specific brain regions that play a role in both the craving and withdrawal symptoms of nicotine. We describe a theoretical implementation of this method through a portable device with a cap-like design to be worn directly on the head. We use LIFU as a way to access targeted brain regions. Although this is a young technique, it shows some promising results. We will use Capacitive Micromachined Ultrasonic Transducers (cMUTs) for its small size and efficiency [6]. We also describe the powering of the cMUT, along with the device design and usage, as well as the surgical implantation of the transducers underneath the scalp. The objective of our prosthesis is to reduce the cravings felt during withdrawal as well as reduce the consumption of nicotine by a significant amount or even completely.

2 Addiction mechanism

Addiction has been defined as the recurrent failure to control the use of a drug and continuation of drug use despite negative consequences, motivated by both the pleasure offered by the drug and the relief from negative stimuli [7]. Addiction to nicotine is a complex process involving many different brain areas and the different processes involved are far from being completely understood, but an outline of the main discovered mechanisms is summarized below as well as the effect of nicotine on the brain so that the targets of our prosthetic system can be understood.

2.1 Midbrain dopaminergic pathway

One of the main and most studied system linked to addiction is the dopamine system. Its link to reward and motivation makes it an easily understandable cause of addiction although many other neurotransmitters have also been linked to addiction[9]. Evidence shows that impairments in the

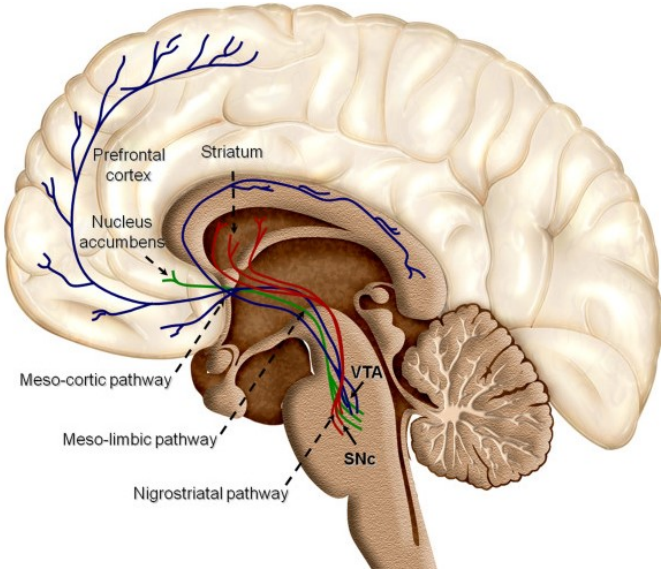

Figure 1: The Dopaminergic pathways (reproduced from [8])

dopamine system are linked to the impairments of the reward system (leading to withdrawal symptoms), of affect regulation (causing vulnerability to negative affects) and of behavioral inhibition (causing short term needs to override consideration for long term consequences), three components of the addictive process[7].

The dopaminergic system consists of many brain areas, some of the most important are the ventral tegmental area (VTA) which contains dopamine-releasing neurons who project to the Nucleus accumbens (NAc), prefrontal cortex (PFC), hippocampus and Amygdala, and the substantia nigra pars compacta which releases dopamine in the dorsal striatum (Figure 1). The dopamine system is separated in multiple pathways and although many of these pathways are implicated in addiction, the mesolimbic pathway is often regarded as the principal pathway of addiction[9] and has been extensively studied. This is the pathway from the VTA to the NAc.

The dopamine system has been shown to have a main function in motivation. dopamine release is necessary to create a conditioned link between cues and reward and helps create motivation to reach high reward goals by regulating the incentive salience of stimuli (how much the reward is wanted). The more established theory is that dopamine release is linked to reward prediction errors. When the given reward is bigger than expected, dopaminergic neurons are highly activated (thus dopamine is released in high quantity), while when the reward is smaller than expected, the activity is small. The same holds when cues predicting small or big rewards are presented[10]. The release of dopamine is then thought to reinforce behaviors linked to the rewards by acting as a signal needed to reinforce synapses in the NAc.

It has also been shown that activation of the dorsolateral PFC (dlPFC) leads to the release of dopamine in the midbrain dopamine system[11] and studies using rTMS found that dlPFC stimulation seems to show decreases in cravings and nicotine consumption[12].

2.2 Nicotine action

Nicotine is a molecule that binds to nicotinic cholinergic receptors (nAChR). These receptors are present in the central nervous system. nAChR normally respond to acetylcholine and are ionotropic receptors, meaning that nicotine binding will cause a net positive flow of ions (mostly Na^+ and Ca^{2+}) inside the cell which will depolarize it and allow neurotransmitter release. Thus nicotine activates these neurons. nAChR have been found to be present in dopamine-releasing neurons in the VTA and in the shell of the NAc. Nicotine consumption thus activates dopaminergic neurons in the VTA which increases the release of dopamine from the VTA into the NAc. After smoking a cigarette, the levels of extracellular dopamine thus increase significantly in the NAc. In this way, nicotine activates the midbrain dopaminergic system[13].

