JUMPSTART

FOUNDRY

BRAIN-COMPUTER INTERFACES

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INTRODUCTION

Brain-Computer Interfaces (BCIs) are systems capable of translating brain signals into actions of computers or prosthetic devices. The purpose of the first BCIs was to restore motor function to people suffering from severe neuromuscular disorders such as ALS and paralysis. [1]

Beginning in 2013, the definition and scope of BCIs slightly changed as technology progressed. Previously, BCIs were "open loop" and information flowed from brain wave signal acquisition to output by either a computer or prosthetic device. Since then, "closed loop" BCIs have developed and can record signals from the brain and nervous system, decode it, and then encode new information back into the nervous system. [2]

With the development of "closed loop" technology, the potential BCI market for health applications has rapidly expanded outside of severe neuromuscular disorders and into disease indications such as Alzheimers, Parkinson's, addiction, and depression. [3]

While BCIs hold a lot of promise toward treating disease and restoring motor function, questions remain around the current and future capabilities of BCIs. In order to bring clarity to the BCI space, below is an overview of the different types of BCIs and a timeline of BCI developments. The next section will provide a rough estimation of the BCI market size for health applications. The third section will include a brief overview of the technical considerations for the different types of BCIs. Next is an overview of the companies in the BCI space. Lastly, a conclusion that outlines the expected speed of future BCI developments.

SECTION 1:

TYPES OF BCIS AND DEVELOPMENT TIMELINE

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There are five different types of BCIs. Many people often limit the definition of BCIs as those fitting within only Category A, but that definition is too narrow. Below is an explanation of the five types of BCIs. [4]

A. **Open-Loop Efferent BCI:** Brain signals control an external device.
   + An example is the original BrainGate BCI (described below in section 4) where an implantable array let a patient control a computer cursor.

B. **Open-Loop Afferent BCI:** Electrical stimulation to the brain by a device.
   + An example is the original deep brain stimulation (DBS) used for Parkinson's treatment in which a neural implant gives off stimulation to the brain.

C. **Closed-Loop Efferent BCI:** Brain signals control an external device and then feedback is given to the user that enables them to change brain signals.
   + An example would be the BrainGate BCI, in which the computer with the cursor also gave off instructions due to the signals it was picking up that then are relayed back to the patient to change the brain signals and thereby affect cursor control.

D. **Closed-Loop Afferent BCI:** Electrical stimulation to the brain by a device and moderated by movement monitoring.
   + An example is a Parkinson's DBS-BCI in which a tremor of the wrist causes the electrical stimulation to change.

E. **Bidirectional Afferent Closed-Loop BCI:** Electrical stimulation to the brain is modulated depending on the recordings.
   + An example is Neuropace's BCI, described in Section 4, in treating epilepsy in which recordings of brain signals are used to modulate the electrical stimulation output.

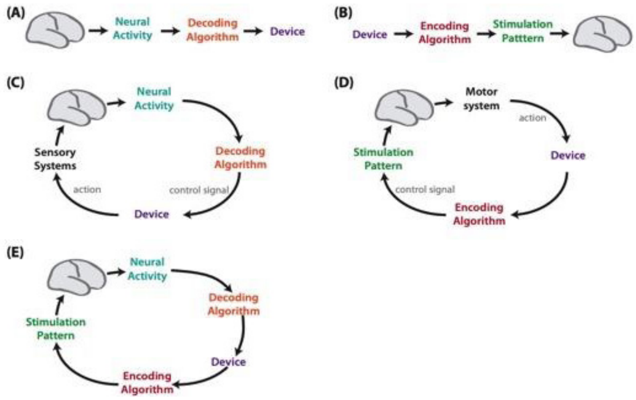

Figure 2: There are five different types of BCIs currently being developed for health applications. 4

TIMELINE OF BCI DEVELOPMENT

In order to get a better understanding of possible future market advances, it is helpful to see how BCIs have developed over time. Below is a timeline of major events in the BCI space. [2]

- **1997** - Deep brain stimulation (DBS) for Parkinson's approved by FDA
- **1998** - Researchers at Emory University implant BCI in a person with 'locked-in syndrome
- **2005** - Tetraplegic person controls an artificial hand using a BCI as part of BrainGate clinical trials
- **2013** - A BrainGate patient demonstrates control of a robot prosthetic limb
- **2013** - FDA approves NeuroPace RNS system - closed loop begins
- **2016** - Neurolife + Battelle paralyzed trial patient could play Guitar Hero
- **2017** - DARPA launches program with goal of recording from one million neurons
- **2018** - Researchers at UC Berkeley create implanted 'neural dust' wireless nerve stimulator
- **2019** - Carnegie Mellon uses non-invasive BCI to control a robotic arm

