Our Team

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Closed loop mechanism and hypoxia detection

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Pathology and Biological target

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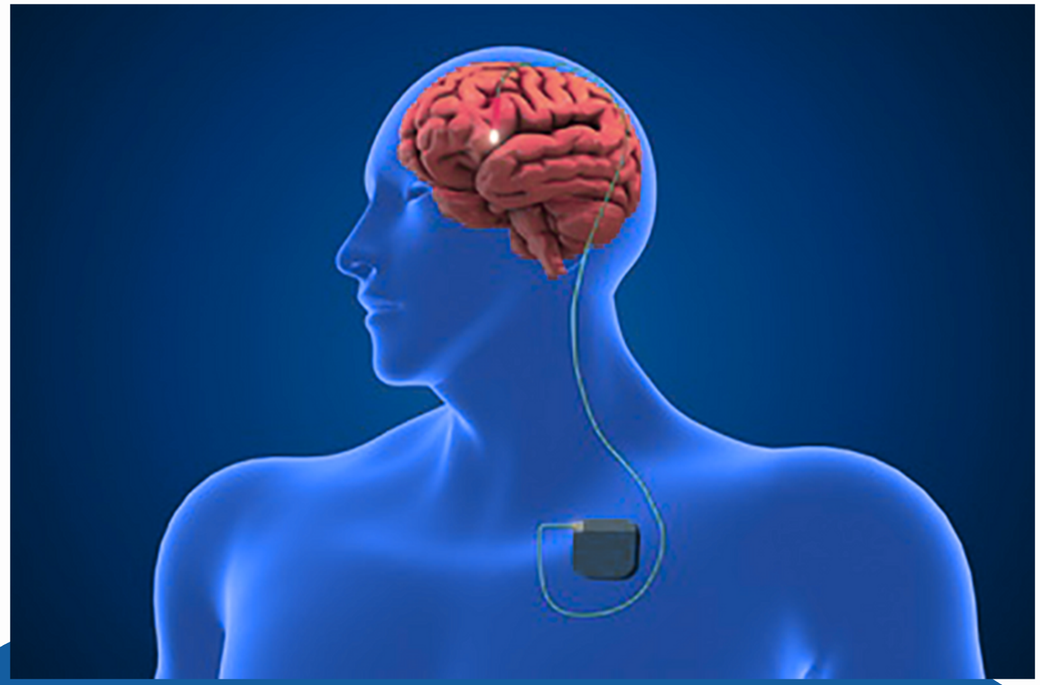
DBS and stimulation parameters

Detection and management of nightly hypoxia phases in Amyotrophic Lateral Sclerosis (ALS)

Picture taken from [45]



Picture taken from [46]

ALS: understanding the global impact

Idiopathic, fatal neurodegenerative disease affecting lower and upper motor neurons[42]

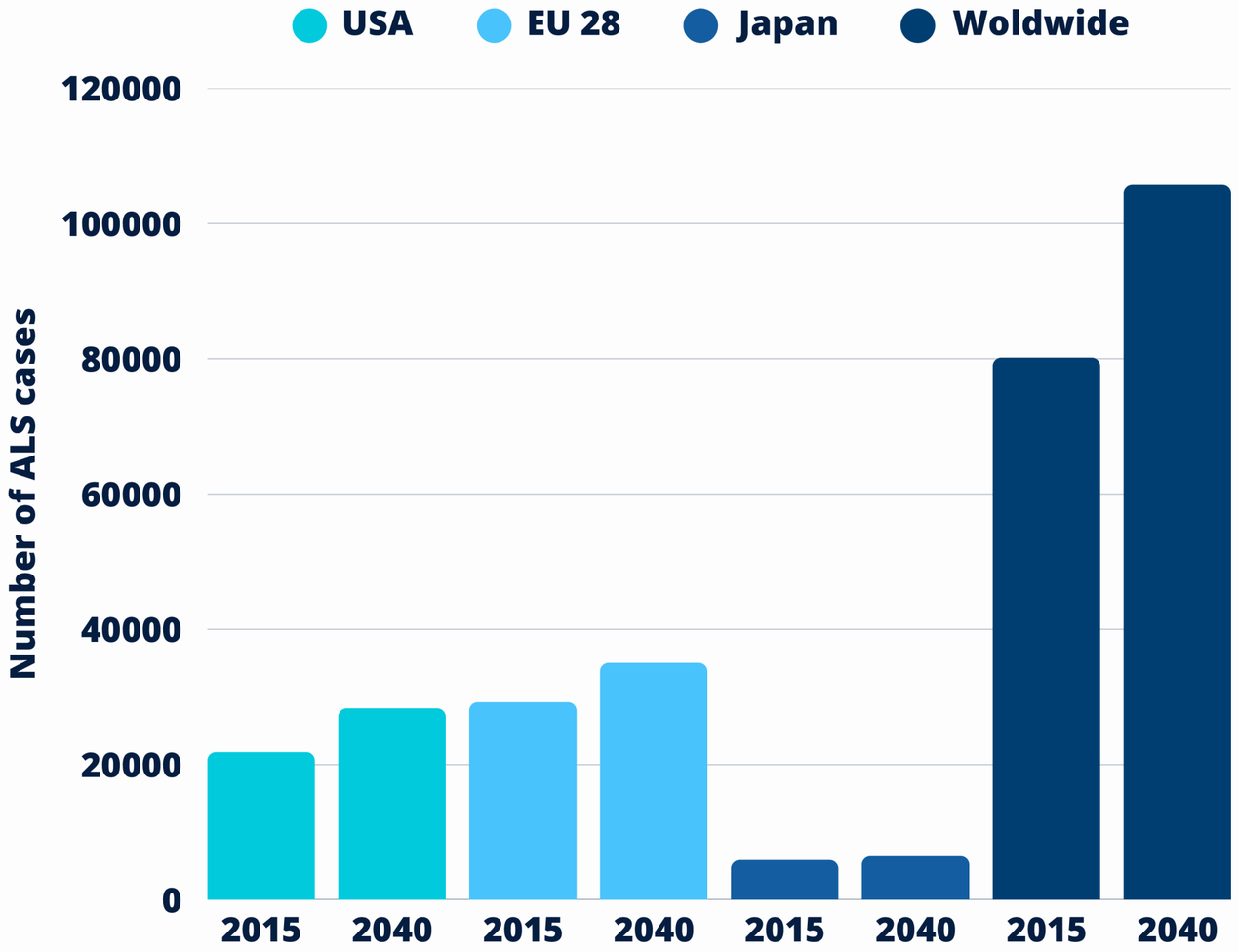
Hallmark: TDP43-positive cytoplasmic inclusions

⅔ of ALS patients have a limb onset form,
⅓ have bulbar onset [1]

Prognosis after first symptoms
2-3 years for bulbar onset
3-5 years for limb onset [1]

Worldwide, prevalence is **5.2/100'000** [1]

Projected number of ALS cases classified by country and year



Adapted from Table 1[41]

Breathing dysfunctions in ALS

Observed in all patients

What ?