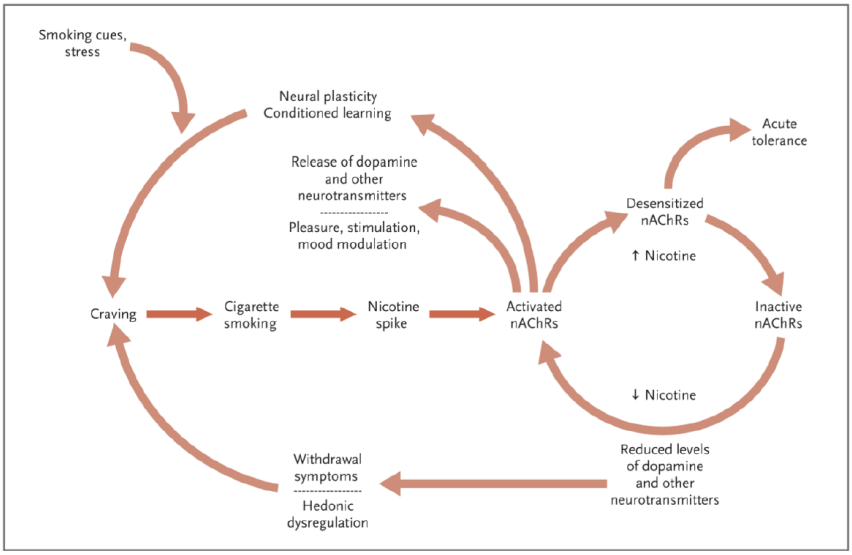

Figure 2: Nicotine addiction cycle (reproduced from [13])

Chronic exposure to nicotine affects the brain in several ways. First, due to the activation of the dopamine system, the rewards from nicotine become associated with the behavior of smoking and to the cues and context linked to smoking (seeing a cigarette, the smell of smoke, etc.). Secondly, nicotine will cause desensitization (decreased response) of the nAChR receptors, which could explain increased tolerance to nicotine, where more nicotine is needed to cause the same effects.[13]

When low levels of nicotine are present, withdrawal symptoms can be felt. These include irritability, anxiety, poor concentration, and cravings. These symptoms appear to be caused by many systems, notably an over-expression of the corticotropin-releasing factor (involved in the stress system) and decreases of activity of the reward system, including decreases in dopamine release. Decreases in natural rewards are also found during withdrawal[14]. These negative affects will push the smoker to smoke to be relieve of these symptoms. Smoking cues, through the conditioning created by nicotine, will also induce cravings.[13] and are often the cause of relapse in addiction

All these mechanisms are summarised in figure 2

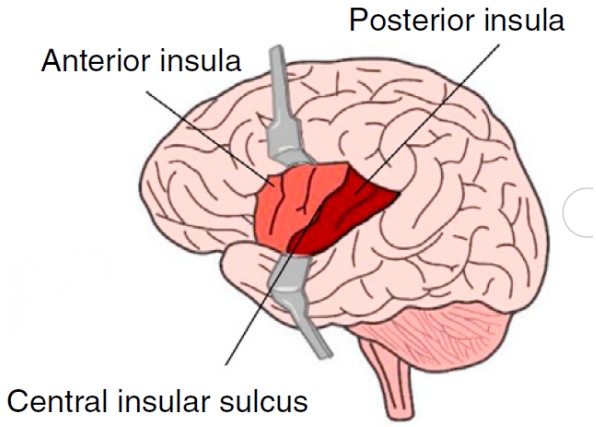

Figure 3: The insular cortex (reproduced from [15])

2.3 Insular cortex

The insular cortex is a cortex region folded inside the lateral sulcus. It is mainly divided into the anterior and posterior insula. The insular cortex has been shown to be involved in many very diverse functions. It is linked to emotion, risk predictions, decision making, empathy, autonomic control, and many others. The insula has connections to many different brain regions. First, the insular cortex has thalamic inputs from all of the different sensory inputs from both external signals and interoceptive signals. It is also connected to the limbic system and to frontal brain regions involved in cognitive control, emotion and executive function. It is also connected to brain regions involved in the dopaminergic pathway. All these connections make it a region capable of integrating cross-modal information and functions. The insula has also been linked to different psychiatric disorders like anxiety disorders, schizophrenia, autism or more interestingly in our case, addiction. [15]

The link between the insula and nicotine addiction has received a lot of attention after Naqvi and al. [16] found that smokers with insula damage were much more likely to quit smoking and remain abstinent and felt less subjective urges to smoke. They also showed that the insula damage did not impair the desire to eat or the pleasure of eating. Neuroimaging studies also found that the insula activity was increased after smoking cues presentation[17] and that this activity was correlated with relapse[18]. Further research on mice found that nicotine self-administration and nicotine seeking behavior when exposed to cues could be decreased for example by a lesion of the insula [19] or by inhibition of insula using electrical stimulation[20]. Mice experiments also seem to show that the posterior insula is implicated in learning the drug-context associations while the anterior insula is implicated in recalling these associations.