SECTION 2:

CURRENT AND FUTURE BCI MARKET SIZE

C04 - CURRENT AND FUTURE BCI MARKET SIZE

The BCI market for severe neuromuscular disorders in which brain waves are turned into computer or prosthetic function has a patient base roughly equivalent to the below numbers:

- ALS - 16,000 in US
- Cerebral palsy - 764,000 people in US
- Stroke - 795,000 strokes a year in US
- Spinal Cord Injury - 5.4M people in the US living with paralysis

BCIs within the broader BCI definition that includes Deep Brain Stimulation technology, BCI-DBS, can influence both the previously mentioned conditions listed above and other neurological conditions. Table 1 depicts the areas where BCI-DBS is currently being evaluated, the stage at which development currently stands, and the potential market size of each condition. [3]

CONDITION	STAGE	SIZE (ADULTS IN US)
Parkinson's	Standard of Care	1M
Major Depression	Phase III	16.2M
OCD	Phase II/III	2.2M
Tinnitus	Phase I	3.4M
Tourette Syndrome	Phase I	200K
Schizophrenia	Preclinical	3.5M
Alzheimer's	Phase II/III	5.8M
Pain (phantom limb)	Phase I/II	1.4M
Addiction	Phase I/II	21M
Anorexia nervosa	Phase II	1.5M
Epilepsy	Phase II/III	3.4M

SECTION 3:

OVERVIEW OF THE TECHNICAL COMPLICATIONS CURRENTLY LIMITING BCIS

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In Section 1, BCIs were divided into five different categories. These five BCI types can also be categorized into three main groups: invasive, semi-invasive, or non-invasive BCIs depending on how brain signals are acquired.

Non-Invasive

Non-Invasive BCIs usually use electroencephalography (EEG) monitoring to gather signals by placing electrodes on the surface of the scalp. While non-invasive EEG based BCIs are the safest BCIs, their signal clarity is often low. Advances in data processing are helping clarify the signal. [5]

Semi-Invasive

Semi-invasive BCIs use electrocorticography (ECoG) signals gathered from electrodes placed just under the scalp. ECoG based BCIs still require patients to undergo surgery to receive the BCI implantation. Signal resolution is higher than non-Invasive and contains less noise. [5]

Invasive BCIs

Invasive BCIs gather action potential signals by directly implanting electrodes into the cortex and currently provide the highest quality signals. Yet, obtaining those signals requires invasive surgery. Over time, the implant causes scarring of the brain as the brain begins to reject the electrodes. This is extremely harmful. Additionally, due to the scarring, the implant eventually becomes less effective. [5]

SECTION 4:

OVERVIEW OF COMPANIES IN THE BCI SPACE

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BCI Invasive Component Manufacturers

Blackrock: Blackrock Microsystems designs and sells tools in the neuroprosthetics and BCI space. Products include data acquisition, stimulation, electrodes, headstages, adapters, video system and analysis software.

- Maturity: Gold-standard in the industry. Utah Array has up to 128 active electrode channels. Devices have been implanted into roughly 20 people.
- Funding: $3.34M (Grant funding)

G.TEC: G.TEC develops BCIs and neurotechnologies for invasive and non-invasive neural recordings.

- Maturity: Claim to have been first BCI in 1999, and created the intendiX in 2007 (P300 speller). In 2008, g.tec released a 256 channel amplifier that can be used for non-invasive and invasive BCI. In 2017, G.TEC brought the first functional electrical stimulator (FES) with a real-time application programming interface (API) to the market. This allowed researchers and developers to begin setting up closed-loop experiments.
- Funding: Unknown

Microprobes: Microprobes is a global provider of implantable neural microelectrodes and multi-channel arrays.

- Maturity: Have multiple types of arrays comparable to BlackRock.
- Funding: Unknown

Intan Technologies: Intan develops specialized integrated circuits to interface with electrical signals in living tissue.

- Maturity: Founded in 2010, spinout of Caltech. Have multiple product lines.
- Funding: Unknown

Smart Ephys: Smart Ephys provides different solutions for all areas of electrophysiology from one source.

- Maturity: A division of Harvard Bioscience, which is publicly traded.
- Funding: Unknown

NeuraLynx: Neuralynx develops high-density, low-noise electrophysiology systems, optogenetics devices, test equipment, and accessories for human electrophysiology research.

- Maturity: Founder began Neuralynx in 1993. In 2011, Neuralynx released the FDA-cleared ATLAS Neurophysiology System for use in clinical environments for the identification and analysis of epileptic signals. In 2017 Neuralynx's wireless technologies provided 16 to 256 configurable channels of wide bandwidth neural recording and real-time signal processing.
- Funding: Unknown

BCI Non-invasive Component Manufacturers

Neuroelectrics: Neuroelectrics builds wireless EEG and tDCS/tACS/tRNS devices.