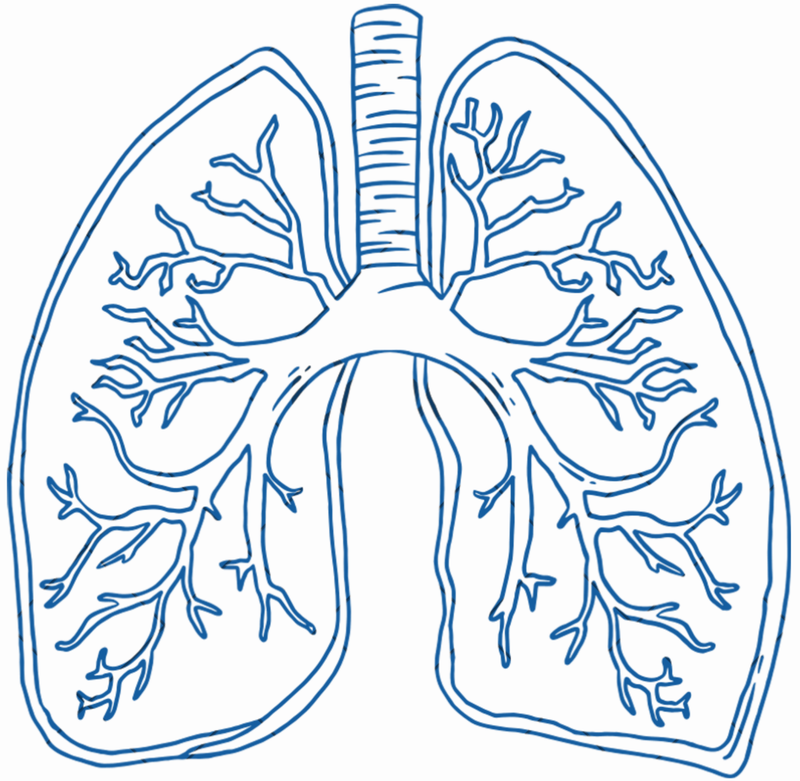
Respiratory failure: first cause of death in ALS patients[4]

Weakness of respiratory muscles is the **main predictor of prognosis.**

Why ?

Degeneration of **lower MNs**[3] → **Bilateral phrenic MNs** degeneration

→ **Respiratory muscles** weaken and atrophy



Voluntary breathing is impaired with M1 diaphragm representation zone suffering from TDP43 inclusions [3]

Breathing management in ALS is crucial

Hypoxia: crucial downstream consequence

Why mainly during the night?
Diaphragm = only active inspiratory muscle during REM sleep, other accessory muscles that can help balance out phrenic MNs degeneration undergo sleep-associated atonia

Respiratory muscles weakness → Dyspnea, Orthopnea, Central sleep apnea → Nocturnal Hypoventilation (NH) → **Hypoxia** = percentage of total sleep time when SpO2 falls below a threshold

DAILY SYMPTOMS

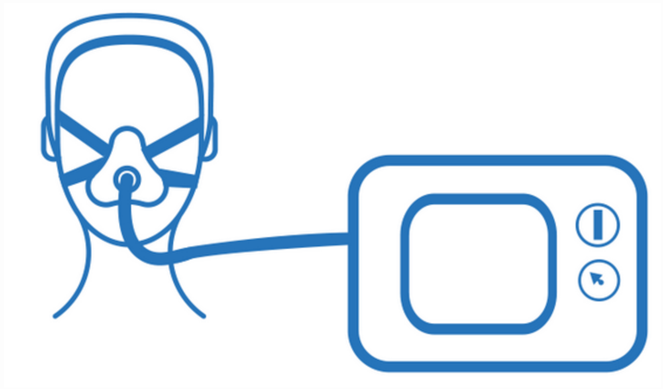
- Decreased quality of life
- Insomnia
- Headaches
- Daytime sleepiness

Aggravates motor neuronal death and cognitive dysfunction in ALS
→ **Precipitative factor of the pathology** [5]

Hypoxia at night has significant consequences throughout the day
Finding a solution -> slowing down ALS progression and improve daily life quality

Breathing management today: Market analysis

Before tracheostomy and mechanical ventilation (IMV), each having their sets of drawbacks



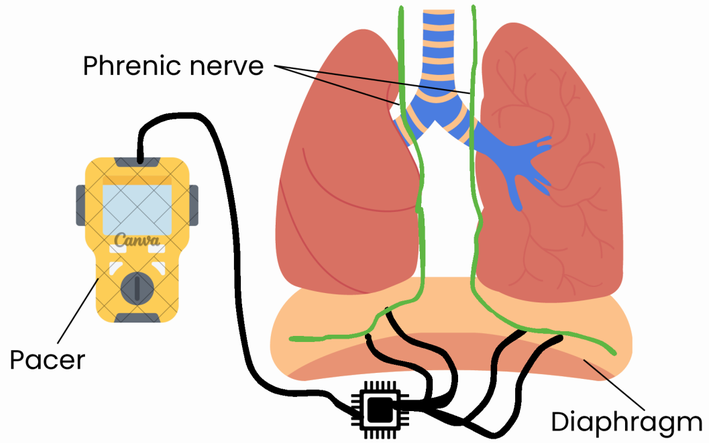
Non-Invasive Ventilation (NIV) - BiPaP masks

-> Part of Standard of Care

Patient spontaneous breathing drives the machine cycle, delivering insp. and exp. pressure

- ✓ Proven to increase survival [6]
- ✓ Efficiently alleviate symptoms of respiratory distress

- ✗ Cumbersome, uncomfortable
- ✗ Mouth leaks in bulbar ALS patients [7]
- ✗ Reduced motor unit recruitment and less phrenic motor neuron activity.