The anterior insula is part of the salience network and the anterior insula seems to have a role in switching between activity in two large scale brain network, the default mode network (involved in internally oriented tasks) and the executive control network (involved in externally oriented tasks) depending on the salience of the different signals arriving to the insula.[21] Craving sensations during withdrawal could activate a switch to the default mode network increasing the attention to interoceptive

sensations[22].

Multiple models have been created to explain the role of the insula in addiction. Naqvi et al.[23] proposed that the insula is implicated when there is a conflict between drug-taking and other goals and is responsible for allowing access to the current value of drug intake and the representation of its interoceptive effects. The goal representation is transmitted to the NAc which links this signal with motivational signals. The output of this system is goal-directed drug-seeking and the craving is the subjective expression of the conflict mentioned above. In this model, insula inhibition would only work if there was a conflict between the goal of drug intake and other goals, for example the desire to stop using the drug because of important negative consequences, in which case the drug and it's predictive value would be decoupled and the goal-directed behavior would be abolished.

Another model proposed by Regner et al.[24] is based on the fact that the insula has limited processing capabilities. It becomes quickly saturated under cognitive tasks. Because of this, they propose that during withdrawal, the insula becomes saturated with interoceptive craving signals and is not capable of functioning normally. Hence it cannot balance between large scale networks and the internal oriented default mode network becomes more active leading to more focus on the craving sensations. Inhibition of the insula would thus decrease its saturation and allow rebalancing of the networks and less craving sensations.

Clearly more research is needed to understand the exact role of the insula but regardless of models, inhibition of the insula seems to be a good target to reduce cravings and in particular, the anterior insula for its role in the retrieval of drug-context associations and implications in the salience network.

2.4 Targets

Our prosthetic system would both excite the dlPFC and inhibit the anterior insula during withdrawal to attenuate the symptoms of nicotine addiction. By targeting the dlPFC, the objective is to normalize the activity of the dopamine system (increasing dopamine release during withdrawal). By targeting the insula at the same time, we hope to decouple the cues and nicotine association, as well as reduce the attention allocation on interoceptive craving signals to reduce the subjective feeling of withdrawal. Our prostheses would then serve to help patients stop smoking without difficulty. We will restrict ourselves to the left insula because there is evidence that left insula damage leads to fewer symptoms of withdrawal compared to patients with right insula damage in the first days of abstinence [25]. We will also focus on the left dlPFC so that our device doesn't become too complicated, although no compelling shows that targeting the left dlPFC is more effective than the left PFC. The target hemisphere effectiveness could also be tested on animal models using our prostheses to get more compelling evidence that targeting one hemisphere is better than the other.

3 Neuromodulation

In the previous section, we noted that two brain areas, the dlPFC and the anterior insula could be modulated to decrease the symptoms of nicotine addiction. In this section, different approaches for modulating the brain are discussed and a suitable solution for our purpose is discussed in detail.

3.1 Current approaches

The first solutions to target nicotine addiction appeared in the form of nicotine patches in the middle 80s and have effectively helped millions of smokers quit smoking. However, side effects including vivid dreams, dizziness, headache, itching, and many others are major drawbacks to those methods and quitting is then not even ensured.[26] More recently, research has been done on the effect of transcranial direct current stimulation (TDCS) and transcranial magnetic resonance (TMS) [27], which both are non-invasive and have proved to show little or no side effects. These methods help to reduce the symptoms of cravings in the short term by increasing prefrontal cortex activity. Those two techniques are however quite bulky and do not allow targeting deep brain areas with good resolutions. Deep brain stimulation of the NAc has been tested to decrease nicotine addiction with some measure of success[28] but the studies had very low sample sizes. To decrease the activity of the Insular neurons, deep brain stimulation thus could be also used but it is clear that it is too invasive for our purposes. A non-invasive version of deep brain stimulation, temporal interference [29], could potentially be a solution but its effectiveness is still very unclear, the ability to activate and inhibit at the same time has not been demonstrated and it has not even been tested on humans yet. This leaves us with the remaining possibility: Low intensity focused ultrasound (LIFU) [30], which is a very active area of research. LIFU can be used to both excite and inhibit deep brain regions and its effectiveness has been tested and validated. Table 1 summarizes existing and explored solutions for targeting nicotine addiction.