- Maturity: Early company but have fully functional products.
- Funding: $250K (MassChallenge)

ANT Neuro: ANT Neuro is an EEG cap manufacturer founded in 1997.

- Maturity: Established company in the space.
- Funding: Unknown

Closed Loop BCI Full Stack

Medtronic: Medtronic is a publicly traded medical device company creating devices for multiple diseases.

- Maturity: In January 2020, Medtronic's "Percept" closed loop DBS device was granted CE approval and expect FDA approval in mid-May 2020.
- Funding: Public, market cap 137B

Neuropace: Neuropace created a closed loop BCI that detects unusual brain waves in each person's unique brain waves that come before a seizure and automatically responds with electrical pulses that can stop seizure symptoms before they occur.

- Maturity: In 2013, Neuropace created the first closed loop BCI for the 1M US citizens with epilepsy. In 2018, they released the second version of the product.
- Funding: $272M

Open Loop invasive BCI

Braingate: Braingate is developing BCI technology to allow for patients to restore function to independence to those who have suffered from immobility due to disease or injury.

- Maturity: The most mature BCI (using Blackrock Microelectrode array). Implanted first BCI in 2002 and the full clinical trial ran from 2004-2006 in which a participant could control a cursor on a screen. Published results of a second study in 2012 in which participants could use robotic arms for reaching and grasping. While the furthest along, trial participation up to this point has been limited to roughly 20 people.
- Funding: $11.75M (Grant).

Battelle: Battelle is a research and development firm that works closely with the US Government and has created a BCI called "NeuroLife."

- Maturity: Completed a small clinical trial in 2016 and published results in Nature. One clinical trial participant was able to play Guitar Hero two years after receiving an implant. Neurolife used the BlackRock Utah Array for the BCI implant.
- Funding: Battelle revenue roughly $6B

CANDO: CANDO is working on a BCI for epilepsy in which an implant provides precisely timed stimulation by continuously monitoring brain waves via implanted electrodes and modifying them with implanted light sources. Doing so requires that some cells are genetically altered using a safe virus to make them sensitive to light.

- Maturity: Began in 2014 at Imperial College London. Want to have it in clinical trial by the end of 2021.
- Funding: $10M

Synchron: Synchron is the developer of a neural interface technology that has created an endovascular electrode array. Synchron's neural interface technology is the Stentrode, an implantable device designed to interpret signals from the brain enabling patients with the treatment of brain pathologies, such as paralysis, epilepsy and movement disorder.

- Maturity: Conducting First Early Feasibility Study
    + Estimated Study Start Date: June 15, 2019
    + Estimated Primary Completion Date: June 2020
    + Estimated Study Completion Date: June 2023
- Funding: $10M

Neuralink: Neuralink is creating a brain-computer interface. neurological conditions in humans to first treat medical conditions and then augment human cognitive powers.

- Maturity: Neuralink built electrode array "threads", that can contain 3,072 electrodes per array. These electrode arrays are composed of 96 threads. Additionally, Neuralink built a neurosurgical robot capable of inserting six threads (192 electrodes) per minute. Each thread can be individually inserted into the brain and is capable of avoiding surface vasculature. Neuralink wants to begin human clinical trials in 2020, but it is unclear if that will occur.
- Funding: $158M (Dreamers VC, Craft Ventures, Valor Equity Partners, DFJ Growth).

Paradromics: Paradromics has created BMI intended to increase the data transmission rate between brains and machines. Paradromics BMI has bidirectional data capabilities. Their first product will act as an assisted communication device, allowing for conversation for those with paralysis who have lost the ability to speak.

- Maturity: Paradromics, together with partner Caeleste developed a novel sensor that enables neural recordings with 60 times lower power consumption than conventional digital readouts.
- Funding: $26.5M (Arkitekt Ventures, Synergy Ventures, Loup Ventures among others).

NeuroRoots: NeuroRoots is looking to build an implantable BCI platform that does minimal damage to neural tissue and has long-term recording stability.

- Maturity: Currently in a Stanford Lab.
- Funding: Unknown, Stanford grant.

Non-invasive BCIs

Kernal: Kernal is building a non-invasive mind/body/machine interface (MBMI) to first improve human health and then "extend human cognition."

- Maturity: In 2017, Kernal acquired Kendall Research systems, a spin-out of MIT. Besides this news, not much else is known around their actual progress.
- Funding: 100M self-funded by founder.

BrainCo: BrainCo has developed a BMI wearable that can monitor, visualize and analyze brain waves in order to quantifies student attention levels in the classroom.