Diaphragm pacing

- ✓ Target source of degeneration: phrenic nerve
- ✗ Very controversial results: scientists are unsure of its impact, lots of cofounders
- ✗ Decreases survival [8]

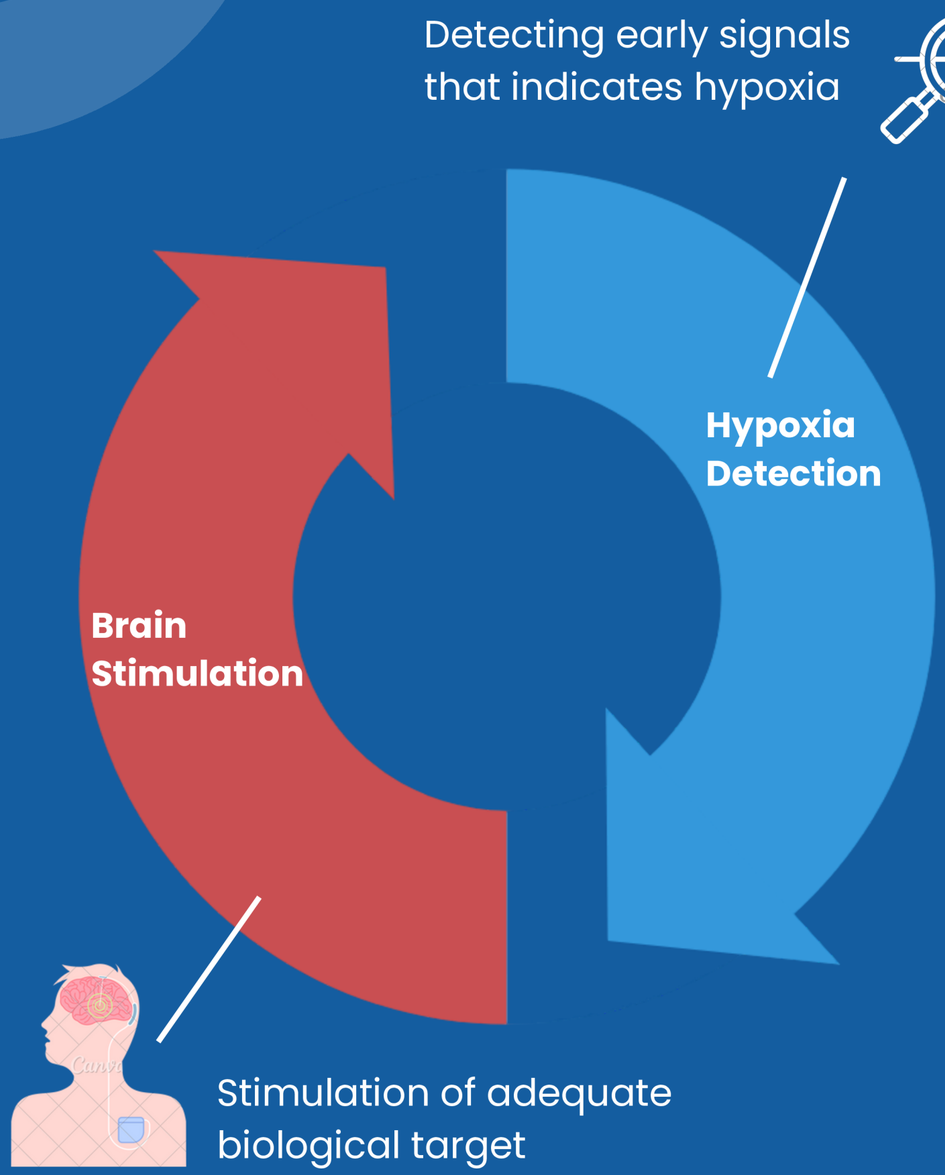
Our Solution

A **bipartite closed loop** doing brain stimulation to enhance Minute Ventilation (MV) when detecting a hypoxia phase at night

Why a closed loop ?

- **Personalization:** adapts to the duration and intensity of the phase
- **Real-time reaction** with minimum latency
- **No unnecessary** stimulation

Our Solution



A **bipartite closed loop** doing brain stimulation to enhance Minute Ventilation (MV) when detecting a hypoxia phase at night

1. **Detection of real-time hypoxia phase** identify early brain activity changes signalling reduced oxygen levels

2. **Targeted brain stimulation** triggered immediately to restore normal breathing rhythm

Hypoxia Detection

How to detect hypoxia ?

What do we want ?

- Highly reliable and sensitive
- Fast detection and short latency

- On bluetooth, wireless
- Battery-operated (8-10 hours)
- Design adapted for night use
- Inter-operability with microcontroller and stimulation tool

What are the options ?

Respiratory rate sensors

Measure breathing rhythm, not its effectiveness [26]

Invasive Neural Sensors

High complexity, regulatory burden, patient risk [28]

Pulse oximeter

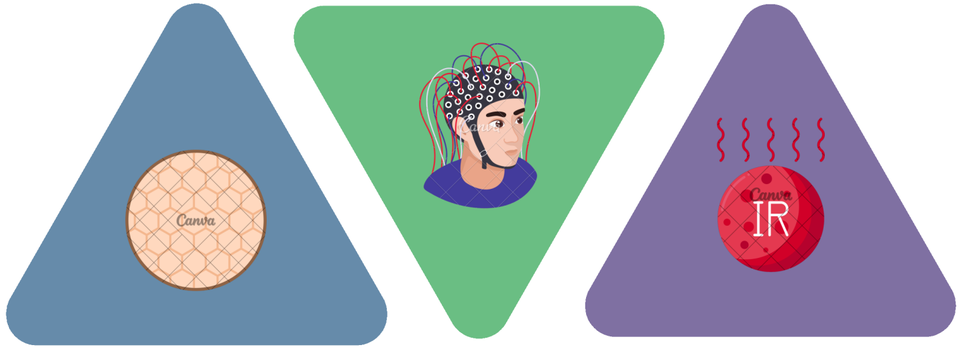
SpO_2 reflects oxygenation after physiological deterioration has already begun [25]

PPG for heart rate variability

HRV is too variable and delayed to be a reliable biomarker for real-time early hypoxia detection [27]

Dry EEG

Can be slow, requires burdening equipment, needs interpretation [30]



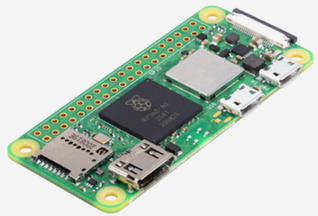
Electrodermal activity

Cannot differentiate between cognitive decline, stress, or thermoregulatory events [29]

NIRS

What sensor ?