Solution	Pros	Cons	Activate/inhibit potential
Standard therapies	Non invasive, easy to use	Not effective, side effects	Not relevant
Deep brain stimulation	Localized, high resolution	Invasive	Both
TDCS and TMS	Non invasive, no side effect	Low resolution, bulky	Both
Temporal interference	Non invasive, localized	Difficult to both activate/inhibit	Not well known

Table 1: Existing solutions along with their advantages/disadvantages, and their ability to both activate or inhibit cells.

3.2 Low intensity focused ultrasound (LIFU)

Focused ultrasound (FUS) is a non or minimally invasive method of delivering mechanical forces to cells deep within the body in the form of an acoustic pressure wave, which can cause numerous bio-effects both by heating the desired location (thermal effect) or vibrating the specific cells (mechanical effects). One of the critical advantages of this method is that the acoustic beams can be focused to the desired location with millimetric spatial resolution without affecting cells along the propagation path of the acoustic waves, and also the focal length of the transducers can be designed to penetrate relatively deep regions [31]. Different studies showed that Low-intensity FUS could result in direct neuromodulation of neurons both on humans and animals [32, 33, 34]. Both inhibition and excitation of the neurons are observed in the studies available in the literature. However, the biophysics behind the nature of this phenomenon is not well understood, and is still an open question.

Ultrasonic neuromodulation can be derived from different biophysical interaction modes, including temperature elevation [35, 36], acoustic streaming [37] , radiation pressure [37, 38] , and stable or

inertial capitation [37] . However, the only model that provides a detailed predictive explanation of specific empirical studies for inhibition an excitation of neuron by LIFU is the intramembrane cavitation hypothesis [39] and the related neuronal intramembrane cavitation excitation (NICE) model [40]. The NICE framework states that the ultrasonic pressure waves cause periodic expansions and contractions of the membrane region of the cells and lead to capacitive displacement currents, which indirectly lead to slow membrane charge accretion. This phenomenon brings the neurons to their action potential (AP) discharge threshold and activates the neuron. NICE model is presented for the cortical neurostimulation of pyramidal neurons. The NICE framework is extended in [41] for examining the effect of LIFU on additional cell types and stimulation modes.

The extended model analyzes the effect of LIFU on the mammalian cortical neurons, which are regular excitatory spiking (RS) pyramidal neurons and the two principal cortical inhibitory interneurons that are LTS and fast-spiking (FS). The effect of LIFU parameters, which are Carrier frequency, Peak pressure amplitude (Intensity), Duration, Pulse repetition frequency (PRF), and Duty cycle, on the NICE model of the cortical neurons was studied and neuromodulation parameter for both inhibition and excitation are introduced. Based on the analyses, only intensity at the interface of the neurons and duty cycle of the ultrasound waves (LIFU) were found to be crucial parameters that change the nature of the neuromodulation. The phase plane diagram of single-neuron responses to different LIFU intensity and duty cycle is shown in figure 4. [41]

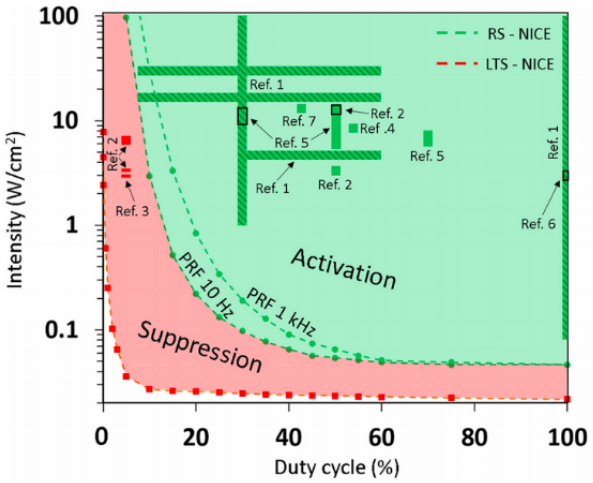

Figure 4: This phase diagram represents the response of the single neurons to intensity and duty cycle of the LIFU. Suppression occurs when only LTS neurons are activated, and when both RS and LTS are activated the excitation occurs. The result of the prediction using the model proposed is aligned with empirical results [41]

Both dlPFC and the insular cortex are part of the Neocortex to which the cortical neurons are related. Therefore, the given model can be used for achieving both inhibition and excitation. Using the figure 4, Intensity of 0.6 W/cm^2 and Duty Cycle of 5 % with PRF of 100 Hz is used to accomplish inhibition for insular cortex and same intensity but duty cycle of 100 % used for exciting the dlPFC neurons. The intensity selected in this section is the requirements at the interface of the neurons.