- Maturity: Came out of Harvard Innovation Lab. Has their first product on the market. Wearable/Commercial grade.
- Funding: $30.37M (Decent Capital and China Electronics).

CNTRL-Labs: BMI designed to increase the interactive capabilities of computers, smartphones and commercial devices. Did not have a health focus. Created a "wristband." Thesis was that the wristband could pick up on clean signals whereas the signals implantables in the brain try to pick up are full of more noise.

- Maturity: Had a workable product, but limited functionality as it could.
- Funding: Acquired by Facebook for $1B after raising $67M from Amazon Alexa Fund, Spark Capital, Matrix Partners, Breyer Capital, FUEL Capital and Lux Capital.

Cognixion: Cognixion is building a BCI that turns brain signals directly the ability to communicate.

- Maturity: Have launched Speakprose Pro+ utilizes the latest iPhone and iPad eye-tracking technology to allow users with limited mobility to navigate the screen with their eyes and select letters or words by blinking or holding their gaze. ay. Traditional eye-tracking technology and the hardware that goes with it can run more than $10,000. Cognixion's app costs $39 a month.
- Funding: Raised $6.05M (Sequel Venture Partners, and others unknown).

Neurable: Neurable created a VR headset and an external EEG based BCI, that allows consumers to transform thoughts into actions for video games.

- Maturity: In 2017 they had an MVP of a video game that they could control with their external EEG BCI. In the last couple of years they have focused on reducing the number and size of the sensors.
- Funding: $13.9M (M Ventures, Loup Ventures, PJC, Innospark Ventures and GoAhead Ventures).

Emotiv: Emotiv has created a BCI external EEG device.

- Maturity: Emotiv was founded in 2011 and has multiple products it is selling directly to consumers.
- Funding: $25.66M (Technology Venture Partners, Epicure Capital Partners and Stillwater Capital Partners back in 2009. Have mostly been doing accelerators for the last few years.

OpenWater: Openwater is working to create a wearable MRI that it can use to create a non-invasive BCI.

- Maturity: Extremely early. Have an "alpha kit" but nowhere close to any BCI.
- Funding: Unknown, investors include Lauder Partners, Bold Capital Partners, Starlight Ventures, and Esther Dyson.

NeuroLutions: Neurolutions has created a non-invasive BCI designed to control the movement of prostheses.

- Maturity: Currently running a clinical trial with 45 participants to test their product, "IpsiHand", which is an exoskeleton.
- Funding: $9.36M (Ascension Ventures, BioGenerator, Prolog Ventures and Gentsch Capital Partners).

Flow Neuroscience: Flow Neuroscience is developing a wearable in order to treat depression using Transcranial Direct Current Stimulation (tDCS).

- Maturity: Has CE certification and is selling direct to consumer .
- Funding: $2.6M (Khosla Ventures, SOSV).

Data Analysis for BCI

Rune Labs: Rune Labs has created a platform designed to integrate with neuromodulation therapies to manage, analyze, and label the data coming from the neuromodulation devices.

- Maturity: Very early, less than a year and half old company. In Fall 2019, they launched a patient facing app that is essentially a patient medication adherence and symptom recording journal.
- Funding: Raised $2.06M from TruVenturo and Loup Ventures.

BIOS: BIOS is creating a platform to enable the detection of physiological biomarkers from brainwaves.

- Maturity: BIOS is early but has made progress around creating a platform that is able to isolate physiological biomarkers from neural interface data.
- Funding: $4.75M (YCombinator, Real Ventures, AME Cloud Ventures, Endure Capital, Heuristic Capital Partners, K5 Ventures).

BrainQ: BrainQ is attempting to build algorithms for determining what feedback to send back into the brain in order to alter its function.

- Maturity: Currently conducting early stage clinical trials in Israel.
- Funding: $8.8M from Qure Ventures, OurCrowd and Norma Investments.

SECTION 5:

CONCLUSION AND FUTURE DIRECTIONS

CONCLUSION AND FUTURE DIRECTIONS

Invasive BCIs that restore motor function for those with paralysis have still only been implanted in just over 20 people as both technology and policy continue to progress. In early 2019, the FDA released guidance on clinical trial design for implantable BCIs. Additionally, companies such as Neuralink and Paradromics have made great progress in building a less invasive implant and improving the power/heating issue. As competition grows, the market will begin to accelerate. Neuralink is looking to begin clinical trials in 2020. The beginning of human clinical trials will spark further interest in this space, increasing the capital invested and most likely speeding up development.

Further Reading

NeuroLink White Paper
IEEE-Brain White Paper
Neural Interfaces Overview (Royal Society)
Technical Aspects of BCIs

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