Cerebral near-IR spectroscopy (cNIBS)
Model chosen: **PortaLite MKII** by *Artinis*



Oxysoft software: Enables real-time streaming of data to Matlab or Python via Lab Streaming Layer (LSL)

STIMULATION

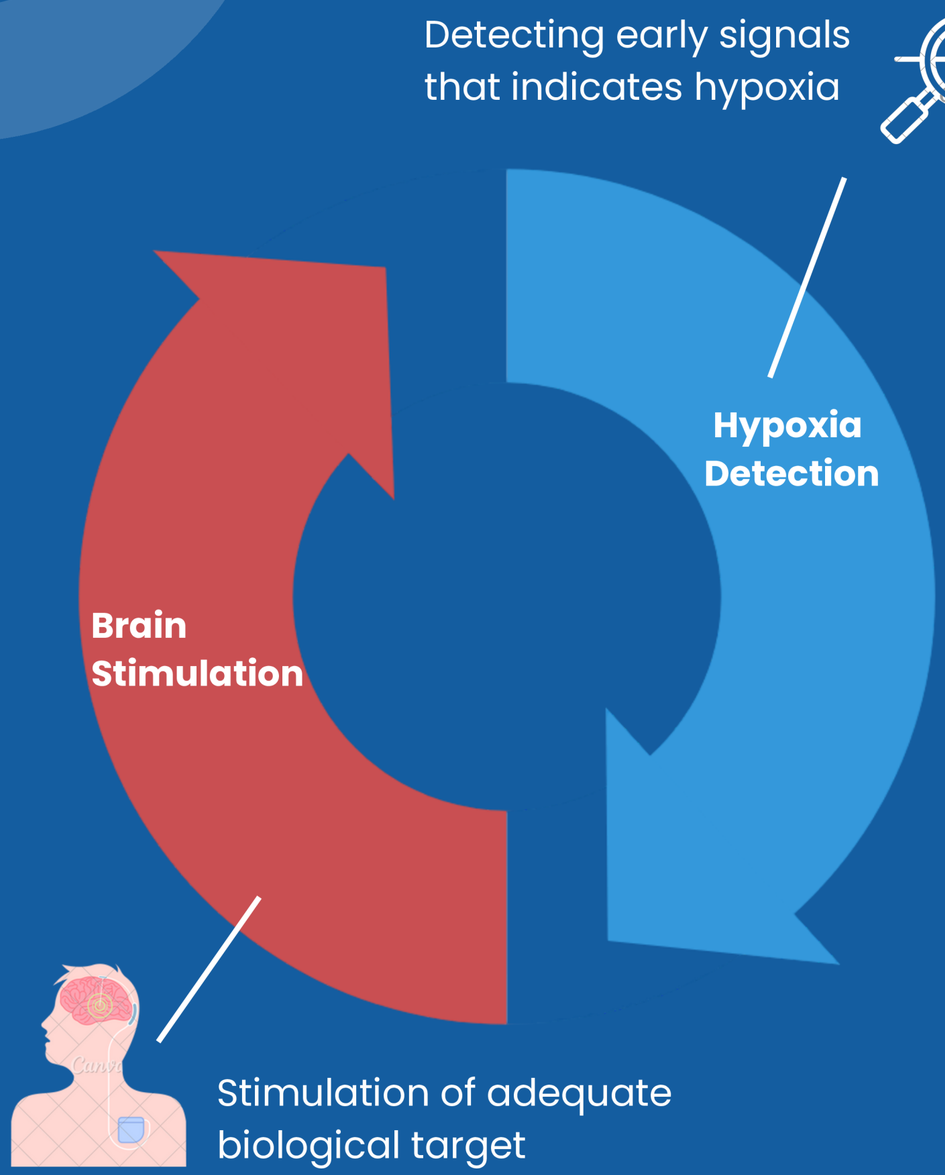
Dual detector designed to help filter noise from the scalp and skull

Detection time: <10s, better than all the other methods [43]

Very **accurate**, used in neonatal intensive care unit [44]

Treshold to detect hypoxia: to be defined. Need to be fine-tuned to the patient during clinical assessment

Our Solution



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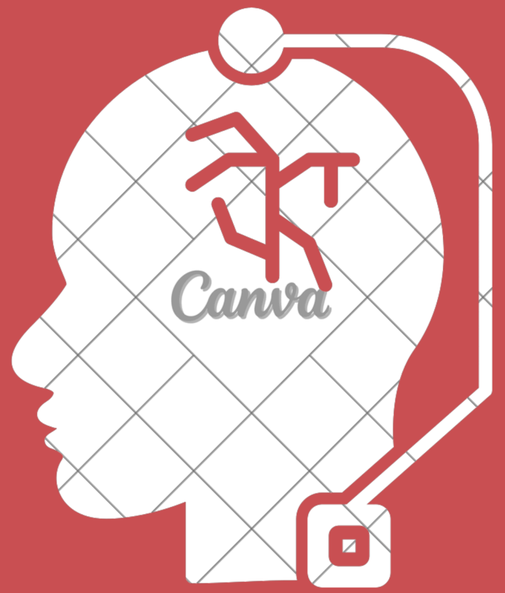
Brain Stimulation

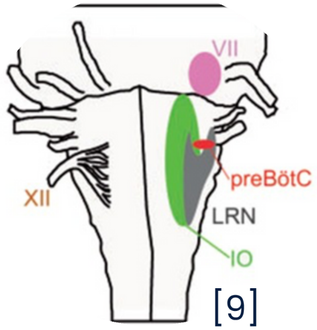


Defining the neurobiological Target: options

1

Pre-Bötzinger complex: primary inspiratory rhythm generator [3]

- In the brainstem, ~1mm
- Close to vital center of commands

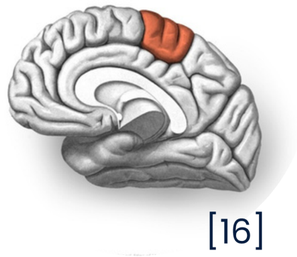


[9]

2

Motor region linked to the diaphragm: M1 & SMA

- ~~Suffer from TDP-43 inclusions compromising the efficiency of stimulation~~ Technically reachable but voluntary breathing is compromised in ALS


[16]

3

Cortico-thalamic regions that could influence breathing pattern

- More accessible to target
- Pathways influencing breathing still being discovered

Anterior Cingulate Cortex (ACC)

- Unknown pathway to respiratory brainstem group

Medial amygdala

- Deep in the brain
- Known projection on PreBötz [10]

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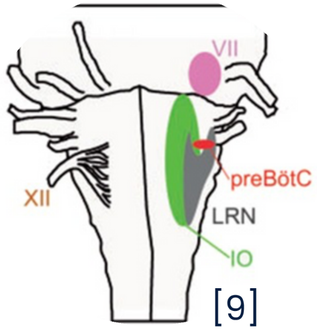

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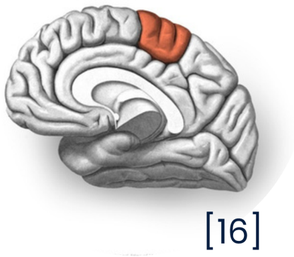
✗ Technically reachable but voluntary breathing is compromised in ALS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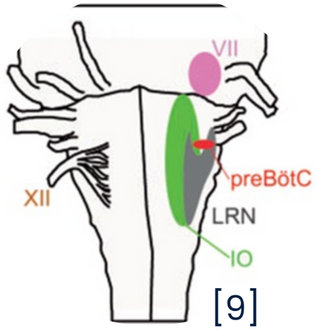

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Motor region linked to the diaphragm: M1 & SMA

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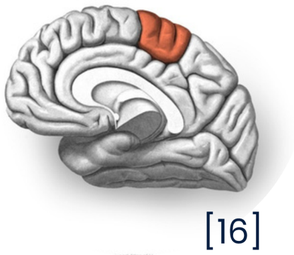
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What are the stimulation technologies?