4 Neuroprosthetic system

In this section, the design procedure of the device for this study is discussed in detail. In the first step, the design of the ultrasonic transducer for delivering the requirements specified in the previous sections to achieve the desired effects on the nervous system is explained. The next step is the method of powering the whole mechanism in order to make it possible for the system to be portable. Finally the cap design is elaborated.

4.1 Ultrasonic Transducer

The first step of the design of the neuroprosthetic system is the ultrasonic transducer, which is the hearth of the whole mechanism. The device should be designed to provide the required intensity to achieve both suppression and activation of the neurons. Moreover, the other specifications of the transducer should be selected appropriately to only target the desired locations.

There are three types of ultrasonic transducer that are mainly used for neuromodulation of animals and humans in the literature. The first option is a single element ultrasonic transducer, which is used in [42] for targeting human thalamus. For having the desired focal point, the lens needs to be designed to focus the ultrasound waves to the desired location. The requirement of the lens for the design has two drawbacks for our work here. After creating the lens, the control over the focal point is complicated, and small changes require the design and fabrication of new lenses. Moreover, Implementing the lens embedded in a device such as a cap would be unsuitable and uncomfortable for the user.

Piezoelectric and capacitive Micromachined Ultrasonic Transducers, which are called pMUT and cMUT, respectively, are MEMS-based ultrasonic transducers. Flexibility in design and the small size of the devices with relatively sizeable focal depth and intensity are the essential factors for the design of the neuroprosthetic system in this project. It should be noted cMUT and pMUT focal points are programmable and can be even steered on demand, which provides flexibility to the device.

There are different pMUT design suggested in the literature for neuromodulation [43, 44, 45, 46, 47]. However, only the design proposed in [47] is tested experimentally in vitro [47]. To our knowledge, there is no available study done in vivo using pMUTs. On the other hand, there is a study done on rats using cMUT [48, 6].In [48] it is stated the same design methodology with different dimensions can be used for human experiments. This research provides solid ground to use cMUT for our study. In the following sections, the required parameter for the transducer is specified based on the requirement for achieving the desired effect on the insular cortex and dlPFC, and finally, the design is proposed for the cMUT loyal to the study done in [6].

4.1.1 Intensity of the Ultrasonic Transducer

The intensity at the interface of the neurons for both regions is already selected. However, attenuation of the intensity of the acoustic waves occurs in the path mostly due to the skull. The ultrasonic transmission to calculate the required intensity of the transducer is crucial.

The ultrasound transmission can be calculated using the following equation[49]:

$$I = I_0 T e^{-kf(\alpha_1 d_1 + \alpha_2 d_2)}$$

$$T = 1 - (\frac{Z_1 - Z_2}{Z_1 + Z_2})^2$$

Where I is the intensity in the brain region, I_0 the intensity at the transducer, k a converting coefficient equal to $ln(10)/10$, α_1 and α_2 the attenuation coefficient of the skull and brain tissues (equal to 8.7 and 1 $dBcm^{-1}MHz^{-1}$ respectively), d_1 and d_2 the thickness of the skull and the distance from the inside of the skull to the brain region and Z_1 and Z_2 the impedance of the skull and brain tissue (equal to $7.8 * 10^6$ and $1.58 * 10^6$ rayls respectively). T is the transmission coefficient of the skull/brain tissue interface. We have not considered refraction as we assume that the ultrasound wave is perpendicular to this interface. The exponential part of the equation models the scattering and absorption happening in the tissue and bone.

The calculations were done for the insula as it is deeper inside the brain than the PFC. By taking an estimate of 3cm as the distance from the skull to the insula (estimated using Allen brain atlas [50]), a skull thickness of 0.6 cm and a frequency of 0.5 MHz, the attenuation from the transducer to the insula (I_0/I) is of factor 5. This value provides us with a good approximation of the intensity needed from the transducer.

Therefore, the minimum required intensity at the interface of the transducers is 3 W/cm^2. Yoon & al.[51] suggests that a cMUT with comparable attributes would require 1W to produce a beam with similar energy density so we based the energy consumption estimation on this. Both cMUTs would thus together consume approximately 2W.

4.1.2 Capacitive Micromachined Ultrasonic Transducer

The center frequency of the device is proportional to t/D^2, where t is the thickness of the cMUT. The center frequency should be selected in the middle of the two different carrier frequencies required for the focal points to not complicate the design process for each transducer. The desired centered frequency is 117 kHz. The cMUT that is designed here is inspired by the one presented in [6]. In the mentioned study, the center frequency is 183 kHz. For amplifying the transducer, the diameter of the design is increased from 8.1 mm to 21 mm. Form the governing relation and equation, the required thickness of the device can be calculated. The thickness of the device should be 4.3 times more significant than the one proposed in [6].

Increasing the area of every element and the whole cMUT array increases the intensity of the transducer. The bigger the area, the more medium is moving while the elements that are oscillating, and this phenomenon causes a shift in the intensity of the device. The idea is to increase the maximum displacement volume of the cMUT elements [52].

An increase in the area of the ring array would cause more volume of the medium to move. We assume that the volume is only changing with the area, and it is proportional to the diameter of the ring array. The next assumption is that the maximum acoustic pressure of the waves is proportional to volume. The intensity has the following relation with acoustic pressure.

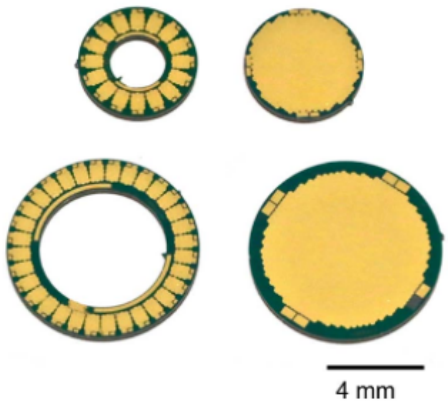

Figure 5: the proposed design of the cMUT [6] [41]

$$I_{max} = P_{max}^2 / 2\rho c$$

Where I_max is the maximum intensity, P_{max} is the maximum acoustic pressure, and ρ and c are the density and sound speed of the medium respectively. From equation and the assumption made earlier, we conclude that intensity is approximately proportional to D^4 (D is ring array diameter). Therefore, while increasing D to 21 mm, with the given assumption, the maximum intensity achievable increases to 8 W/cm^2.

It should be noted that as the dimensions for each cMUT element increased with the same factor in area, the thickness of the devices also changes. The displacement would be more than what is approximated here, and higher intensities can be achieved. Intensity can be adjusted by voltage, and appropriate voltages can be characterized when the device is fabricated to fulfill desired requirements.

4.1.3 Carrier frequency

The carrier frequency of the ultrasound waves generated by the transducer gives the focal zone of the cMUTs. The nature of the beams generated from the transducer is represented in figure 6. The focal zone of a transducer is around $0.6 * Nf$, where Nf is the near field zone shown in figure 6 ([53]). The following equation gives the near field zone:

$$Nf = D^2 / 4\lambda$$

D is the diameter of the transducer, and λ is the wavelength of the waves. The relation between wavelength and frequency of the wave is $\lambda f = c$, where c is the sound velocity in the medium, and f is frequency. Therefore, the relation between the near field and the frequency is as follows:

$$Nf = D^2 f / c$$

The focal distance required for insula and dlPFC is estimated to be 3 cm and 1 cm, respectively.

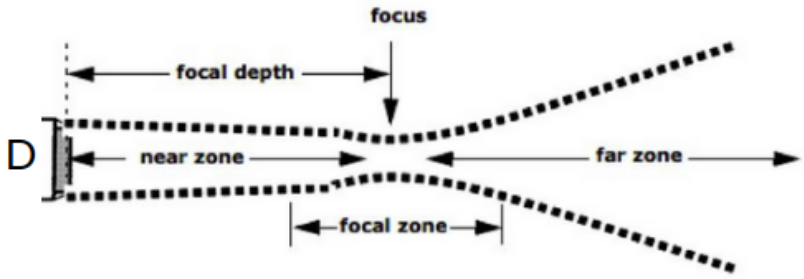

Figure 6: Different region of the beam generated by the ultrasonic transducer

However, for every individual, this value needs to re-evaluated accurately. For the estimated values, the required carrier frequency can be calculated. From the equation stated above, the required Nf values are 5 cm and 1.67 cm for insula and dlPFC, respectively. Given the D obtained in the previous section, and speed of sound of in the brain, which is 1543 [54], the carrier frequency for the two regions are 175 kHz (insula) and 59 kHz (dlPFC).

4.2 Power transmission

Coil power transmission is an effective way to wirelessly transmit energy from a transmitter to a receiver coil. According to [55], up to 15 watts can be transferred for coils of a reasonably small size typically included in the latest smartphones (thickness in the order of mm). For 30 mm diameters Qi consortium coils (Qi is currently the most established solution on the market with over 230 approved devices) and a distance of 5 mm separating the coils, a reduction factor of power can be expected to be around 0.4 which still offers a possibility to generate a maximum of 6 watts (see Figure 7) which shows that such a coil could power the device we are aiming for. For our device, as determined in the previous section, each cMUT requires to be powered by 1W so the transmitter coil would need to be powered by 6W so that with a 0.4 reduction factor, the receiver coil would receive a power of 2.4 W above the 2W required.