Non-Invasive

- Transcranial Electrical Stimulation (tES)
  - tDCS, tACS, TI, mTI
- ~~Transcranial Magnetic Stimulation (TMS)~~
  - ~~TMS, rTMS, TBS~~
- ~~Transcranial Ultrasound Stimulation (TUS)~~
  - ~~TPS, LIFU~~

Invasive

- Deep Brain Stimulation (DBS)
- ECoG-based stimulation
- Intracortical Microstimulation (ICMS)

Non-negotiable constraints

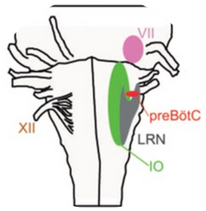
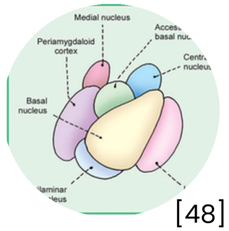
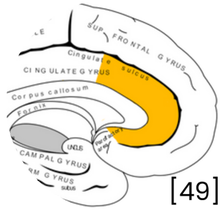
- ✓ At home-use
- ✓ No frequent hospital visit
- ✓ Needs to be financially accessible

No TMS due to power consumption and size [15]

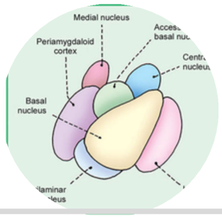
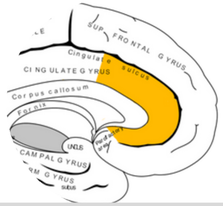
No TUS due to cost [11]

Feasability assessment

Non-invasive techniques

		tDCS, tACS	TI	mTI
Pre-Bötzinger complex		Too deep	Unreachable focality and safety issues [12][21]	Too experimental and unsure effects [13]
Medial amygdala	 [48]			
Anterior Cingulate Cortex (ACC)	 [49]	Reachable via HD techniques (a) but lack of stimulation intensity.	Lack of stimulation intensity	

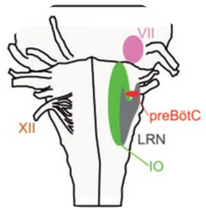
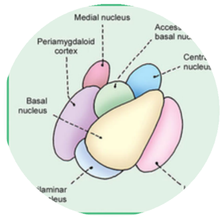
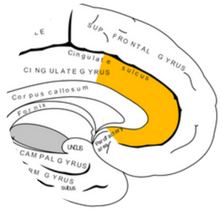
Non-invasive was not an option - necessity to use invasive solutions -> **DBS, EcOG, ICMS**

	Medial amygdala 	Anterior Cingulate Cortex (ACC) 
tDCS, tACS	Too deep	Reachable via HD techniques but lack of stimulation intensity
TI	Unreachable focality and safety issues	Lack of stimulation intensity
mTI	Too experimental and unsure effects	Lack of stimulation intensity
ECoG, ICMS	Only work on the cortical surface	Only work on the cortical surface
DBS	Feasible	Feasible

Non-invasive was not an option - necessity to use invasive solutions -> **DBS, EcOG, ICMS**

Feasability assessment

Invasive techniques

		EcoG	ICMS	DBS
Pre-Bötzinger complex		Only work on the cortical surface		Brainstem is too sensitive
Medial amygdala				Feasible
Anterior Cingulate Cortex (ACC)				Feasible

Medial amygdala as a potent target

In *Talavera B et al.* [10], SEEG stimulation of the Medial amygdala with specific parameters **increases minute ventilation** (MV)

»» **Decrease in ETCO2**
Increase in SpO2

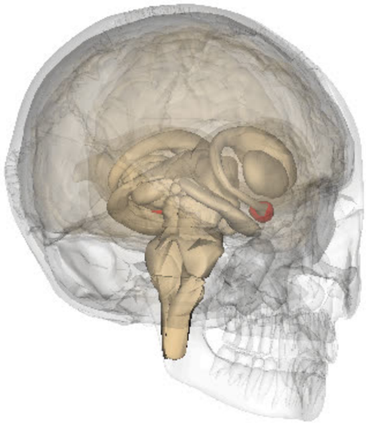
Why does it work?

[14]

In medial amygdala, GABAergic and glutamatergic neurons
→ stimulation has **excitatory effect** on inspiratory neuronal drive

Why does it makes sense?

Main function of amygdala: act appropriately in case of "fight or flight" response.
Medial amygdala is related to control of autonomous system such as the breathing rate.



Life Science Databases (LSDB) [37]

DBS

What are the choices for the DBS setup ?

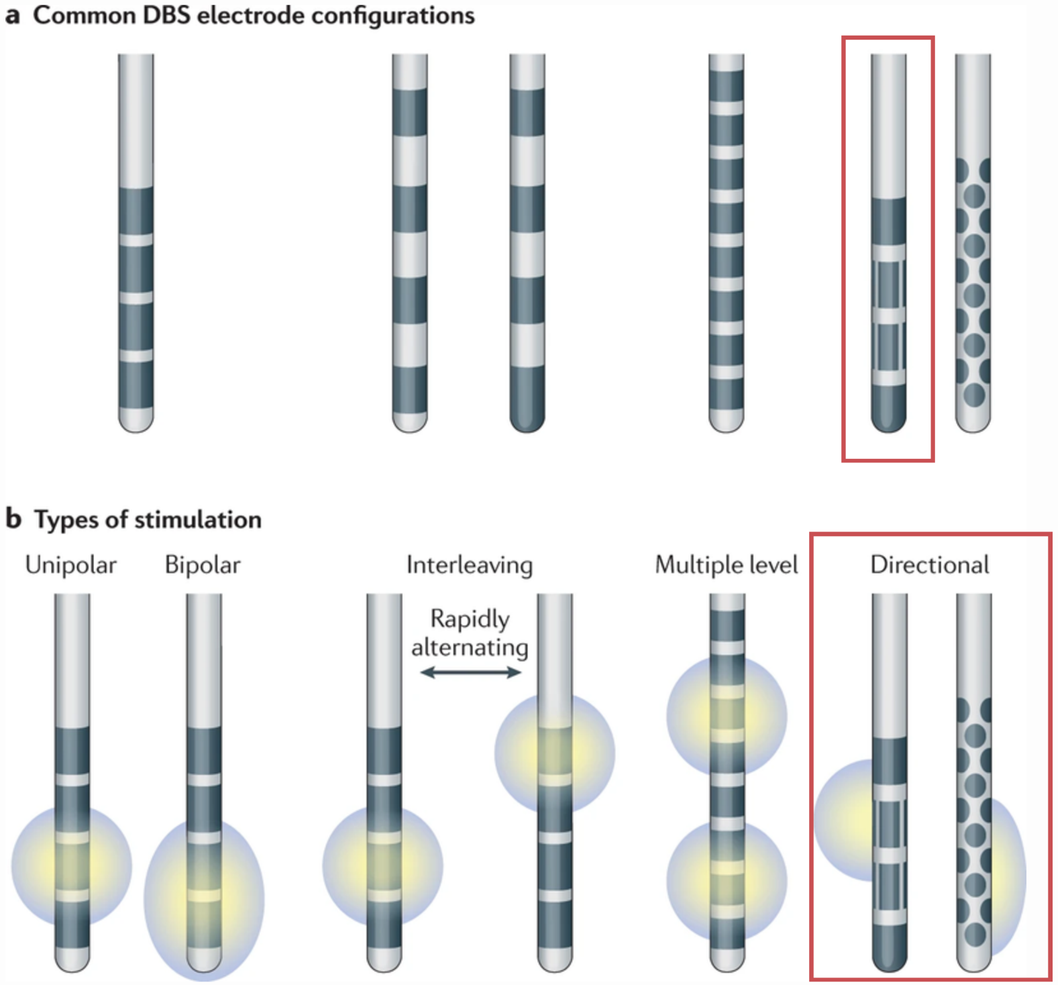
01 Which electrodes?