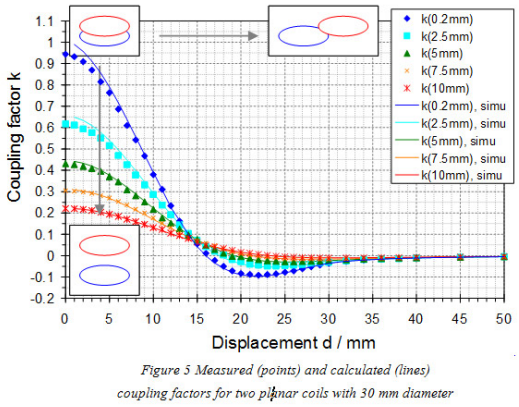

Figure 7: The reduction factor is 0.4 for 30mm diameters coils separated by a distance of 5mm (https://www.wirelesspowerconsortium.com)

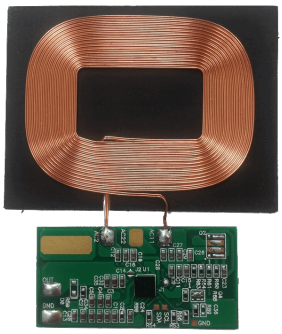

Figure 8: WPC Qi Wireless RX Module (30mm*30mm*1.2mm) which would be suitable for our application (http://www.inpaqgp.com/rw_4803c99f250aadcb2de1013a3b6c0afb)

Alternatively, the coils could also be specifically designed for our device. The progress in the miniaturizing of power transmission to implanted electronics have been significant recently. It has been found that for a coil size of $2mm$ for the inner diameter ($200\mu m$ wire diameter), using a copper wire wrapped around 3 times (3 turns), we would get a $200\mu W$ transmitted power with a coupling factor of 0.004. [56]. Although this is clearly very low, many parameters are subject to modification for our device. Decreasing the distance between both coils to around 5mm would potentially augment the coupling factor by 100 times. Adapting the coil size parameters(setting the inner diameter to 2cm and augmenting the number of turns to about 30 turns) could lead to an increase of power transmission of about 100 times. Given these estimated adjustments, the 2W of power could again be achieved. Given the nature of this study, this would of course subject us to performing practical tests and actually pushing the results found in the previously mentioned work to design the wireless power transmission with the desired specifications. The conclusions drawn in [56] are also an indicator of the promising potential of such solution for power transmission at any location in the human body.

4.3 Batteries

As our device needs to be wearable and without any external power source, one key aspect we need to look for is the system's battery. Clearly, it must, on the one hand, be powerful enough for the system to work and on the other hand, be small and compact enough to fit in the proposed device. This power-to-size trade-off is a challenge faced by a tremendous amount of products similar to ours. That is why, we chose to opt for a specific type of miniaturized battery, which alone delivers a maximum of $4V$ and a maximum current of $15mA$ for a size of $0.080cm^3$ (approx. $15mm$ in length and therefore, $\frac{0.080cm^3}{15mm} = 5.33mm^2$ disk area) [57]. The benefit of such a battery is that we can take advantage of its electrical properties and its size by creating a modulating array of miniaturized batteries. Given that connecting batteries together in series increases the voltage in an additive fashion and that connecting them in parallel improves battery life and current discharges control [58], connecting several of those batteries in such an array to create one battery cell could help achieve the desired power supply. Such cells will remain compact enough to fit in the system, while at the same time deliver the desired power approximately 6W as shown in the previous section. An array of 100 of those batteries would lead to a cell of $10 \times 15mm = 15cm$ by $1 \times \sqrt{\frac{5.33mm^2}{\pi}} = 10 \times 1.30mm = 1.3cm$ for a desired output of $40V$ and

$150mA$ which in turn would result in a $40V \times 150mA = 6W$ power output. No more than $500mA$ would hence be ensured so that our system does not risk overheating.

4.4 Device design and usage

The part to implant would thus result in the 1.2mm thick coil with copper tracks connected to an electronic chip including an amplifier and the necessary components to generate the appropriate pulses to power the cMUTs. The insula cMUT and the PFC cMUT would be placed on both sides of the coil. The whole thing would then be encapsulated with a 0.2mm deposited PDMS layer. Using PDMS silicone can be an appropriate way to encapsulate an implantable material. It is bio-compatible and highly resistant to oxidation[59]. We could hence expect the whole implanted device to have a shape of around 35mm x 30mm x 2mm.

The outer parts, meaning the batteries and the outer coil, would have thin dimensions too, allowing them to be wearable and have a cap-like design. The device design can be observed in figure 9. The cap would be in cotton and would have the outer coil placed in the appropriate position (in front of the head, on the left side) so that when put on, the center of the coil would approximately match the center of the inner coil. The batteries would be placed anywhere in the cap and connected to the coil with a discrete on/off switch button. Figure 10 summarizes visually how the system works.

The usage would be quite simple: Whenever the patient feels cravings, he would just have to turn on the cap and place it on his/her head. Whenever the cap is not used, it could be plugged to charge the batteries. With the follow-up of a doctor, a protocol should be established to diminish the cap usage over time and hope to reach a point where the patient does not feel the need to use the cap anymore.