02 Where to place them?

03 Which pulse generator?

04 Stimulation Parameters

- Frequency
- Amplitude
- Pulse Width
- Duration



Extractred from Figure 2 in [23]

Which Electrodes?

What configuration are we aiming for?

Similar target size to STN stimulation for PD treatment, we use directional electrodes with standard 0.5mm spacing.

What type of stimulation?

Directional and bipolar stimulation -> superior precision and reduced side effects compared to unipolar stimulation. [34-36]

For our project, we are using the ***SenSight™ directional lead kit B3300542M*** by ***Medtronic*** [38]

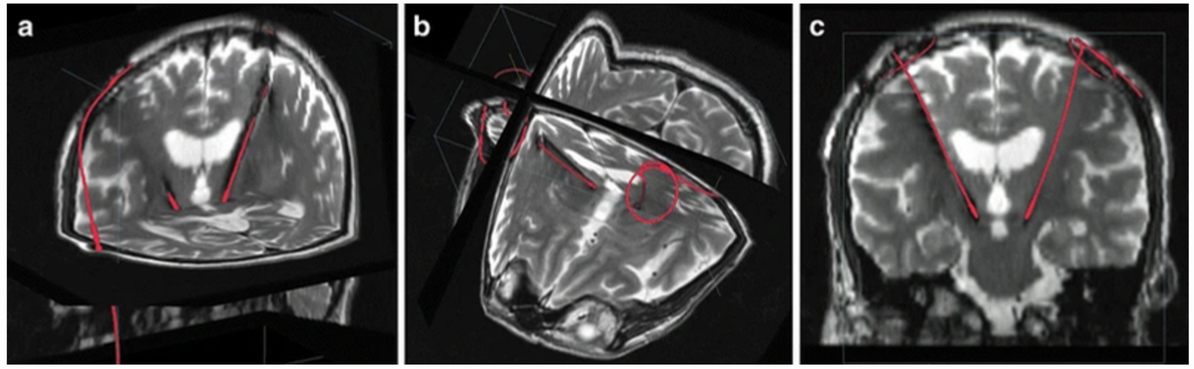
Where to place them?

First, MRI for Visualizing the Target

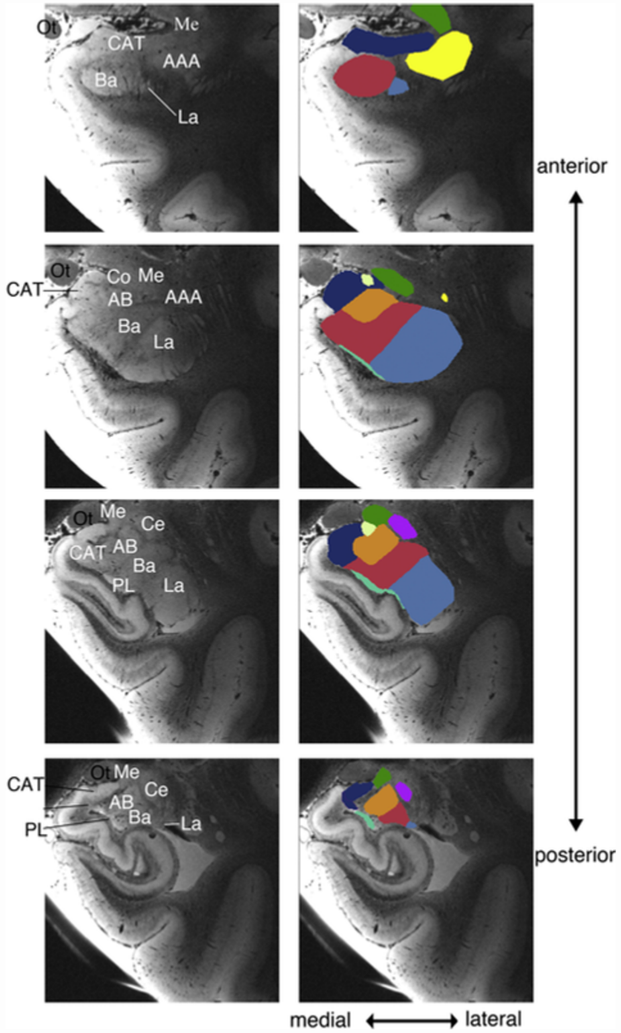
High-Resolution Magnetic Resonance Imaging (7-T imaging) is used for detailed visualization of brain structures, including deep nuclei. [18]
→ MRI provides the target anatomy

Then, CT scan for Spatial Accuracy and Navigation

The CT scan is used to register the patient's head position. It shows frame for surgical guidance.
→ CT provides the coordinate system



Extracted from Figure 3 in [20]



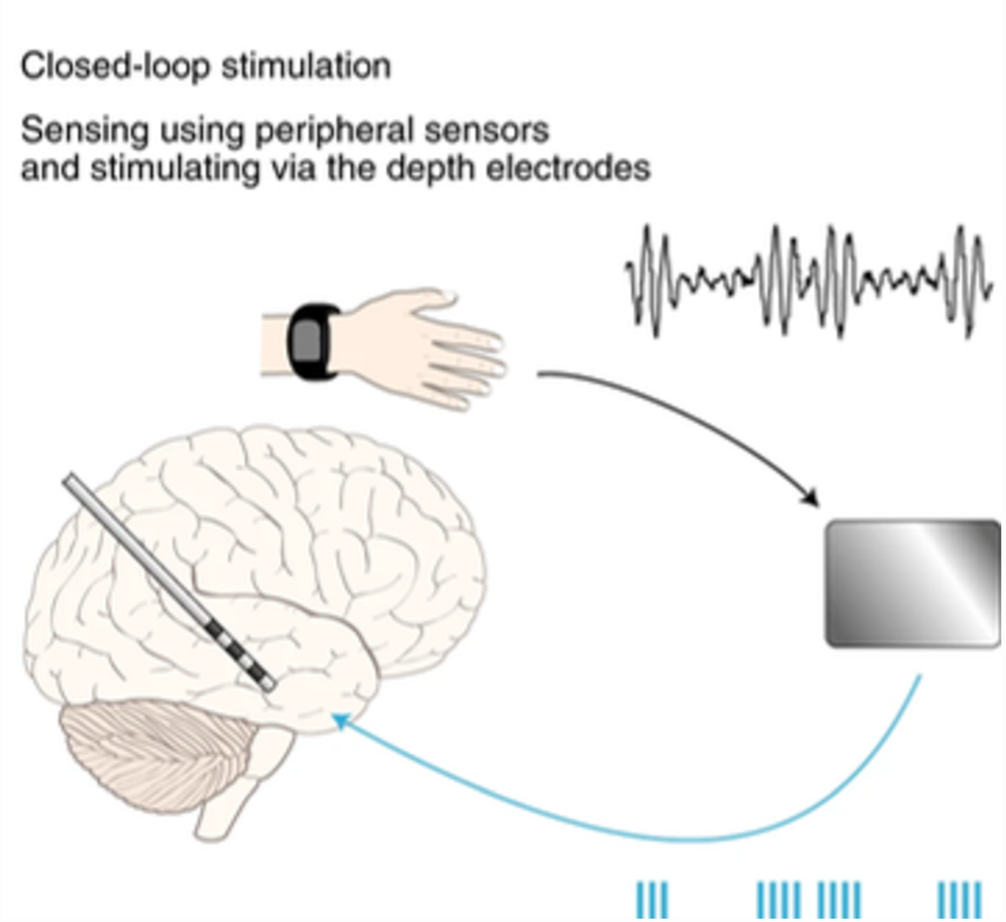
Extracted from Figure 1 in [19]

Which Pulse Generator Type?

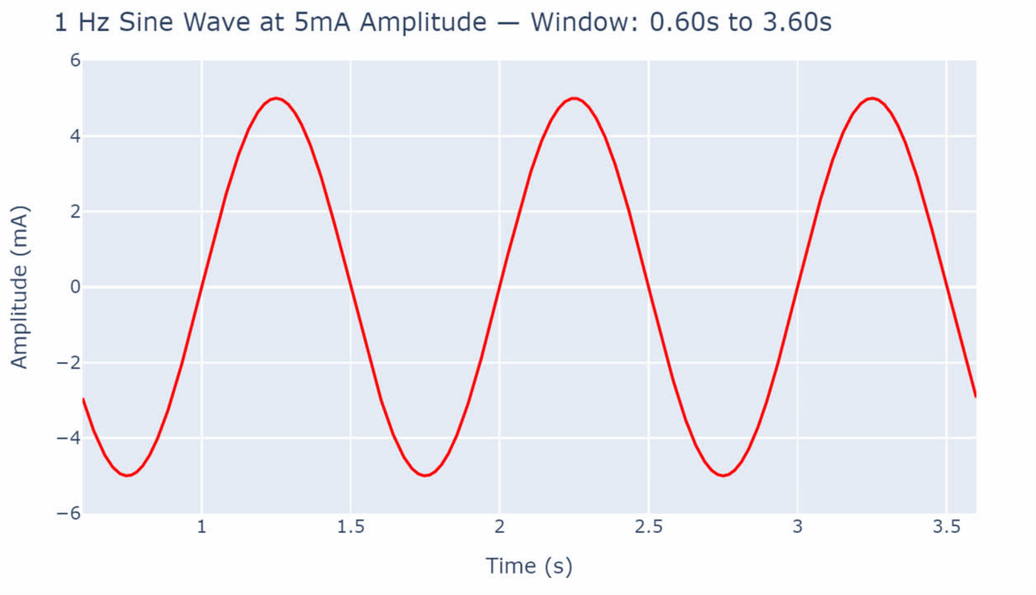
Closed Loop Generator

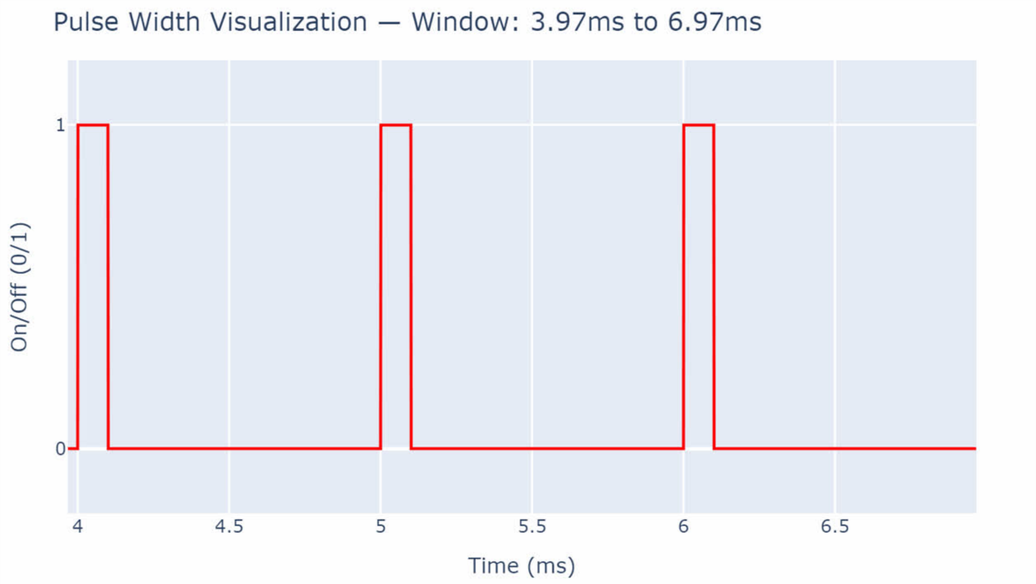
Since our system is conceived to respond in real-time, a **closed-loop generator is required**.

For our project, we are using the ***Percept™ PC B35200*** by ***Medtronic*** [39] that allows that.