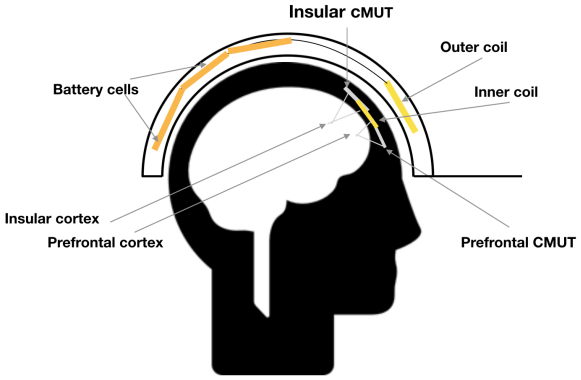

Figure 9: Design of the device and placement of each components relative to the user

4.5 Surgical implantation

The transducer and the inner coil will be placed under the skin, on top of the skull. Thus surgery is needed to insert the system on the skull and fix them to the correct location. Although discussion with a neurosurgeon will surely be needed to get the exact procedure, an outline of the surgery is explained in this section.

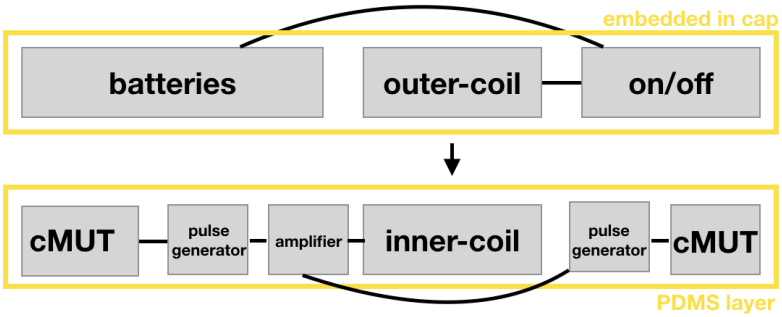

Figure 10: Scheme of the system

First MRI and/or CT scan will be used to create a map of the brain of each patient. The two target regions will be delimited on these scans using brain atlases. The precise location and stimulation parameters of the transducer to give the maximum efficiency of stimulation could be calculated using a computational model of wave propagation and the anatomical information given by the scans. This computer model could be created in MATLAB using the k-wave library in a similar way than done by Legon et al.[42].

Neuronavigation will be used during the surgery to place the transducer at a precise location. Neuronavigation allows the neurosurgeon to have a precise 3D map of the brain of the patients on which they are operating. MRI/CT Preoperative images are fused with images taken during the operation (by using marker placed before the preoperative images were taken or by contour recognition) and objects like scalpels can be tracked and added to the images as well. The surgeon will then be able to monitor the prosthetic system position in real-time and have a precision close to 1mm [60] which should be enough for our purposes.

Bone screws similar to those used in cranial bone fixation[61] will be used to fix the transducer to the skull. Bone screws are used in many operations and are safe. They will thus restrict the transducer's movement during the time of usage of the prosthetic.

The surgery in itself will only consist of cutting the scalp above the transducers and the coil implantation location, inserting the implant, screwing the transducers to the skull and finally sewing the scalp back together. This should be a relatively simple operation compared to more invasive intracranial surgeries.

5 Product development and experimental approach

First, the different components of the system need to be manufactured. Next, the function of the different parts of the system have to be verified, for example, the transducer could be tested on materials similar to bone and brain tissues to verify that the intensities and focus needed can be achieved. Some basic biocompatibility tests should also be done at this point. Then, the device could be implanted in animals to test the surgery methods, test the device safety, and test if the device does not move after implantation and if the transducer can inhibit or activate specific regions of the cortex. Finally, clinical trials need to be made on animals to see if the transducer can achieve a decrease in drug addiction

and cravings. In these studies, the effectiveness of targeting each hemisphere could also be tested, as mentioned earlier. Any side effects should also be monitored, for example, the stimulation should have minimal effect on other motivated behaviors like food intake.

6 Conclusion

In this report, we described a neuroprosthesis to reduce symptoms of nicotine addiction. Our device involves novel techniques like cMUTs and wireless powering to target the problem with neuromodulation. The relatively low invasiveness and the portability of our solution makes it a better alternative than other proposed neuroprosthesis like Deep brain stimulation. Our device could also potentially be applied to other addictions as the targeted areas in the brain are involved in many other addictions.

The amount of evidence that our prostheses will manage to reduce cravings and nicotine consumption is however not significant and would require more investigation. Our prosthesis might also not affect some of the symptoms of addiction as the latter involves many different systems and may differ from person to person. Personalized approaches could hence be further discussed.

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