Extracted from Figure 3.d in [24]





Made with Plotly and Numpy Python libraries

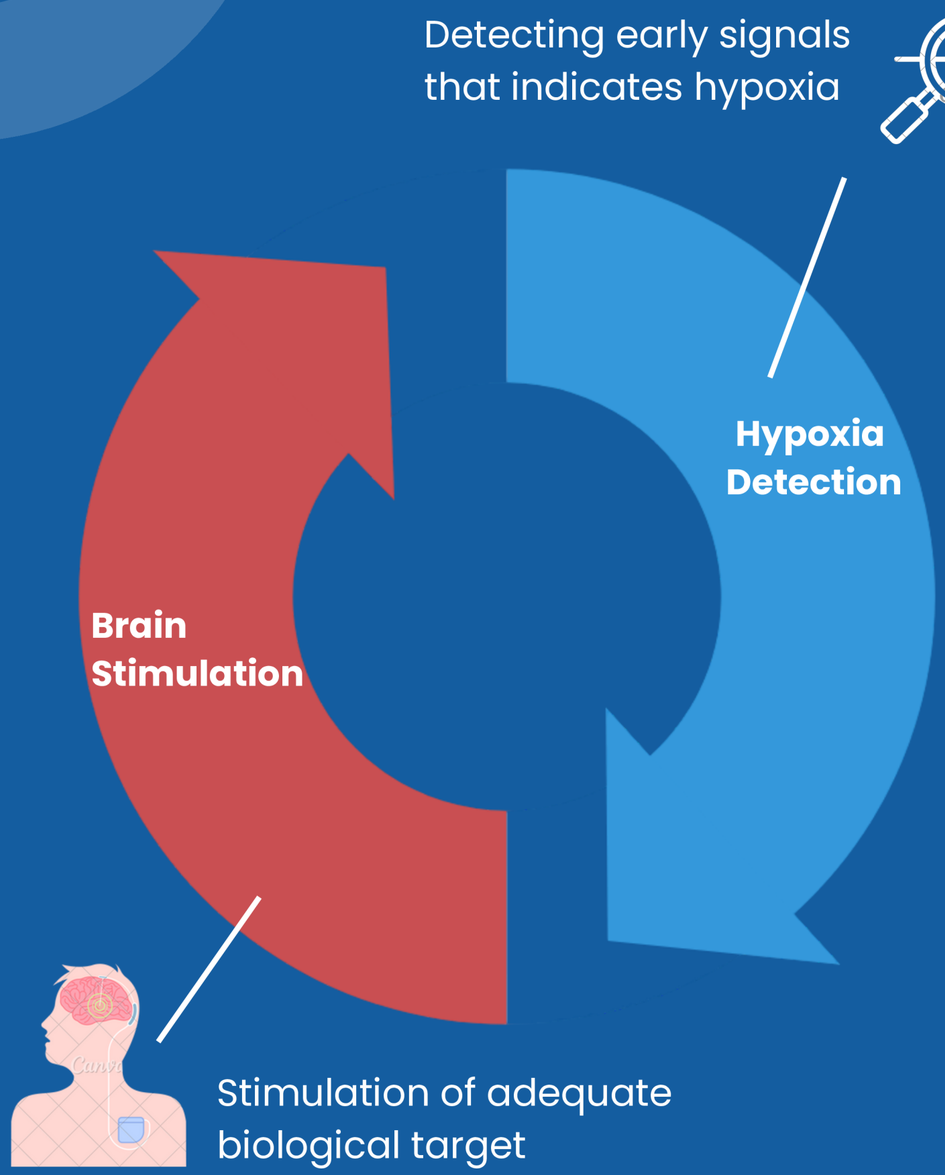
What are the Parameters?

Induced current parameters

Stimulation parameters on medial amygdala which have shown to be effective [10] are:

- Low Frequency (0.5-1.5Hz)
- Low Intensity (<5mA)
- Long Pulse Width (100μs)
- Duration is defined during the clinical assessment

Our Solution



A **bipartite closed loop** doing brain stimulation to enhance Minute Ventilation (MV) when detecting a hypoxia phase at night

1. **Detection of real-time hypoxia phase** identify early brain activity changes signalling reduced oxygen levels

2. **Targeted brain stimulation** triggered immediately to restore normal breathing rhythm

Expected results

What will we test for during the clinical assessment ?

Increased survival compared to NIV alone

Fewer symptoms related to hypoxia

Higher comfort under NIV

Disparition of morning headaches

Less day-time sleepiness

Less insomnia

Less cognitive dysfunction

Clinical assessment

PHASE 1 : Hypoxia detection assessment

Test hypoxia detection with cNIRS

- Healthy patients
- Sensitivity/Specificity vs SpO2

Sleep-based silent hypoxia detection

- Healthy and ALS patients
- Assess overnight detection performance

Threshold adjustment

- ALS patients
- Hypoxia threshold update

PHASE 2 : Brain stimulation testing

DBS safety and feasibility

- ALS patients
- Parameters fine-tuning, efficacy and side effects evaluation

PHASE 3 – Closed-loop integration and evaluation

Test of closed-loop reactivity

- ALS patients
- Test of system responsiveness & safety

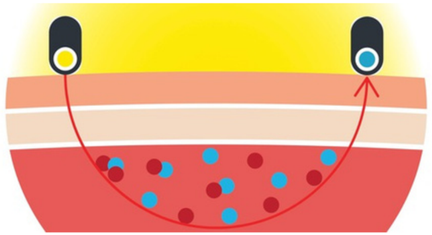
Real-world trial

- ALS patients
- Assess stability and usability outside clinic

Limitations

Hypoxia detection

Limitations of cNIRS: measures superficial cortical areas and not capture deep brain structures where hypoxia may also occur



Brain stimulation

DBS is an invasive and risky neurosurgery
→ Patient acceptability: risk vs benefit
→ Clinician hesitation to recommend surgery
→ Effectiveness compared to standard of care

Unknowns in ALS pathophysiology

Future perspectives

Once large amount of data gathered → create an **ML model predicting hypoxic events in advance** with increased accuracy.

Personalised based on patient-specific patterns, improving both efficacy and safety

Reactive → **Anticipatory**

CONCLUSION

"Let us keep looking, in spite of everything. Let us keep searching." Charcot (1889)

Fitted for bulbar onset

Discrete

Closed-loop and adaptative

Complementary to NIV in later stages

Clinical data collection

Home-based

Enhancement of Minute Ventilation (MV)

Early-stages ALS

References

[1] Wijesekera, L.C., Nigel Leigh, P. Amyotrophic lateral sclerosis. Orphanet J Rare Dis 4, 3 (2009). https://doi.org/10.1186/1750-1172-4-3

[2] Nimish J. Thakore MD et al. A Cost-Effectiveness Framework for Amyotrophic Lateral Sclerosis, Applied to Riluzole. Value in Health, Volume 23, Issue 12, December 2020. https://doi.org/10.1016/j.jval.2020.06.012

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